An exploratory study to identify risk factors for the development of capecitabine-induced Palmar Plantar Erythrodysesthesia (PPE)

Penelope Anne Law

Health and Life Sciences
De Montfort University Leicester UK

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ABSTRACT

Background

Previous literature showed contradictory evidence on the subject of predictors of chemotherapy-induced Palmar Plantar Erythrodysesthesia (PPE). While there is evidence to suggest that dose and schedule of the drugs play a large role, the fact that many still go on to develop severe PPE following dose reduction would indicate that there are other factors involved. Since the incidence of PPE is more prevalent during the first three cycles of treatment this would also indicate that there are factors other than a cumulative effect. The contradictory evidence in the literature relates to biographical factors, performance status, co-morbidities and renal function. There is a lack of empirical evidence to support the theory that PPE is caused by damage to the microcapillaries due to everyday activities that cause friction or pressure to the hands or feet.

Purpose

The aim of this exploratory study was to identify pre-treatment risk factors for the development of PPE prior to cycle four.

Patients and methods

The study was made up of two phases, a retrospective phase and a prospective phase, using mixed strategies to collect data. Thus providing two independent samples to compare and validate or refute results.

Phase I

A retrospective notes review of patients who had received Infusional 5FU or capecitabine containing regimes over a 1 year period (n=392).

Phase II

Prospective data collection from participants receiving capecitabine monotherapy (n = 125). Data was collected during semi-structured interviews, from participant's diaries, physical examination of the hands and feet and notes review. Data relating to activities that cause friction, pressure or heat were collected during this phase.

Data from both samples were analysed independently using bivariate (chi-square and *t*-test) tests where each independent variable was analysed against PPE. The variables which achieved statistical significance were entered into a multivariate (binary logistic regression) model. The multivariate analysis employed a specific modelling algorithm using a relaxed alpha value applied to various entry methods to produce multiple models. The outcomes from these models were entered into a ROC curve test to establish which model was the best predictor of PPE.

Results

Phase I

The bivariate analysis demonstrated that those at most risk of developing PPE prior to cycle 4 of capecitabine monotherapy were males with non-metastatic colorectal cancer, who had either developed PPE with previous chemotherapy regimes or not had previous chemotherapy and who started their treatment during the winter months.

When variables were combined in a multivariate logistic regression model, those that were associated with an increased risk of PPE were male, no metastatic spread, no inflammatory condition as co morbidity, smoked, did not drink, had weight loss prior to treatment, a low/normal pre treatment ALP level and started their treatment during the winter.

Phase II

The bivariate analysis demonstrated that those at most risk of developing PPE prior to cycle 4 of capecitabine monotherapy were those with no metastatic disease, had an inflammatory condition as co morbidity, were receiving capecitabine as adjuvant treatment, had a good performance status (0-1) and had a tendency to have warm hands.

When variables were combined in a multivariate logistic regression model, those that were associated with an increased risk of PPE were younger (< 65) had no metastatic disease, an inflammatory condition as co morbidity, drank alcohol regularly, had a good performance status, had not received previous

radiotherapy, were overweight or obese, had a pre treatment creatinine clearance of 30-50mls/min and had a tendency to have warm hands.

Conclusions

Similarly to the literature, contradictory findings were seen between the two samples within this study. There was only one variable that was associated with the development of PPE prior to cycle 4, which was the absence of metastatic disease. Limitations of retrospective data may explain variation in some variables which may have been underreported; however it is likely that it is not possible to identify specific factors that increase the risk of PPE.

This is the first study to have collected and analysed data related to friction, pressure and heat causing activities. These activities have been suggested as increasing the risk of developing PPE and form the basis of patient education to avoid these activities. Data from this study indicates that only a tendency to have warm hands is associated with an increased risk of PPE. Whilst this finding would need validating in larger studies, it is a unique contribution to the body of knowledge of PPE. This finding indicates that avoidance of activities that cause friction and pressure has no evidence base. Patients may therefore be avoiding activities that add to their enjoyment which at this stressful time in their lives may add to any psychological distress.

Despite limitations of this study, the importance of the findings presented here lie in its usefulness in shaping future research to investigate identified variables, where before no direction was available.

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PUBLICATIONS

October 2011 a poster was submitted and presented at the United Kingdom Oncology Nursing Society (UKONS) conference held in Glasgow.

The findings from phase 1, retrospective data, were presented to 200 delegates.

ABBREVIATIONS

>	greater than
<	less than
≥	greater than or equal to
≤	less than or equal to
H_o	Null hypothesis
H_1	Alternative hypothesis; research hypothesis
X^2	Chi-square
ẋ	Mean
α	alpha level of significance
ALP	Alkaline Phosphatase Normal levels 40-130 iu/L
ALT	Alanine Aminotransferase Normal levels 2-53 iu/L
AST	Aspartate Transaminase Normal levels 2-53 iu/L
β	beta value in logistic regression
BMI	Body Mass Index
BNI	British Nursing Index
BSA	Body Surface Area
Ca	Cancer
CAPOX	Capecitabine and oxaliplatin
CDD	Cytidine deaminase gene
CHOP	A chemotherapy regime containing cyclophosphamide, doxorubicin (hydroxydaunomycin), vincristine (oncovin) and prednisolone
CI	Confidence interval expressed as a % degree of confidence that the interval contains the population mean
CINAHL	Cumulative Index to Nursing and Allied Health
CrCl	Creatinine clearance Normal creatinine level 60-120 umol/L
d.f	degrees of freedom
5-DFUR	5'-deoxy-5-fluorouridine a metabolite of capecitabine
DIY	Do it yourself
DLQI	Dermatology Life Quality Index
DMSO	Dimethyl Sulfoxide

DNA	Deoxyribonucleic acid
DPD	Dihydropyrimidine Dehydrogenase
DPYD	Dihydropyrimidine Dehydrogenase gene - implicated in the catabolism of 5-FU
DXT	Radiotherapy
ECG	Electrocardiograph
ECOG	Eastern Oncology Cooperative Group
EGFR	Epidermal growth factor receptor
F	Female
FBAL	2-fluoro-beta-alanine – a major catabolite of 5-FU
FOLFOX	5-FU and oxaliplatin
5-FU	5-Fluourouracil
G-CSF	Granulocyte colony stimulating factor
HER-2	Human epidermal growth factor receptor
HFS	Hand-foot syndrome
HFS14	Hand-foot syndrome 14. A tool to assess impact of PPE on quality of life
INR	International normalised ratio. Normal level 0.8-1.2
LBM	Lean body mass
LV	Leucovorin
M	Male
MESH	Medical Subject Headings
mg/m^2	milligrams per square metre
N	Number
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Toxicity Criteria of Adverse Events
NCIC	National Cancer Institute of Canada
OR	Odds ratio
OS	Overall survival
p	alpha value of significance
PATEO	Periarticular Thenar Erythema and Onycholysis
PG-CSF	‘pegylated’ form of G-CSF

PLD	Pegylated Liposomal Doxorubicin
PPE	Palmar Plantar Erythrodysesthesia
PS	Performance status
PVD	Peripheral vascular disease
R^2	the proportion of variance explained for a pair of variables
RCC	Renal Cell Carcinoma
RNA	Ribonucleic acid
ROC	Receiver operator characteristics
RR	Relative Risk
R_x	Treatment
Sic	sic erat scriptum
TKIs	Tyrosine Kinase Inhibitors
TTP	Time to progression (of disease)
TP	Thymidine Phosphorylase
TS	Thymidylate Synthetase
ULN	Upper limit of normal
WHO	World Health Organisation
X-Act	Clinical trial of bolus 5-FU versus oral capecitabine as adjuvant therapy for early stage Colorectal Cancer

GLOSSARY OF TERMS

ABCB1 gene	The membrane-associated protein encoded by this gene is a member of the super family of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. This protein is a member of the MDR/TAP subfamily. Members of the MDR/TAP subfamily are involved in multidrug resistance.
Acral	Acral distribution of a dermatosis means it affects distal portions of limbs (hand, foot) and head (ears, nose)
Acrodynia	Scaly dermatitis due to vitamin B_6 deficiency in rats
Actinic Keratosis	Small rough areas on skin exposed to the sun, usually the hands, face, scalp, back of hands and chest
Acute radiation reaction	Radiation dermatitis
Adjuvant	Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.
Alanine aminotransferase	Blood test to detect or monitor liver disease
Albumin	The main protein of plasma. Its main function is to regulate osmotic pressure. Also binds cations (Calcium, sodium and potassium), bilirubin, drugs and hormones. Normal level 35-55g/L
α-fluoro-β-alanine	Major catabolite of 5-FU
Alkaline phosphatase	An enzyme in the cells lining the biliary ducts of the liver. ALP levels in plasma will rise with large bile duct obstruction, and diseases of the liver. ALP is also

	present in bone, so it is higher in patients with bone metastases.
Allopurinol	A purine analog. The primary use of allopurinol is to treat hyperuricemia and its complications such as chronic gout. Also commonly used in chemotherapy treatments to both reduce side effects (some regimes can rapidly produce tumour lysis syndrome of which severe hyperuricemia is a feature) and to increase their effectiveness (allopurinol inhibits the breakdown of mercaptopurine, therefore increasing its effect).
alpha level of significance	Risk of type I error (falsely rejecting a Ho when it is in fact true) recorded in findings as *p* value. (A type II error, also known as a false negative, occurs when the test fails to reject a false null hypothesis.
Amlodipine	Calcium channel blocker used for hypertension and angina
Antigen-antibody reactions	A reaction that occurs when an antigen combines with a corresponding antibody to produce an immune complex.
Angiogenic	Induction of blood vessel growth
Anthracycline	A type of antibiotic that comes from certain types of Streptomyces bacteria. Anthracyclines are used to treat many types of cancer. Anthracyclines damage the DNA in cancer cells, causing them to die. daunorubicin, doxorubicin, and epirubicin are examples of anthracyclines.
Antimetabolite	A drug that is very similar to natural chemicals in a normal biochemical reaction in cells but different enough to interfere with the normal division and functions of cells. 3 groups of antimetabolites; folate antagonists (methotrexate, pemetrexed); purine antagonists (6-mercaptopurine, dacarbazine, fludarabine) and pyrimidine antagonists (5-FU,

	capecitabine, gemcitabine)
Anti-neoplastic	Inhibiting or preventing the development of neoplasms
Antioxidant	Antioxidants are substances that may protect your cells against the effects of free radicals. Free radicals are molecules produced when your body breaks down food, or by environmental exposures like tobacco smoke and radiation. Free radicals can damage cells, and may play a role in heart disease, cancer and other diseases.
Aquaphor	A petroleum based ointment, containing mineral oils, ceresin and lanolin
Autosomal recessive	Autosomal recessive is one of several ways that a trait, disorder, or disease can be passed down through families.
Bag Balm®	A lanolin based cream originally used to treat cow's sore udders.
Bevacizumab	Monoclonal antibody. Blocks Vascular Endothelial Growth Factor – anti-angiogenic
Bilirubin	Yellow pigment of bile. Produced during the breakdown of red blood cells. Normal values 3-17 umol/L
Bleomycin	An anti-tumour antibiotic
Body Mass Index	Measure of body fat based on height and weight. Underweight < 18.5; Normal weight 18.5-24.9; Overweight 25-29.9; Obesity ≥ 30
Body Surface Area	Calculated surface of the human body used to calculate drug doses
Brivudin	Anti-viral agent to treat Herpes Zoster infection
Bullous	Blister
Cachexia	Cancer cachexia describes a syndrome of progressive weight loss, anorexia, and persistent erosion of host body cell mass in response to a

	malignant growth.
Caelyx	Liposomal encapsulated form of doxorubicin
Capecitabine	Capecitabine is a prodrug, that is enzymatically converted to 5-fluorouracil in the tumour, where it inhibits DNA synthesis and slows growth of tumour tissue.
Catabolism	The process involving a series of degradative chemical reactions that breaks down complex molecules into smaller units, usually releasing energy in the process.
Celecoxib	Non-steroidal anti-inflammatory and selective Cox-2 inhibitor
Cetuximab	Monoclonal antibody. Epidermal growth factor receptor inhibitor.
Chlorphenhydramine	Anti-histamine
Chronomodulation	Delivery of chemotherapy at a time of day where the maximum dose can be given with the minimum toxicity.
Cimetidine	Histamine H_2 receptor antagonist inhibits production of stomach acid
Circadian rhythm	A roughly-24-hour cycle in the biochemical, physiological or behavioural processes of living beings. Regular changes in mental and physical characteristics that occur in the course of a day (circadian is Latin for "around a day"). Most circadian rhythms are controlled by the body's biological "clock."
Cisplatin	Platinum-containing compound which forms aducts with DNA
Cockroft-Gault formula	A formula to calculate plasma creatinine clearance
Coefficient	A number or symbol multiplied with a variable or an unknown quantity in an algebraic term

Collagen	Naturally occurring protein mainly found in connective tissues
Correlation	Expresses the strength of a relationship in a single figure
Cox-2	Isoenzyme of cyclooxygenase (Cox) enzyme responsible for the formation of prostanoids such as prostaglandins
Cyclophosphamide	Nitrogen mustard alkylating agent Intercalates with DNA
Cytidine deaminase	Enzyme with helps maintain the cellular pyrimidine pool
Cytokine	Cell signalling proteins
Cytosine arabinoside	Also known as cytarabine. Combinations of cytosine and arabinoside which inhibits DNA synthesis
Cytostatic	Inhibiting or suppressing cellular growth and multiplication
Dactylitis	A painful swelling of the hands and feet (dactylitis) in very young patients with Sickle Cell Disease
Daunorubicin	Anthracycline. Intercalates with DNA
Degrees of freedom	A calculation of standard deviation – calculating how many scores vary around the sample mean
5'-deoxy-5-fluorouridine	Part of the metabolism of capecitabine. Metabolised to 5-FU
Dermatology life quality index	Questionnaire to assess the quality of life of a variety of skin conditions
Desquamation	Peeling of skin
Dihydropyrimidine dehydrogenase	Enzyme involved in the metabolism of uracil and thymine.
Diphenhydramine	Anti-histamine
Dipyramidol	Inhibits thrombus formation
Disease progression	Worsening of disease over time
Docetaxel	Taxane. Antimitotic agent.
Dorsum	The back of a structure e.g. back of the hand

Dose intensity	Refers to the interval and dose level of the chemotherapy regimen. When treatment intention is cure the aim is for the patient to receive the maximum tolerated dose at the recommended interval to achieve the best possible survival advantage.
Doxorubicin	Anthracyline antibiotic. Intercalates with DNA
Dysesthesia	Impairment of sensation, especially that of touch. characterized by sensations of numbness, tingling, burning, or pain
Dysgeusia	Taste changes
Eccrine glands	Sweat glands
Effect size	A measure of the strength of a relationship between 2 variables
Epirubicin	Anthracyline antibiotic. Intercalates with DNA
Erlotinib	Tyrosine kinase inhibitor which acts on the epidermal growth factor receptor
Erysipelas	a type of skin infection usually caused by group A Streptococcus bacteria
Erythrodysesthesia	Tingling sensation of the palms and soles of the feet
eta-squared	Provides an indication of the magnitude of the differences between the groups. Ranges from 0 to 1 and represents the proportion of variance in the dependent variable that is explained by the independent variable
External validity	When the tools used or the findings from a study can be used in another setting to the one where the original research was carried out. Generalisability.
Folic acid	One of the vitamin B group. Works with vitamin B^{12} to form healthy red blood cells
Focus 2 trial	Oral capecitabine versus infusional 5-FU in elderly patients with colorectal cancer
Folate	Naturally occurring folic acid in the body. Required for DNA synthesis and repair

Fluorouracil (5-FU)	Pyrimidine analogue. A suicide inhibitor and works through irreversible inhibition of thymidylate synthase
G_2 phase	Stage of the cell cycle which lasts until the cell enters mitosis. Significant biosynthesis occurs during this phase, mainly involving the production of microtubules, which are required during the process of mitosis. Inhibition of protein synthesis during G_2 phase prevents the cell from undergoing mitosis.
Gemcitabine	A nucleoside analog. The triphosphate analogue of gemcitabine replaces one of the building blocks of nucleic acids (cytidine), during DNA replication.
Graft versus host disease	Complication after a stem cell or bone marrow transplant where the newly transplanted material attacks the transplant recipient's body
Granulocyte colony stimulating factor	G-CSF is a substance produced naturally by the body that stimulates the bone marrow to produce white blood cells particularly neutrophils. GCSF is given to try to prevent neutropenic episodes during treatment, and thus allowing dose intensity to be maintained in patients where the treatment intention is cure.
Hazard ratio	A measure of how often a particular event happens in one group compared to how often it happens in another group, over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups. A hazard ratio of greater than one or less than one means that survival was better in one of the groups.
Henna	A flowering plant used as a dye
Hyperpigmentation	Darkening of the skin or nails caused by an increased

	production of melanin
Hypothesis	A proposed explanation of a phenomenon
Hyperhydrosis	Abnormally increased perspiration, more than what is normally required for the regulation of body temperature.
Hyperkeratosis	Thickening of the skin due to excessive accumulation of keratinin in the outer layers of the skin
Ibandronic acid	Bisphosphonate used to treat osteoporosis, hypercalcaemia or pain from bone metastases
Inflammatory response	The inflammatory response (inflammation) occurs when tissues are injured by bacteria, trauma, toxins, heat, or any other cause. The damaged cells release chemicals including histamine, bradykinin, and prostaglandins. These chemicals cause blood vessels to leak fluid into the tissues, causing swelling. This helps isolate the foreign substance from further contact with body tissues.
International Normalised Ratio	A test to assess the clotting ability of blood
Inter-triginous	Where 2 skin areas touch or rub together
Irinotecan	Topoisomerase inhibitor
Isoniazid	Anti tuberculis drug
Kaposi's Sarcoma	A tumour caused by the human herpes virus but more commonly now caused by HIV
Keratinocytes	Skin cells which produce keratin. Keratin strengthens skin, hair and nails.
Keratoderma	Diffuse thickening on hands and feet and hyperpigmentation
Keratolytic	Thickening of the skin due to an excess accumulation of keratin in the outer layers of the skin
Lac-hydrin	Lactic acid based moisturising cream
Lapatinib	Tyrosine kinase inhibitor which interrupts the HER_2 growth receptor pathway

Lentigo Maligna	Non-invasive melanoma which presents as blue/black in colour
Leucovorin	A reduced folic acid and used in combination with other chemotherapy drugs to either enhance effectiveness or as a chemoprotectant
Lipophilic	Having an affinity for, tending to combine with, or capable of dissolving in lipids.
Melanocyte	A cell in the skin that produces and contains melanin
Metabolite	Any substance produced during metabolism
Metastases	Spread of disease from one part of the body to another
Methotrexate	Antimetabolite. Inhibits the metabolism of folic acid
Microtubules	Important for maintaining cell structure
Mitomycin	Antitumour antibiotic
Mitotane	Antineoplastic agent usually given to treat a rare cancer of the adrenal glands, adrenal cortical carcinoma, either in its advanced stage or relapsed.
Mucositis	Inflammation of the mucosa lining the gastrointestinal tract commonly as a side effect of chemotherapy. Often used to refer to inflammation of the oral mucosa although the correct name is stomatitis
Multiple Myeloma	Cancer of the plasma cells of the bone marrow
Myxoedema	Hypothyroidism
Neuritis	Inflammation of the nerves
Neurotoxic	Exposure to toxic substances that cause damage to nerves
Neutropenia	A reduction in the number of circulating neutrophils often seen after chemotherapy and renders the patient susceptible to life-threatening infections.
Nominal	Variables coded numerically but number does not Have a value. Also known as categorical
Nonagenarian	Aged between 90 and 99 years of age
Octogenarian	Aged between 80 and 89 years of age

Ondansetron	$5HT_3$ receptor antagonist anti-emetic
Onycholysis	Detachment of the nail from the nail bed
Onychomadesis	Total separation of the nail plate from the nail bed that begins at the proximal area and then progresses to the free edge with the nail shedding. It may be due to systemic illness or drug-induced.
Ordinal	Hierarchical ranking e.g. Likert. No equal distance between numbers
Overall survival	A term used to describe the chances of survival from cancer. Often described as the 5 year survival in trials which is the number of people still alive 5 years after participating in the trial
Oxaliplatin	Platinum agent which inhibits DNA synthesis
Paclitaxel	Taxane. Mitotic inhibitor
Palliation	To relieve symptoms of a disease or disorder
Paraneoplastic syndrome	The collective signs and symptoms caused by a substance originating from a tumour or in reaction to a tumour. Paraneoplastic syndromes can be due to a number of causes including hormones or other biologically active products made by the tumour.
Paronychia	Inflammation of tissue surrounding a nail
Parsimony	Adoption of the simplest assumption in the formulation of a theory or in the interpretation of data, especially in accordance with the rule of Ockham's razor. (A rule in science and philosophy stating that entities should not be multiplied needlessly. This rule is interpreted to mean that the simplest of two or more competing theories is preferable and that an explanation for unknown phenomena should first be attempted in terms of what is already known. Also called law of parsimony.)
Pathogenesis	Mechanism by which a disease is caused
Pegylation	Process of covalent attachment of poly (ethylene

	glycol) polymer chains to another molecule, normally a drug or therapeutic protein that can help to meet the challenges of improving the safety and efficiency of many treatments.
Pegylated G-CSF	'pegylated' form of G-CSF, which means it is attached to a substance called polyethylene glycol. This increases the length of time that the G-CSF works for.
Performance status	Relative scale used to describe a patient's overall physical well-being, based upon his or her ability to do everyday tasks. Clinical trials often specify a minimum performance status level for entry in order to make sure that patients are well enough to receive certain chemotherapy drugs given at necessary dosages and Oncologists use this as a basis for their decisions on the appropriate type and dose of chemotherapy for individual patients. The scale used in local clinical practice is the ECOG scale (Appendix 2.1)
Periarticular Thenar Erythema	Redness particularly over the muscle mass at the base of the thumb on the palms of the hands
Peripheral neuropathy	Damage to the nerves of the peripheral nervous system
Pharmacodynamics	How the drug acts on the body
Pharmacokinetics	How the body acts on the drug
Phase I study	Earliest trials of a new drug to find the maximum tolerated dose and to test for side effects
Phase II study	To test efficacy of treatment and type of cancer it has an effect on. Finding more about side effects and how to manage them and more testing of the best dose
Phase III study	Compare a new treatment with standard treatment, or different doses or a new way of giving a standard treatment
Predictive values	The positive predictive value is the proportion of

	subjects with PPE correctly diagnosed. The negative predictive values is the proportion of subjects without PPE who are correctly diagnosed
Proliferation	Cell growth including cell development and cell division
Protein synthesis	A process whereby DNA encodes for the production of amino acids and proteins
Pyridoxine	Pyridoxine (Vitamin B_6) plays a vital role in the activities of many enzymes. It is essential for the breakdown and use of proteins, carbohydrates and fats from food and for the release of stored carbohydrates for energy. It is involved in the production of red blood cells and antibodies and in the maintenance of a healthy skin and healthy digestion. It is also important for normal function of the nervous system and several hormones.
Quadriceps	Large muscle group on the front of the thigh
Radiation recall	Occurs months to years after radiation treatment. A reaction that follows recent administration of chemotherapy where erythema occurs over a previously irradiated site
Ratio	Interval scale with an absolute zero.
Reynard's disease	Reynard's disease is a common condition that affects the blood supply to certain parts of the body, usually the fingers and toes. The condition occurs because blood vessels go into a temporary spasm which blocks the flow of blood. This causes the affected area to change colour to white, then blue and then finally red as the blood flow returns. Usually triggered by cold temperatures or by stress or anxiety.
Sclerodactyl	Localised thickening and tightness of the skin on the fingers or toes
Seborrhoea	Greasy skin

Sensitivity	The proportion of actual positives who are correctly identified as such
Septuagenarian	Aged between 70 – 79 years
sic erat scriptum (Sic)	"thus was it written" added immediately after a quoted word or phrase, indicates that the quoted words have been transcribed exactly as spelled or presented in the original source, complete with any erroneous spelling or other presentation.
Skindex-16	A questionnaire developed as a measure of dermatological health-related quality of life, including symptoms, emotions and functional aspects
Sorafenib	A small molecule inhibitor of several tyrosine protein kinases; Vascular endothelial growth factor receptor and Platelet-derived growth factor receptor (VEGFR and PDGFR)
Specificity	The proportion of negatives that are identified as such
Spectroscopy	Study of the interaction between matter and radiated energy
Staphylococci	Gram negative bacteria
Sunitinib	A small molecule, multi-targeted receptor tyrosine kinase inhibitor (VEGFR and PDGFR)
Synergistic	Acting together
2-tailed	tails refer to ends of a normal distribution curve. 1-tailed test used when directional hypothesis stated, 2-tailed in other situations when it is possible for positive or negative association
Taxane	Chemotherapy produced by the plants of the genus Taxus (Yew tree)
Temozolamide	Oral alkylating agent. Interferes with DNA replication
Thiotepa	Alkylating agent
Thymidine Phosphorylase	An enzyme involved in the breakdown of thymidine, which helps maintain the pool of nucleosides in the cells

Time to progression	A measure of time after a disease is diagnosed until the disease starts to get worse
Troxacitabine	A nucleoside analogue
Tumour response	Response evaluation criteria in solid tumours (RECIST) is a set of definitions when cancer patients improve (respond), stay the same (stabilize) or worsen (progression)
Type I error	A true null hypothesis incorrectly rejected
Type II error	Failure to reject a false null hypothesis
Tyrosine Kinase Inhibitors (TKIs)	Tyrosine kinases are domains of growth factor receptors. TKIs inhibit growth factors from attaching to these receptors
Udderley Smooth®	Greaseless water-based moisturiser
Uracil	One of the 4 nucleobases in RNA the others are adenine, cytosine and guanine
Vincristine	Vinka alkaloid. Mitotic inhibitor
Vinorelbine	Vinka alkaloid. Mitotic inhibitor
X-ACT trial	Capecitabine versus bolus 5-FU/LV as adjuvant therapy for patients with Dukes' C colon cancer

CHAPTER 1 INTRODUCTION

1.1 Introduction and research background

There have been significant developments in the treatment of cancer as a result of scientific research leading to the use of multimodality therapy. Unfortunately, the use of chemotherapy is accompanied by substantial risks and can influence the quality of life of the individual. Palmar Plantar Erythrodysesthesia (PPE) is a distinctive and relatively frequent toxicity related to some anti-neoplastic agents. PPE appears to be dose dependent, as both peak drug concentration and total cumulative dose determine its occurrence. The areas affected become dry and peel, with numbness and tingling, progressing to painful erythema, blistering and ulceration (Burgdoff et al 1982, Nagore et al 2000). Although this presentation is common in the majority of cases, there have been reports of dissimilar and sometimes unusual presenting features in people with dark skin (Park et al 2003, Narasimhan et al 2004, Saif & Elfiky 2007) and between chemotherapy agents (Zimmerman et al 1995, Chu et al 2000, Lipworth et al 2009,). The pain and discomfort can interfere with the individual's ability to carry out normal activities and can cause difficulty in walking when the soles of the feet are affected. This can result in delays in treatment, dose reduction or cessation of treatment in severe cases. This in turn can lead to anxiety in the patients who express concern that their cancer will return if unable to complete the full course of chemotherapy.

The pathogenesis of PPE remains unclear, with two theories gaining consensus. The first that extravasation of the drug occurs from damaged microcapillaries due to trauma caused by everyday activities (Hoff et al 2000, Lotem et al 2000, Molpus et al 2004, Saif 2011). The second that the drug is carried to the surface of the skin by sweat, and with the hands and feet having a high concentration of sweat glands, explains why they are the most affected areas (Hoff et al 2000, Jacobi et al 2005).

While there is evidence to show that dose and schedule of the drugs play a large role in the development of PPE, the fact that many still go on to develop severe PPE following dose reduction or who commence on a reduced dose, would indicate that there are other factors that influence the risk of developing PPE. Biographical data, performance status, co-morbidities and renal function have all been analysed as potential risk factors of PPE with contradictory results.

Numerous approaches have been taken to prevent and/or reduce the severity of PPE. Two universally accepted methods to the management of PPE are, firstly for moderate to severe symptoms, treatment delay and dose reduction. Secondly, supportive care in conjunction with patient education, and it is this latter approach that has yet to be established in clinical trials.

Personal experience, supported by Banfield et al (1995), is that the impact of PPE on the patient's quality of life is greater than many think. In the past PPE has not been treated as a serious side effect, since it is not life-threatening. This often meant that patients were not questioned thoroughly about any symptoms of PPE that may have occurred between cycles, resulting in more severe PPE with subsequent cycles (Edwards 2003, Gerbrecht 2003). Case reports have built up evidence that PPE can cause more serious problems. These include amputation, (Narasimhan et al 2004, Palaia et al 2006) and severe infections particularly in neutropenic patients, (Zimmerman et al 1995, Poikonen et al 2004). This evidence, suggesting that PPE can have potential serious and life-threatening consequences in a small number of patients and the increase in the number of PPE-inducing agents, has led to an increased understanding of the importance of a full assessment of symptoms between cycles.

It is this personal experience, and the lack of empirical evidence to support the theory that PPE may be caused by damaged microcapillaries due to everyday activities that provided the impetus to undertake this study. This

exploratory study to examine the role that patient activities may play in the development of PPE is unique and will add to the body of knowledge of risk factors for PPE.

The initial intention was to include patients receiving pegylated liposomal doxorubicin (PLD), docetaxel, infusional 5-fluorouracil (5-FU) or capecitabine containing regimes. The rationale for this choice was that these agents appeared to have the highest incidence of PPE. Following discussions with consultant oncologists and chemotherapy nurses, PPE was seen infrequently with PLD and docetaxel in the unit where the study would be carried out. Collection of data in phase I was thus restricted to infusional 5-FU and capecitabine containing regimes. Following this phase, it was evident that capecitabine monotherapy had a significantly higher incidence of PPE than infusional 5-FU or capecitabine in combination regimes. Further analysis of the retrospective data using only those who had received capecitabine monotherapy was performed. Phase II of this study then focused only on patients prescribed capecitabine monotherapy.

The term ‘patient’ is used to refer to potential recruits to the study before consent to participate was gained. It is also used when discussing evidence in the literature where the authors use this term. The term ‘participant’ is used throughout when referring to individuals participating in the current study.

1.2 Purpose of the research

The aim of this research is to identify factors that contribute to the occurrence of PPE using quantitative methodology. Empirical research is necessary to ensure that the outcomes of the study are relevant to, and can be applied to, a specific client group, namely patients receiving capecitabine known to cause PPE.

Patient education strategies to minimise the severity of PPE are based on anecdotal evidence and consensus and is one of the mainstays in managing PPE. Since the development of nurse-led clinics, nurses play a key role in the

education, support and monitoring of patients receiving chemotherapy. The findings from this study will provide an evidence base for nurses caring for patients receiving PPE-inducing agents to enable them to provide focused education, supportive measures and monitoring for those most at risk of developing PPE. These strategies would aim to reduce the incidence and severity of PPE that would allow for the maximum dose to be administered, and reduce the impact on an individual's quality of life.

1.3 Research questions

This thesis intends to answer the following questions;

- Can risk factors be identified to predict the development of PPE?
- Do individual patient activities that cause friction or exposure to heat, increase the risk of developing PPE?

In order to answer these questions a statistical model was used to explore and assess the contribution of risk factors for the development of PPE. This model is based on one described by Hosmer and Lemeshow (2000) and demonstrated by Bursac et al (2007). The hypotheses and research model employed are described in detail in chapter 3.

Addressing the gap in the literature in the next section will describe the contribution this research makes in terms of building upon existing literature.

1.4 Research contribution

This research explores numerous potential risk factors of PPE. The findings will add to the current evidence of biographical data, performance status, co-morbidities and renal function as risk factors of PPE. Since this is the first time that individual activity related risk factors for PPE have been studied, this is the unique contribution made by this research.

Findings from this research will add to the literature by;

- Contributing originality in the form of empirically tested activity-related risk factors of PPE
- Providing nurses with an evidence-base on which to base educational programmes
- Providing valuable information to support future research and development

1.5 Thesis outline

The *Introductory chapter* establishes the focus of the study and provides the rationale for its choice. The purpose of the study based on its aims and objectives precedes the research questions to be answered. Gaps in the literature are identified to demonstrate how the findings from this study will make a unique contribution to the existing body of knowledge. An outline of the thesis is provided in figure 1.1.

Chapter 2 provides a general literature review. It commences by detailing the search strategy used to identify relevant literature. Since PPE is known by many guises, the many definitions are discussed justifying the one used throughout this thesis. The overall scale of the problem (PPE) is presented, with subsections for 5-fluorouracil and capecitabine, the drugs to be studied. Existing knowledge on the presentation, pathogenesis and aetiology of PPE is discussed emphasising the controversial evidence and the difficulties in making comparisons between studies. The wide variety of suggested strategies to manage or minimise the severity of PPE is included for completion of the subject, and to highlight the lack of empirical evidence to support these strategies. The chapter concludes with the nurses' role in the assessment, monitoring and education of patients receiving PPE-inducing agents.

Chapter 3 describes the theoretical framework on which the research is based and presents the choice of methods used to collect and analyse the

data. The research hypotheses which provide the basis for the formulation of the research questions are presented. The process of data analysis using bivariate statistical tests and single and multivariate regression is explained. A rationale for the choice of the multivariate logistic regression modelling algorithm is given and the chapter concludes by identifying limitations in the study design.

Chapter 4 outlines the results of the data analysis. It is set out in three sections, one for each sample, each presented in the same order and format for consistency. A substantial amount of data were gathered and analysed, therefore data are presented in tabular form within the text and appendices to illustrate the findings. Individual cases with unusual presentation of PPE linked to co-morbidities are discussed.

Chapter 5 provides a discussion of the findings based on the data analysis in chapter 4. This chapter is divided into sections similar in order to those in chapter 2. Graphs and photographs are provided to illustrate some of the comparisons made between the samples in this study and those in the literature. The emphasis is placed on risk factors for capecitabine-induced PPE since this was the agent of choice following the data analysis from phase 1 of the study. The chapter concludes with a summary of the key findings emphasising the original contribution these findings make to the existing literature.

Chapter 6 commences with a summary of the research to remind the reader of the methods employed to collect the data. The process of data analysis is described including the rationale for the choice of the modelling algorithm applied to the selection and retention of variables in the multivariate logistic regression. This is followed by an outline of the conclusions to answer the research questions, focusing on the more accurate and richer data collected from the prospective sample. The contribution the research has made to the existing body of knowledge and to nursing practice is followed by details of

the limitations of the study. The chapter concludes with recommendations for future research.

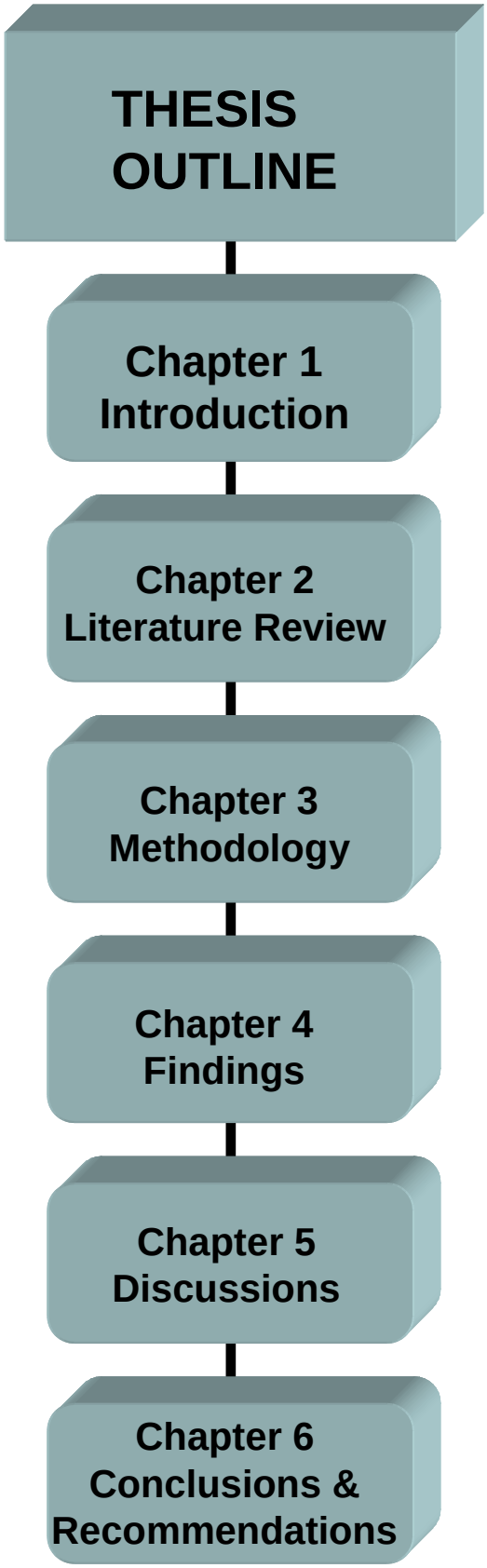


Figure 1-1 Thesis Outline

CHAPTER 2 REVIEW OF THE LITERATURE

2.1 Search strategy

The approach employed to explore the literature surrounding Palmar Plantar Erythrodysesthesia (PPE) was to initially identify the search terms to be used. The universally recognised hand-foot syndrome (HFS) was the preliminary term used, expanding to include other key words as identified from articles and database MESH (Medical Subject Headings) terms. Table 2.1 outlines the findings of the search and terms used to explore four databases, Allied and Complementary Medicine; British Nursing Index (BNI); Cumulative Index to Nursing and Allied Health (CINAHL) and Medline.

	Terms used	Number identified	Number of repeats	Not applicable*	Non-English articles
1	Hand-foot syndrome	468	20	79	27
2	Palmar Plantar Erythrodysesthesia	139	0	12	4
3	Plantar Palmar Erythrodysesthesia	6	1	0	0
4	Palmar Plantar Erythema	17	0	8	1
5	Plantar Palmar Erythema	5	0	0	0
6	Acral Erythema	97	4	37	8
7	Acral Erythrodysesthesia	3	0	0	1
8	Palmar Plantar Keratoderma	485	1	473	1
9	Peculiar Acral Erythema	3	1	0	0
10	Burgdorf reaction	2	0	0	1
*Articles that did not include chemotherapy-induced cutaneous reaction					

Table 2-1 Search strategy

There was no mention of this cutaneous reaction in the published literature before 1974; little attention was paid to it until the 1980s; it was not mentioned in common toxicity classifications until the 1990s; and the evidence for risk

factors of this reaction is based on case reports and consensus. Given these facts, the search of the databases had no restrictions applied such as date or research based articles only.

Since the terms Hand-foot syndrome and Palmar Plantar Erythrodysesthesia revealed the largest number of articles, these two terms were entered into ZETOC and SCOPUS alert services which e-mailed details of new literature as it was published throughout the time this study was carried out.

Of necessity only English literature articles were selected. The reference list of each article obtained was examined for any literature not identified from the searches of the databases.

A further search of the two databases CINAHL and medline was carried out to identify evidence from phase III trials of capecitabine monotherapy. The purpose of this additional search was to be able to compare the findings of the data analysis of phase 2 of this study with those in the literature (table 2.2).

Database	Number identified	Number of repeats	Not applicable	Non-English articles
CINAHL	47	13	18	0
Medline	22	13	0	0

Table 2-2 Search strategy capecitabine Monotherapy

Articles available electronically from De Montfort University, University of Leicester, NHS evidence or the Royal College of Nursing were obtained. Journals not available electronically but held as a hard copy at other universities in the East Midlands were identified and visits were made to obtain this material. The final source used to obtain published articles was via the inter-library loan service.

2.2 Introduction

Palmar-Plantar Erythrodysesthesia (PPE) is rarely serious and never life-threatening; however, the pain and discomfort it causes can have a significant impact on the patient's ability to carry out normal daily activities and on their quality of life (Webster-Gandy 2007). A literature search revealed multiple definitions of this side effect to anti-neoplastic agents. The multiple definitions will be briefly discussed to support the rationale for the one used throughout this piece of work. An attempt will be made to identify the incidence, followed by the symptoms of PPE and theories of the pathophysiological mechanisms involved. An analysis of the risk factors identified in the literature and which has informed the development of the hypotheses and data collection tools used in this study will be presented. Reference to risk factors for PPE caused by agents other than 5-FU and capecitabine have been included since many of these factors have not yet been tested with 5FU or capecitabine and cannot therefore be excluded as possibilities. Strategies to prevent and manage PPE are briefly discussed and are useful to complete the whole picture to show the difficulties in identifying effective interventions even though this does not form part of the current study. The nurses' role in the assessment and recognition of PPE and patient education needs will conclude this chapter.

2.3 Definitions and common causative chemotherapeutic agents

Described as a painful, erythematous skin lesion of the palms and soles, (Alley et al 2002), this local cutaneous reaction to certain systemic anti-neoplastic agents was first described as Palmer Planter Erythrodysesthesia in 1974 by Zuehlke in patients with hypernephroma (renal cell carcinoma) receiving mitotane. In the early 1980s it was referred to as chemotherapy-induced acral erythema (Nagore et el 2000, Lassere & Hoff 2004). The term palmar-plantar erythema was first used in 1984 (Laack et al 2001). Other terms used include acral erythema (Arias et al 1997, Bhasin et al 2005); acrauding erythema; Burgdorf's reaction (Bardia et al 2006); toxic acral erythema (Lotem et al 2000); toxic erythema of palms and soles (Nagore et el

2000); or hand-foot syndrome (HFS) (Lotem et al 2000, Alley et al 2002). Rosner (1998) appears to take exception to the use of HFS to describe this side effect since haematologists have used this term for decades to describe a painful swelling of the hands and feet (dactylitis) in very young patients with Sickle Cell Disease. He suggests that HFS should be reserved for this condition and that acral erythema or Palmar Plantar Erythema should be used for the chemotherapy-induced side effect. It is for this reason and the increasing use in more recent publications that Palmar-Plantar Erythrodysesthesia (PPE) will be used throughout this piece of work. In response to this criticism, Hoff et al (1998a) while acknowledging Rosner's concerns, pointed out that the HFS used to describe dactylitis in Sickle Cell Disease is very different in pathogenesis and presentation to chemotherapy-related HFS and that although Palmar Plantar Erythema may be the preferred name, HFS is well established and has wide acceptance within the oncology community and is doubtful that there will be any confusion in using the same name.

As the term PPE would indicate, the hands (palmar) are most commonly affected followed by the soles of the feet (plantar), although the sides and dorsal surfaces of these can also be affected (Wood 2004). There have been reports of other areas of the body also being affected, particularly inter-triginous sites and those areas where body heat is greatest. These include the axilla (Jacobi et al 2005), groin, vulva (Sharma & Chan 2003) and perineal areas (Cady et al 2006). Similarly at pressure points (elbows, scapula, sacrum) and where tight fitting clothing (Sharma & Chan 2003) or belts press against the skin (Lotem et al 2000). It has even been reported at the site of recently applied electrocardiograph (ECG) pads (Zimmerman et al 1995). There have been reports of the trunk, neck, chest and scalp being affected (Gerbrecht 2003), as well as scars anywhere on the body (Von Moos et al 2008) and a few reported cases of penile and scrotal involvement in men receiving infusional 5-FU or capecitabine (Sorscher 2004, Sapp and Desimone 2007, Lee et al 2009). Because of the severity of the symptoms of

PPE in penile and scrotal involvement, Sapp and Desimone (2007) suggest that this should be graded as grade 4 toxicity.

Alongside 5-FU, the first agent to be identified as the main causative agent for PPE (Lokich & Moore 1984, Lassere & Hoff 2004), the other agents commonly implicated are capecitabine; pegylated liposomal doxorubicin (caelyx®) (Molpus et al 2004, Bareggi et al 2005); docetaxel and cytarabine (Waltzer & Flowers 1993, Hoff et al 2000). PPE has also been reported with the use of vincristine; cyclophosphamide (Komamura et al 1995); bleomycin; thiotepa (Alley et al 2002); methotrexate (Hellier et al 1996); gemcitabine (Laack et al 2001); high dose vinorelbine; (Edwards 2003), paclitaxel; (DeArgila et al 1996), temozolomide (Kanat et al 2007), and hydroxyurea (Bhasin et al 2005). PPE is known to be caused by many cytostatics and it is for this reason that monitoring of PPE is included in protocols for many clinical trials for these agents (Van Cutsem et al 2004). Many novel agents that target specific pathways crucial to the growth and development of tumours have emerged and are used to treat a variety of cancers. Skin toxicity, including PPE, is the principal side effect associated with many of these agents especially those that target the epidermal growth factor receptor (EGFR) signal transduction pathway. The true incidence rates are not yet known (Robert et al 2005, Lacouture et al 2007), but, could potentially be used as a marker for the efficacy of treatment (Perez-Soler 2003). Examples of these novel agents include cetuximab (Monoclonal antibody targeting EGFR) for colorectal cancer (Monti et al 2003), sunitinib and sorafenib (tyrosine kinase inhibitors (TKI)) for renal cell cancer (Dasanu et al 2007), and lapatinib (EGFR and HER-2 inhibitor) (Cancerbackup 2009). The incidence of PPE in these TKIs have been reported as between 10-28% with sunitinib and 10-62% with sorafenib, with grade 3 reported as between 4-12% and 2-36% respectively (Lipworth et al 2009). The EGFR is upregulated in several cancers and it is also important for normal skin development and function.

Toxicities that have been suggested as markers of efficacy of treatment with the newer novel therapies include the rash seen with erlotinib and cetuximab

(Gurney 2005). There have been similar findings in patients receiving capecitabine either as monotherapy or in combination with other agents. A correlation (p = 0.01) between severity of PPE and tumour response was reported in a study by Chua et al (2003). However, this finding was based on a small sample of ten who developed PPE from a total sample of 17 Chinese patients receiving capecitabine. In another study (Kaufmann et al 2010) of 161 patients taking capecitabine monotherapy, the incidence of PPE, median time to progression (TTP) and median overall survival (OS) rates were compared with those who did not develop PPE. The participants that developed PPE had a longer TTP and OS. In the same study, a multivariate analysis showed that, patients aged over 65 years and PPE were found to be the only independent predictors of TTP and PPE was the only independent predictor of OS. The study concluded that PPE and age > 65 years were correlated with improved activity outcomes. Since this study was carried out on women with breast cancer the older age as a predictor of OS is to be expected given that breast cancer in younger patients tends to be more aggressive with a poorer outcome in terms of TTP and OS. (BreastCancer 2006). This positive correlation between the occurrence of PPE and longer OS was also observed in a meta-analysis of 13 retrospective studies of patients receiving capecitabine monotherapy for colon, gastric and breast cancer (Roche 2010), and in the results from the X-Act trial (Twelves et al 2008). Correlation between severe PPE and clinical outcome was reported in a retrospective study in patients with metastatic breast cancer which found that those with grade 3 PPE had a longer TTP and OS compared to those with grade 1 or 2, thus suggesting that PPE may be a valuable tool that could help appraise and monitor the efficacy of capecitabine, although further studies are required to confirm this finding (Kurt et al 2006).

Some reports of PPE with tyrosine kinase inhibitors (TKI) were found in patients who had previously received pegylated liposomal doxorubicin. Lacouture et al (2007) propose that this is a ‘recall reaction’ and that doctors and nurses treating patients with these new agents should be aware of the possibility of this reaction. This recall reaction has also been reported by Hui

et al (2002). In their report, 6 patients who developed PPE with previous troxacitabine treatment was recalled with later treatments of a variety of regimes. Although the PPE could be related to the direct effect of the current drug being administered, they felt that the common denominator of previous exposure to troxacitabine suggested a recall reaction. Until large numbers have been treated with these agents (TKIs) as first line treatment we will not be able to establish whether PPE is due to 'recall' from previous chemotherapy or if PPE is caused directly by the TKIs. The increasing size of the problem would indicate that PPE is an area worthy of further investigation and therefore an attempt will now be made to define the incidence.

2.4 Incidence

Formulation of the drugs and period of exposure can impact on the incidence of PPE. Examples include pegylated-liposomal doxorubicin which has a higher incidence of PPE that the standard formulation of doxorubicin (Lotem et al 2000). Fluorouracil (5-FU) administered by intermittent bolus injection has a low incidence of PPE, but, when given as a continuous infusion, PPE is common (Alley et al 2002). Capecitabine, which is converted to 5-FU, provides prolonged exposure to tissue and has an incidence of PPE of between 50–69% with approximately 10-22% having severe PPE (Blum et al 1999, Abushullaih et al 2002, Cassidy et al 2002, Twelves et al 2005, and Roche 2010). Whilst the overall incidence of PPE reported in the literature was easily interpreted, the reporting of severe PPE proved more difficult.

A substantial amount of literature was retrieved that either made reference to PPE within the text or specifically contained PPE (or other associated term) in the title. This showed that although there was the occasional mention that the onset of PPE between cycles was possibly underreported, only one study was identified that specifically collected and analysed this type of data. A prospective study of 1470 patients receiving continuous infusion 5-FU 300mg/m^2/day alone or with bolus mitomycin 7mg/m^2 every six weeks. Data were examined in detail to measure whether the time of onset of grade 1 PPE

had any predictive significance for the development of more severe toxicity in subsequent cycles (Tebbutt et al 2003). Their findings showed that 55.1% of patients who developed grade 1 PPE early went on to develop grade 2 or worse compared with 27.3% who did not develop early grade 1 PPE ($p < 0.001$). The data were then tested by univariate Cox regression analysis which revealed that for every extra day after the commencement of chemotherapy before any symptoms of grade 1 PPE were reported, there was a lower risk of developing grade 2 or worse in subsequent cycles (hazard ratio 0.99, 95% CI 0.98-0.99; $p < 0.001$). Other factors were analysed by multivariate Cox regression to assess their predictive ability for PPE. Older, females with a good performance status (Appendix 2.1); increased bilirubin levels and early grade 1 diarrhoea were identified as independent risk factors for grade 2 or worse PPE in following cycles of chemotherapy. They suggest that the timing of the appearance of grade 1 toxicities could be used to identify patients who have a higher risk of later presenting with more severe grades of toxicity. Recommending that older females with a good performance status, impaired liver and renal function, and early grade 1 PPE alone or in conjunction with grade 1 diarrhoea should be considered for early dose reduction, since this group are at an increased risk of going on to develop grade 2 or worse PPE.

Very few studies have examined any association between PPE and tumour type, but a systematic review of 4883 patients from eleven trials receiving sorafenib found an increased rate of PPE in those with renal cell carcinoma (RCC) compared to any other malignancy (Chu et al 2008). However, it is possible that this may be due to other factors or a unique link between the pathophysiology of PPE and RCC which would need confirming in further studies.

Whilst reviewing the literature it became evident that there are several difficulties in determining the true incidence of PPE. Many studies are small scale or isolated case reports. The larger studies are often based on a retrospective meta-analysis or medical notes review, provide little detail of

cutaneous reaction and used different PPE grading systems (Appendix 2.2). Since PPE is often subjectively reported, standardisation is difficult and cross-study comparison a challenge. These observations were also reflected by Janusch et al (2006) and Nagore et al (2000) in their review articles. Incidence by grade of PPE is often not reported in studies or only the severe grades (2-4) presented as an overall figure. The overall incidence of PPE from the literature has been quoted in a review paper as being between 6 – 64% across the full range of chemotherapy regimes with 80% of these patients experiencing less severe grades (Nagore et el 2000).

While it is acknowledged that PPE can occur in patients receiving many different anti-neoplastic agents, since this study collected data from patients receiving 5-FU or capecitabine, it is the incidence of PPE with these agents as monotherapy or in combination that will now be presented.

2.4.1 Fluorouracil (5-FU)

5-FU is an antimetabolite and acts as a false pyrimidine base (uracil), interfering with the synthesis of DNA by blocking the action of the enzyme thymidylate synthetase. Approximately 22-45% is metabolized in the liver, with its catabolites excreted in urine and 7-20% excreted unchanged in the urine (Perry 2006, EMC 2011). Reduction of the dose is advisable in patients with any of the following: cachexia; reduced bone marrow function and impaired hepatic or renal function (EMC 2011). Common side effects include stomatitis, diarrhoea, mild nausea and vomiting, anorexia, hyperuricaemia, epistaxis, fatigue, however, PPE is the side effect of interest, and it is this that will be discussed further.

There were some consistent findings indicating a higher incidence with infusional (27-34%) rather than bolus 5-FU (7-13%) (Feldman & Ajani 1985, Chiara et al 1997, Meta-analysis group in cancer 1998, Elasmer et al 2001, Laack et al 2001, Chabner & Longo 2006), with some evidence to suggest that PPE toxicity with 5-FU is cumulative (Bareggi et al 2005). A meta-

analysis of 1219 patients from 6 randomised controlled trials comparing the toxicities of 5-FU bolus versus continuous infusion confirmed that PPE is more frequent with continuous infusional 5-FU (13% bolus and 34% continuous infusion p <.0001). The adjusted risk ratio for PPE was 1.87 (95% CI; 1.50-2.34) which indicates that there is almost twice the risk of developing PPE when 5-FU is given by continuous infusion (Meta-analysis group in cancer 1998). In 1989 Curran and Luce presented a series of 9 cases of PPE reported to the 5-FU manufacturers, which they suggested, indicated that the likelihood of PPE in association with 5-FU bolus is greater than previously thought. Of the 9 cases 44% (4 of 9) received continuous infusional 5-FU and 55% (5 of 9) received 5-FU as a bolus regime. The article did not provide details of the dose or interval of the regimes and since the number of patients is very small consideration has to be given that these findings could have occurred by chance. The rationale for the use of continuous infusion of 5-FU is that it has a short half-life which makes high dose intensity achievable. Tumour response rates are high and the range of side effects differs to those seen with bolus regimes, however, PPE emerges as one of the most frequent problems (Chiara et al 1997).

The circadian rhythm in plasma concentration of drugs may also contribute to the toxicity profile of some drugs suggesting that chronomodulation of drugs may be a means of managing the incidence and severity of PPE (Bjarnason et al 1993, Milano & Chamorey 2002, Tan & McLeod 2005, Chabner & Longo 2006). The optimal time for 5-FU infusion achieving low toxicity and better efficacy is between 2200 and 1000 hours with the peak delivery at 0400 hours (Coudert et al 2008). Some studies have shown that modifying continuous infusion rates to plasma concentrations of oxaliplatin and 5-FU limited the incidence of adverse events allowing for dose escalation (Caussanel et al 1990, Metzger et al 1994, Bochicchio et al 1999). Problems that have prevented the implementation of this in practice include practical and economic reasons (Jansman et al 2001).

2.4.2 Capecitabine

Capecitabine is a fluoropyrimidine carbamate and interferes with RNA processing and protein synthesis. It is converted to 5-FU initially in the liver with the final conversion by the enzymes cytidine deaminase and thymidine phosphorylase. 54% of capecitabine is bound to protein, in particular albumin (35%) with a half-life of 0.5 to 0.7 hours. 96% is excreted in urine most as FBAL (a metabolite of capecitabine) (61%) with only 2.6% excreted in faeces which indicates that the majority is absorbed via the gastrointestinal tract which may impact on co-medications (discussed elsewhere) (Roche 2011).

PPE was the only adverse event occurring in 45%-68% of patients, with grade 3 occurring in up to 17% and is more frequent than with 5-FU (Cox et al 1999, Twelves et al 1999, 2001 & 2005, Elasmer et al 2001, Hoff et al 2001, McGavin & Goa 2001, Van Cutsem et al 2001, Abushullaih et al 2002, Cassidy et al 2002, O'Shaughnessy et al 2002, Gerbrecht 2003, Scheithauer et al 2003, Lassere & Hoff 2004, Marse et al 2004, Van Cutsem et al 2004, Walko & Lindley 2005, Wiseman & Lyseng-Williamson 2005). A large pool of safety data from phase II and III clinical trials of pre-treated breast cancer patients and first line colorectal cancer patients (n = 875) receiving capecitabine 2500 mg/m^2/day intermittent regimen found PPE and diarrhoea to be the most common adverse events (52.2% and 48.8% respectively). Patients who experienced grade 2-4 PPE/diarrhoea received a reduced dose in subsequent cycles. A small proportion (13% and 12% respectively) experienced a recurrence of grade 3 symptoms (Blum 2001). This raises the possibility that PPE is not solely dose related. Studies have demonstrated that this reduced dose had no statistically significant difference in outcome such as disease recurrence or 2-3 year survival (El-Helw & Coleman 2005, Yun et al 2010).

Toxicity due to capecitabine may be managed by symptomatic treatment, interruption of treatment and dose reduction. The manufacturer's recommendations for interruption or reduction are given in table 2.3

Toxicity grades*	Dose changes within a treatment cycle	Dose adjustment for next cycle/dose (% of starting dose)
• *Grade 1*	Maintain dose level	Maintain dose level
• *Grade 2*		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
• *Grade 3*		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
• *Grade 4*		
-1st appearance	Discontinue permanently or If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
-2nd appearance	Discontinue permanently	Not applicable

Table 2-3 Manufacturers guidelines for interruption or dose reduction (EMC 2012)

Pooled data from four prospective trials of capecitabine in combination with other agents showed that combined use of docetaxel was the only independent risk factor for capecitabine-induced PPE (p = .001) (Heo et al 2004). This confirms findings from other studies and suggests that the addition of other neurotoxic agents enhance this toxicity of capecitabine (Park et al 2003, Giordano et al 2006). This finding is not surprising given that docetaxel is recognised as an agent which has also been implicated in the development of PPE. In a phase III trial of docetaxel combined with epirubicin compared with docetaxel combined with capecitabine as first line adjuvant therapy for breast cancer, grade 3 PPE was higher in the capecitabine

combination group (4%) with none in the epirubicin group $p = .024$ (Mavroudis et al 2010).

There is a gradual move to replace infusional 5-FU with oral capecitabine in combination regimes, since capecitabine is simpler and more convenient to administer. The patient does not require insertion of a long term central venous catheter or cope with the presence of an ambulatory chemotherapy pump for several days (Aisner 2007). In phase III studies of capecitabine in combination with oxaliplatin or irinotecan the incidence of PPE is shown to be lower (36% and 41% respectively) than that seen in capecitabine as monotherapy (54%) and could be explained by the lower dose of capecitabine administered in these regimes (Cassidy et al 2004, Patt et al 2004a). This contradicts the theory that PPE is not merely related to dose. However, a retrospective analysis of toxicities before and after a dose change of capecitabine (reduction from 2000mg/m^2/day to 1700mg/m/day) in combination with oxaliplatin reported no statistically significant difference in gastrointestinal and cutaneous toxicities. However, a difference in neutropenia and hyperbilirubinaemia ($p = .03$ and $p < .001$ respectively) (Baird et al 2011), again throws doubt that dose alone is a factor in the development of PPE and so the debate continues with contradictory findings.

When a comparison is made between oxaliplatin in combination with either infusional 5-FU (folfox) or capecitabine (capox) an increased incidence of grade 3 PPE is seen in the capox group (OR = 3.90; 95% CI 2.13 – 7.12) (Cao et al 2010). Similarly, in a large meta-analysis of 10 randomised controlled trials n = 3208 (RR = 3.40; 95% CI 2.25 – 5.15; $p < .001$), no significant difference in time to progression and overall survival between the folfox and capox groups was found, indicating that capecitabine can be used safely as a substitute for infusional 5-FU (Zhao et al 2010). Cassidy et al (2011) reported an increased incidence of PPE in the capecitabine/oxaliplatin group compared with the 5-FU/oxaliplatin group (31% versus 11%) and an even higher incidence when bevacizumab was added to both combinations (40% versus 14%). In combination with cisplatin a higher incidence was found

in the capecitabine group compared with the infusional 5-FU group (Kang et al 2009). These findings mirror those found in comparisons between infusional 5-FU and capecitabine monotherapy with an incidence of PPE 6.2% and 53.3% respectively (Walko and Lindley 2005).

Phase II and III trials evaluated the addition of leucovorin (LV) to capecitabine, which is commonly used with 5-FU. However, the addition of LV was found to increase the incidence of toxicity especially PPE and diarrhoea without any increase in anti-tumour efficacy, and it is therefore not recommended (Van Cutsem et al 2000).

In section 2.4.1 it was shown that circadian rhythm of plasma concentration of drugs influences the toxicity profile of that drug. A nonblinded study (Qvortrup et al 2010) of 139 patients were randomized to receive standard XELOX (capecitabine and oxaliplatin) with short-time infusion (30 minutes) of oxaliplatin or chronomodulated XELOX (80% capecitabine administered in the evening and oxaliplatin in the afternoon).There was no significant difference in toxicity and severe toxicity between the two groups or in overall response rate. Another small study (Santini et al 2006) of 36 patients receiving oxaliplatin as a continuous infusion over 12 hours and chronomodulated capecitabine (25% at 0800 hours, 25% at 1800 hours and the remaining 50% at 2300 hours). With a good safety profile and high tumour growth control, this schedule may be of interest but would require further study in a large randomized trial to confirm these findings (Qvortrup et al 2010).

One of the factors that may influence this difference is the circadian variation in the activity of many enzymes, involved in the anabolism and catabolism drugs. Dehydropyrimidine dehydrogenase (DPD), the rate limiting enzyme of capecitabine has its peak activity between 0100 (Harris et al 1990) and 0230 hours (Zeng et al 2005).

2.5 Presentation, grading and impact on the patient

PPE was not mentioned in common toxicity classifications until the 1990s, (Chiara et al 1997) and many of the published clinical trials of agents associated with PPE were initiated prior to the introduction of a standard grading system (Gressett et al 2006). There are several different toxicity classification systems currently in use; WHO (1979); NCI (NCI 2006); capecitabine clinical trial criteria (Blum et al 1999) (Appendix 2.2). Von Moos et al (2008) states that these classification systems may be useful in clinical trials, but may not accurately reflect the clinical severity of PPE, and that it is difficult to differentiate between the grades making their use in clinical practice questionable. In a study to establish the consistency in the use of two toxicity scales (NCI and WHO) Brundage et al (1993) used 7 experienced data managers and 12 simulated patients. They found that there was variability between the application of the toxicity criteria, the interpretation of the data and interviewing skills, which although there was no difference between the two scales, this variability makes interpretation of toxicity frequency and severity difficult.

Having discussed some of the difficulties in establishing the incidence, the presenting features are much clearer in most instances. Common presenting features include a tingling and numbness in a glove and sock distribution pattern with or without erythema (Akash & Bhounsule 2011). This is followed by pain, marked erythema and swelling (Nagore et al 2000, Lassere & Hoff 2004). Finally progressing to blisters, ulceration, severe pain and moist desquamation, this can result, rarely, in full thickness necrosis (Burgdoff et al 1982, Laack et al 2001, Von Moos et al 2008). This adversely effects the patient's quality of life, interfering with general activities of daily living (Lassere & Hoff 2004). In a study of patients with PPE, 47% of all patients and 78% of those with grade 3 identified it as the most unpleasant side effect of chemotherapy (Webster-Gandy et al 2007). Other features which may occur at any stage include dryness, rash, pruritus and skin breaks particularly on the finger tips (Hoff et al 2000).

The symptom which distinguishes PPE from other erythematous diseases of the hands and feet is the dysesthesia (impairment of sensation) (Janusch et al 2006). Neurologically, strength, and reflexes are generally not compromised, however, light touch may induce burning, tingling or pain, while pin prick and temperature sensation may be reduced or absent (Von Moos et al 2008). A diffuse rash on the trunk, limbs and sometimes the face can also accompany the severe grades of PPE (Cady et al 2006). If left untreated the symptoms will progress rapidly and will require more aggressive management and necessitate prolonged cessation of chemotherapy until resolved completely (Gordon et al 1995, Edwards 2003). In the majority of cases skin regeneration following cessation of the causative agent occurs within 1 to 2 weeks (Gressett et al 2006). Banfield et al (1995) present a case report of a patient who developed PPE during 5-FU treatment and whose symptoms of abnormal sensation and appearance of the affected digits persisted for many months following cessation of treatment despite the administration of pyridoxine, which is thought to reduce the severity of PPE and will be discussed later. They suggested that this case implies that in some instances the impact on a patient's quality of life may be greater than first thought. Another case that supports this suggestion is presented by Palaia et al (2006) where they report a 53 year old female treated with pegylated liposomal doxorubicin for advanced ovarian cancer that developed severe grade 3 PPE with ulceration of the tip of one finger which became necrotic and required amputation. A possible explanation for this is that the absence of pain sensation, probably due to the neuropathy from her previous chemotherapy, led to an underestimation of the onset of PPE in this patient. Conversely symptoms may resolve between cycles particularly 3-4 weekly schedules, and, if not reported by the patient subsequent episodes of PPE may be more severe, therefore highlighting the importance of questioning the patient carefully before each cycle (Edwards 2003). PPE is rarely serious and never life-threatening, or so it is alleged in the literature. A multivariate analysis in a phase III trial of docetaxel identified PPE as the only independent predictive factor for severe infections in neutropenic patients (Poikonen et al 2004).

Infections with Staphylococci, gram-negative bacteria or erysipelas have been observed as complications in patients with PPE which may prolong healing time (Janusch et al 2006). Hoff et al (2000) provides a four stage continuum along which symptoms of PPE progress with stage 4 including infectious complications and hospitalisation. An example of a patient treated with docetaxel who required hospitalisation secondary to infected ulcerated skin lesions in the groin and other areas of the body is presented by Zimmerman et al (1995). These findings suggest that PPE can have potentially serious and life-threatening consequences in a small number of patients.

Some authors have observed that black patients treated with capecitabine develop PPE more often, although no actual figures were presented, and more importantly, that their presenting features and incidence of serious manifestations (grade 2 and 3 PPE) are different to those seen in white patients (Narasimhan et al 2004). The term 'black' here includes people with naturally dark skin, for example, Afro-Caribbean, Philipino, and Korean. A study of 23 patients receiving a combination of capecitabine and docetaxel for advanced gastric cancer revealed an incidence of 52% (12) of grade 3 PPE which is higher that the previously reported figure of 24%. Ethnicity (Korean) was suspected to underlay this significant difference, although it is acknowledged that there may be other reasons (Park et al 2003).

The conventional signs of grade 1 PPE are hidden in black patients who instead develop a progressive hyperpigmentation of the palms and soles (Hood and Reeck 2006, Saif & Elfiky 2007). Simultaneous gradual thickening of the skin (keratoderma) of the palms and soles leads to stiffness of the hands and soles with pain and loss of function (Narasimhan et al 2004, Schellens et al 2005,). This difference in presentation may not be recognised widely which may have led to the under reporting of PPE in dark skinned individuals. In a study (Bjarnason et al 1993) of infusional 5-FU, darkening of the nails and hyperpigmentation in 3 dark skinned patients was documented. However, this was not defined as PPE and was not, therefore, included in the incidence figures for PPE. In black patients with diabetes, PPE may worsen

rapidly into a severe form of grade 3 resulting in life-threatening complications, such as infection affecting the underlying bones and a compromised circulation, which could lead to the possibility of amputation of a limb (Narasimhan et al 2004). The latter statement is, however, based on a single case report of a black patient with diabetes who had already lost one leg due to complications of his diabetes and a larger number of reported cases would be required to support the suggestion that black patients have a higher incidence of the more serious grade 3 PPE.

Since presentation of PPE in black patients differs from that of white patients, suggestions have been made that the definition of grade 1 PPE should be amended to include hyperpigmentation instead of erythema and that progression to grade 2 PPE should include palmar-plantar keratoderma (PPK) (Narasimhan et al 2004, Saif & Elfiky 2007).

Do & Kim (2007) present two cases of palmar-plantar keratoderma following the administration of capecitabine for breast cancer. Acquired PPK is associated with pre-existing inflammatory skin conditions, infections, circulatory problems (e.g. lymphoedema), metabolic abnormalities (e.g. myxoedema), malignancies and toxic agents (NZ dermatological society 2009). Both cases presented by Do & Kim (2007) had metastatic breast cancer and it is possible that the keratoderma might be paraneoplastic. Since the keratoderma progressed rapidly following signs of PPE during treatment with capecitabine, and resolved spontaneously after discontinuing treatment, it is more likely to be a result of the capecitabine rather than any other factors. The authors reported these cases from Korea, although the ethnic origin of the two cases was not defined.

Having said that there can be differences in presentation between ethnic groups, there appears also to be variation in the presentation of PPE between different agents. Bullous (blister) variants have been described with cisplatin, methotrexate, TKIs and the monoclonal antibody bevacizumab. PPE induced by TKIs presents more often as localised patches in weight bearing areas and

areas that rub against each other (Fife et al 2009), and usually occurs within the first 6 weeks of treatment (Lipworth et al 2009). Docetaxel-induced PPE has been reported to present as discrete patches of erythema and not always limited to the hands and feet (Zimmerman et al 1995). Because of this unique and clinically distinct presentation Childress and Lokich (2003) propose that this cutaneous toxicity associated with docetaxel should be renamed as Periarticular Thenar Erythema and Onycholysis (PATEO), or fixed erythrodysesthesia plaque (Chu et al 2000). There are occasional reports of unusual presentations with capecitabine monotherapy. One case report of a 56 year old man with colorectal cancer, developed cutaneous lesions resembling sclerodactyl-like changes after the seventh cycle (Trindade et al 2008).

Presentation of skin eruptions in haematology patients following stem cell transplantation can cause difficulties in diagnosis as chemotherapy-induced PPE and acute graft versus host disease are difficult to distinguish apart (Azurdia et al 1999). So, having initially stated that presenting features are clearer than incidence, it would seem that in some instances it is not. These include; dark skinned individuals; the anti-neoplastic agent being administered and those who have received stem cell transplants.

An understanding of the pathophysiological mechanism of PPE is necessary to be able to identify potential risk factors.

2.6 Pathogenesis

The exact mechanism involved in the cause of PPE is unclear but occurrence appears to be related to prolonged exposure as with infusional drugs, daily ingestion or liposomal encapsulation which extends the drug half-life resulting in drug accumulation in the skin (Gordon et al 1995, Molpus et al 2004). Two theories have emerged from the literature; the first that extravasation of the drugs occur from damaged microcapillaries due to trauma caused by normal daily activities such as walking, exposure to heat and grasping objects which

results in an inflammatory response (Molpus et al 2004, Saif 2011); secondly many chemotherapy agents concentrate in eccrine sweat glands such as those found in the hands and feet and sweat acts as a carrier of the drug to the skin surface (Azurdia et al 1999, Molpus et al 2004, Lorusso et al 2007). The latter theory would explain the areas of the body commonly affected by PPE and is supported by the presence of the drugs in sweat (Jacobi et al 2005, Gressett et al 2006, Martschick et al 2009). This theory reminds healthcare professionals that penile involvement in male patients with PPE should be considered since this is an area with a high concentration of eccrine sweat glands and may be under reported by patients until it becomes severe, due to their embarrassment (Sorscher 2004, Lee et al 2009).

No clear correlation between plasma levels of metabolites from capecitabine and incidence of PPE has been seen (Gieschke et al 2002, Jeung and Chung 2010). A suggested cause of PPE by capecitabine is that keratinocytes in the skin have high levels of the enzyme thymidine phosphorylase (TP) involved in the conversion of capecitabine to 5-FU which could result in metabolite accumulation in the skin (Asgari et al 1999, Fischel et al 2004). similar to 5-FU itself (Jeung and Chung 2010). Biopsies taken from the palms and backs of 4 patients receiving capecitabine monotherapy found a marked expression of TP in both sites but a paucity of the dihydropyrimidine dehydrogenase enzyme (DPD) in the samples from the palms of the hands. Since DPD catabolizes 5-FU, the dearth of this enzyme in the palms may explain the localised accumulation of 5-FU causing PPE (Ferrero et al 2006). A similar picture for TP levels in the palm (p = .04) was found in a pilot study by Milano et al (2008) in 12 healthy volunteers. However they found a higher level of DPD in the palms than the back (p = .01), the opposite of the previous report. Milano et al (2008) found a significantly higher proliferation rate in the palms than the back (p = .008) and suggested that it was this that could make them more susceptible to the localised action of chemotherapy. Furthermore, a significant association between high levels of TP in tumour cells and the development of PPE (p = 0.01) with tumour response (p = 0.004) has been demonstrated in a phase II study of 30 patients receiving capecitabine in

combination with docetaxel for non-small cell lung cancer (Han et al 2005). This poses the question of whether it is the TP level in tumour cells (which is not routinely measured) that influences the efficacy of the treatment thus indicating that PPE is a clinical sign of these raised levels. Further research is warranted to compare TP levels and efficacy with the incidence of PPE.

Schedule-dependent PPE has been demonstrated in the use of caelyx and is thought to be linked to the turnover time of keratinocytes and epidermal transit time (3-4 weeks). A three weekly schedule may hit the skin during its sensitive repair time causing an inflammatory response which increases the permeability of the microcapillaries leading to extravasation and further damage (Lotem et al 2000, Lyass et al 2000). This is supported by Markman et al (2004) who presented a case report of a patient who became sunburnt between courses of caelyx whereby even with a dose delay and visual resolution of the sunburn, severe PPE developed with the subsequent dose highlighting the skin's sensitivity to multiple insults. A photo-enhanced melanocyte-based reaction is suggested as the reason for extensive hyperpigmentation of normal sun exposed areas of the face (despite strict precautions) which accompanied severe painful PPE in one Portuguese patient (Tavares-Bello 2007). If we accept these theories as probable, potential risk factors can be identified.

2.7 Aetiology and risk factors

There is variability in the frequency and severity of PPE which appear to be determined by pharmacokinetic and pharmacodynamic properties of the individual drugs (Lyass et al 2000, Lorusso et al 2007) and/or patient-related factors (Lassere & Hoff 2004). The properties of 5FU and capecitabine were addressed in section 2.4. In this section a review of the literature of other factors will be presented. These factors include biographical details, past medical and drug history, health status, organ function, genetics and activities of living.

2.7.1 Age and Gender

Age and gender have been suggested as risk factors for PPE, with some evidence that older, female patients have an increased risk of PPE (Meta-analysis group in cancer 1998, Schellens et al 2005, Chabner & Longo 2006), while others found no significant difference in age and gender (Comandone et al 1993, Chiara et al 1997, Abushullaih et al 2002, Heo et al 2004, Feliu et al 2005, Sun et al 2009).

Normal physiological changes associated with ageing are known to affect the pharmacokinetics and dynamics of drugs often leading to slower metabolism and excretion, therefore, it is no surprise that the older patient would be at risk of developing chemotherapy-induced toxicities (Jansman et al 2000). When analysing the significance of age as a risk factor it is important to note that despite the incidence of cancer in the over 70s, there has in the past, been a lack of data addressing toxicities in this age group, possibly due to a reluctance to treat the very elderly and the age limit (70 years) for entry into trials (Zalcberg et al 1998).

An increase risk of PPE has been reported in older patients (p = .009) and females receiving 5-FU (p = 0.04) (Meta-analysis group in cancer 1998), and may be due to a lower capacity to clear 5-FU in women (Milano et al 1992), but not in association with capecitabine (Abushullaih et al 2002, Cassidy et al 2002). A small study of 41 older (> 65 years) Chinese women receiving a combination of capecitabine and docetaxel for metastatic breast cancer reported an incidence of PPE grade 1 and 2 of 22% (9) with no grade 3 PPE, suggesting this is an effective treatment in elderly women (Wang et al 2010). One study comparing the incidence of toxicities between those under the age of 65 years and those above 65 years found a similar incidence for PPE of any grade and for severe PPE in patients receiving capecitabine monotherapy (Scheithauer et al 2003). Stein et al (1995) collapsed age into two categories below 70 years and above 70 yrs and found a statistically significant association between the older age group and any severe toxicity (p < .001) in

patients receiving 5-FU treatment. This finding was not replicated with capecitabine monotherapy in patients under 75 years compared with over 75 years, although only 18 out of a sample of 178 fell into the over 75 year age group (Jensen et al 2006). In a small Spanish study of 17 patients with metastatic breast cancer who were older than 70 years, PPE grade 3 occurred in 18% at the standard dose and reduced to 7% when the dose was reduced to 1000 mg/m^2 (Zamora et al 2004). In another study, carried out in China, of 45 patients with advanced gastric cancer, treated with a fixed dose of capecitabine 1000mg/day continuously for four weeks followed by one week's rest, PPE of all grades occurred in 35.5% with only 2.2% developing grade 3 PPE (He et al 2011). The authors of both of these two studies concluded that capecitabine was tolerable in patients over the age of 70 if given a reduced dose and no difference in efficacy was seen. Oral therapy is thought to be preferred by patients, either because of the convenience of this, or assuming that there will be reduced toxicities (Labianca et al 2001, Saif & Elfiky 2007). However, the Focus 2 trial which recruited elderly and frail patients with advanced colorectal cancer from 61 UK centres, found there was increased toxicity with capecitabine monotherapy and no evidence of improved quality-of-life. The scores used for measuring whether treatment interfered with the patient's normal activities indicated a preference for 5 FU rather than capecitabine. However the difference was not significant (Seymour et al 2011). Having said that there is little difference between the incidence of PPE in older patients in the studies above. Reddy & Fakih (2007) suggests that patients over 80 years old require substantial dose reduction to avoid severe toxicities of capecitabine or 5-FU since they appear to behave differently to those in their 70s.

One factor linked to gender which appeared to occur more frequently in patients who developed capecitabine-induced PPE for metastatic breast cancer was the hormone receptor status of the tumour. There was a significant difference between progesterone receptor positive and negative tumours (p = 0.003), but no difference in oestrogen receptor status (Kurt et al

2006). Since only one study has reported this association further study is required to confirm this finding.

2.7.2 Ethnicity

No evidence has been found in the literature prior to 2005 to indicate that PPE prefers a particular race or ethnicity (Janusch et al 2006). However, since the presentation of PPE in people with dark skin differs from the white population (as previously discussed in section 2.5), the incidence may have been under reported. More recently a higher incidence of PPE has been seen in Japanese (Hyodo et al 2006) and Korean patients (Yun et al 2010), but with a lower incidence in grade 3 PPE which was also seen in Asian patients compared to other ethnic groups (Haller et al 2008, Lee et al 2008).

2.7.3 Past Medical History

Other patient-related factors linked to the development of PPE include; a pre-existing peripheral vascular disease; compromised peripheral nervous system; (e.g. carpal tunnel syndrome) (Zimmerman et al 1995), peripheral neuropathy from previous chemotherapy (Palaia et al 2006), diabetes (Narasimhan et al 2004, Wilkes & Doyle 2005) dermatological disorders; and previous irradiation therapy (Hood & Reeck 2006). Previous exposure to chemotherapy especially if the patient experienced toxicities such as mucositis (Heo et al 2004), diarrhoea (Wagstaff et al 2003) and neutropenia (Jansman et al 2000) have been linked to the development of PPE. Whether these factors are statistically significant is unclear in some of the literature and are mostly based on case reports, and small scale studies and would require validation in larger studies.

There have been some reports that patients with diabetes may have an increased risk of developing PPE due to the presence of diabetic neuropathy which may reduce sensory perception of the early symptoms of PPE

(Narasimhan et al 2004, Goutos et al 2009), although, this finding has only been described in single case reports.

The prime aim of one study of 179 patients receiving capecitabine-containing combination chemotherapy from 4 prospective clinical trials which reported an incidence of PPE in 64.8% (116) and grade 3 in 4.5% (8) was to analyse prognostic factors for PPE (Heo et al 2004). They assessed baseline clinical factors including age, sex, pre-treatment performance status, regimen and combined use of drugs, also performance status per cycle and other toxicities. Their findings suggested that docetaxel in combination with capecitabine (multivariate Cox regression p = .001) and previous occurrence of mucositis (time-dependent Cox regression p = .029) were the only factors that were significant prognostic indicators for the development of PPE. Interestingly they also found that the occurrence of docetaxel-induced nail toxicity (45.1%, 23 of 51) was significantly associated with the incidence of PPE (p = .022, chi-square test). Another study by Chiara et al (1997) of PPE in patients receiving infusional 5-FU (n = 70) found that previous exposure to 5-FU was significantly associated with the development of PPE in subsequent chemotherapy (p = 0.003). Of the 70 patients, 36 developed PPE, 15 with PPE alone and the remaining 21 PPE and other toxicities; diarrhoea (58.3%); mucositis (50%), nausea and vomiting (41.6%) and conjunctivitis (25%). The latter were only presented as descriptive statistics and no significance testing or correlation between grade of PPE and additional toxicities were presented.

Disel et al (2010) reported a 65 year old Turkish man with advanced gastric cancer who had had a previous stroke leaving him with a right-sided hemiplegia. He developed grade 2 PPE 10 days after the start of cycle 4 of capecitabine treatment. The PPE developed in his left hand and foot and they state that this is the first reported case of unilateral PPE. They hypothesised that changes in the skin due to vascular insufficiency led to capecitabine metabolites having reduced access to the skin in the extremities affected by the hemiplegia and were unable to accumulate and cause PPE. Whilst this hypothesis seems plausible unilateral PPE may be partly due to the lack of

exposure to other factors, such as friction and heat implicated in the development of PPE, due to reliance on using his left side for day to day activities.

Another case report in the literature was of a 53 year old Italian female with ovarian cancer receiving PLD every 4 weeks who had persistent peripheral neuropathy following previous chemotherapy treatment. A past medical history of poliomyelitis had left her with a right quadriceps paralysis. She developed grade 3 PPE after cycle 3 with a dark, cold and ulcerated area of the distal phalange of the 2nd finger on the left hand which led to amputation of that part of the digit. This is the first reported case of irreversible skin toxicity probably due to the absence of pain sensation caused by the peripheral neuropathy. This may have led to an underestimation of the severity of the erythema seen after cycle 2 as the patient reported no pain or burning (Palaia et al 2006). This finding is support by Tanyi et al (2009) who found that those with peripheral neuropathy were twice as likely to develop PPE than those who did not have peripheral neuropathy from previous treatment (p = .0001) and suggested that peripheral neuropathy damages the nerves of the blood vessel walls causing them to lose their ability to respond to temperature changes which enhances the mechanism of PPE.

2.7.4 Drug to Drug Interaction

Concomitant medications may lead to drug-drug interactions resulting in increased toxicity of anti-neoplastic agents or affect the efficacy of the co-medication (Jansman et al 2000, Chabner & Longo 2006). There have been case reports of an increased incidence of PPE in patients who receive pegylated G-CSF (PG-CSF) with each cycle of docetaxel, where the PPE resolved without dose reduction after the PG-CSF was stopped (Bardia et al 2006). This association is supported by Burnstein et al (2005) who report grade 2 or 3 PPE in 4% of patients who received PG-CSF in a prospective clinical trial of dose dense docetaxel chemotherapy, although exact details of sample size or alterations to treatment were not provided. The absence of

PPE in a large trial of patients receiving docetaxel supported with non PG-CSF suggests that it is the pegylation of G-CSF contributes to PPE toxicity (Citron et al 2003). In addition, the substitution for non-pegylated G-CSF in patients who developed PPE following PG-CSF support while receiving doxorubicin and cyclophosphamide (AC) resulted in resolution of the PPE without any alterations to treatment (Lee & Lynch 2007). PG-CSF has a longer half life and therefore increased tissue concentration than non-pegylated G-CSF and is cleared through a mechanism controlled by neutrophils (Kotto-Kome et al 2004). One of the histological features of PPE is the infiltration of the lesions by white blood cells and it is possible that pegylation of G-CSF enhances and increases neutrophil infiltration in some patients, provoking the inflammation observed with PPE (Bardia et al 2006, Lee & Lynch 2007).

Other concomitant medications that increase the toxicity of 5-FU or capecitabine are allopurinol, dipyramidol, metronidazole and cimetidine (Jansman et al 2000), with a single case report of severe PPE when capecitabine is administered concurrently with brivudin, an anti-viral agent to treat Herpes Zoster infection (Baena-Canada et al 2010). Capecitabine causes an increase in phenytoin levels and the close monitoring of phenytoin levels or the use of alternative antiepileptic medication is recommended (Berg 2006, Privitera and de los Rios La Rosa 2011, Roche 2011). Capecitabine increases the effect of warfarin and leads to raised International Normalised Ratio (INR) levels and can fluctuate during 3-weekly cycles. Suggestions have been made that the patient should be transferred to low-molecular weight heparin during treatment with capecitabine (McGavin & Goa 2001, Berg 2006, Giunta 2010, Roche 2011).

Finally, antacids interfere with the absorption of capecitabine and should either be avoided or taken 2 hrs before or after taking capecitabine (Van Cutsem et al 2000, McGavin & Goa 2001).

2.7.5 Performance status

Surprisingly unlike other toxicities, PPE had a higher incidence in patients with a good performance status (n = 70, *p* = 0.053) (Chiara et al 1997) (n = 41, *p* = 0.03) (Abushullaih et al 2002). Contradictory findings are presented by others who found no significant association with performance status (Comandone et al 1993, Heo et al 2004). Comandone et al (1993) based their findings on just 12 cases of patients receiving 5FU who developed PPE, whereas, Heo et al (2004) used a larger sample of pooled data from four trials (n = 179) of Korean patients who received capecitabine-containing regimes. One study, in patients with leukaemia receiving a combination of cytosine arabinoside and daunorubicin, indicated a correlation between poor performance status and the development of severe PPE which also resolved slowly (Demirçay et al 1997), though again this was based on small numbers with only 2 out of the 15 who developed PPE having poor performance status.

2.7.6 Nutrition and weight

A risk factor identified in the literature which could include both drug and patient factors is the role that malnutrition plays in the development of PPE. Nutritional deficit has been implicated particularly since pyridoxine (Vit B6) has been shown as a possible treatment of PPE (Lassere & Hoff 2004). Decreased serum albumin and increased bilirubin levels could contribute to an increased risk of toxicity, particularly related to drugs that are at least 90% protein-bound (Jansman et al 2000). A reduction in this carriage mechanism or an increase in bilirubin (as bilirubin is also protein bound and competes with the drug for attachment) results in an increase of free circulating drug which is partly responsible for the development of toxicities (Jansman et al 2000). A study of prognostic factors for the toxicity of 5-FU in 130 patients revealed that baseline serum albumin was not predictive of toxicity and since 5-FU is only 10% protein-bound, this result is not surprising (Steinberg et al 1992). With capecitabine, the amount bound to protein is low, although higher than 5-FU at 54%, mostly bound to albumin (35%) (McGavin and Goa 2001,

Reigner et al 2001). In a study by Sharma et al (2006) high levels of dietary folate have been linked to increased tumour response but also resulted in development of toxicities with Capecitabine. Folate is required for the binding between 5FU metabolites to the enzyme thymidine phosphorylase (TP) during the metabolism of capecitabine. They found that high levels of pre treatment serum folate levels were significantly associated with increased toxicity during cycle 1 and over the entire treatment period (p = 0.02), particularly grade 2/3 diarrhoea (p = 0.001) and grade 2/3 nausea and vomiting (p = 0.032) when compared with grade 0 and 1. These results are based on a sample of 38 patients, thereby lacking sufficient power to draw firm conclusions. The USA has had voluntary addition of vitamins (including folates) and minerals to foods such as bread, flour, spreadable fats, milk and milk products since 1924 which became mandatory in 1943. In the UK it has been mandatory to fortify flour and margarine since the 1940s. However, the addition of folates is still subject to debate (DH 2011). The presence of fortified foods in the diet of those from the USA in Haller et al's (2008) study may partly explain the higher incidence of grade 3/4 toxicities, although this is not proven.

Weight loss prior to a diagnosis of cancer was linked to an increased incidence of severe PPE compared to those who had not lost weight (p < 0.002). This is thought to be due to altered response to chemotherapy in patients with weight loss, since even 5% weight loss can alter measurable physiological values such as immune response (Andreyev et al 1998). Data in their study, however, did not establish how much weight loss was significant and the accuracy of the weight loss was doubtful. Weight was not recorded prior to the diagnosis of cancer, was based on subjective reporting by the patient, and was not validated independently.

The influence of cachexia (a common presenting feature of cancer), on the pharmacology of chemotherapy agents is unclear and has not been evaluated as a risk factor for toxicities (Jansman et al 2000). Conversely, some doctors are reluctant to prescribe PLD to overweight patients as they suggest that being overweight intensifies the risk of PPE due to increased friction in the

inter-triginous areas especially the axilla, breast and waist areas (Griggs et al 2005 & 2007). There are several physiological changes that occur in overweight individuals that may affect the way drugs are processed by the body. These include alterations in lean body mass, adipose tissue mass, organ size, blood volume and cardiac output. However, prospective pharmacokinetic studies are required to demonstrate whether increased body weight is a risk factor for toxicities from chemotherapy agents (Jansman et al 2000). Gordinier et al (2006) tested this hypothesis in a retrospective analysis of patients records over 7 years (n = 103). They found that there was no significant difference in body mass index (BMI) between those that developed PPE and those that did not, suggesting that BMI is not a risk factor for PPE.

Individual patient chemotherapy doses are based on calculated Body Surface Area (BSA) because of convention rather than scientific research (Gurney et al 1998). Being first described to scale the doses from lower mammals such as rodents to humans, this led to the myth that BSA based dosing provides safe and effective administration schedules of chemotherapy (Pinkel 1958, Gurney et al 1998, Ratain 1998). Two small studies have challenged the convention of using BSA to calculate dosage. The first evaluated patients who received epirubicin of the same dose regardless of BSA, organ function or other factors, finding no correlation between BSA or weight and toxicity (Gurney et al 1998). The second with a fixed dose of capecitabine 1000mg/m^2 twice a day for 14 days every 3 weeks, again finding no difference in the frequency of adverse events and BSA (Sun et al 2009). It has been suggested that Lean Body Mass (LBM) correlates better to drug clearance than BSA, but has been tested in too few studies to draw conclusions (Ratain 1998). An analysis of 5FU and LBM found the latter to be a significant predictor of toxicity in female patients (Prado et al 2007), which can be partially explained by the difference between men and women, since women have a lower proportion of LBM (Jansman et al 2000, Prado et al 2007). Zalcberg et al (1998) in a bivariate analysis of toxicity and LBM found a statistically significant association between low LBM and grade 3/4 neutropenia in patients receiving 5FU (p = 0.009). However, the significance disappeared in

a multivariate analysis suggesting that the bivariate effect was caused by gender reflecting the fact that females have lower LBM than males. The LBM compartments in the body include metabolic tissues such as the kidneys and liver, bone and intra and extracellular water. Since 5FU is fairly hydrophilic, it will be distributed in and metabolized by the LBM, which would explain the higher incidence of toxicity seen in patients with a low LBM (Gusella et al 2002, Prado et al 2007). Until a simple standard and accurate method to calculate LBM is available practice cannot change (Ratain 1998).

2.7.7 Organ function

A link between renal impairment and an increased incidence of severe toxicities with capecitabine have been demonstrated due to a reduction in the excretion of its metabolites (Gieschke et al 2002, Poole et al 2002) suggesting that capecitabine should not be given to patients with severe renal impairment. Another study comparing pre-treatment creatinine clearance (CrCl) values with the incidence of PPE determined that for every 10 millilitres/minute reduction in CrCl the risk of developing PPE increased by 7% (95% CI: 2 – 11) (Hénin et al 2009). A dose reduction of 25% of capecitabine is required in moderate renal failure (CrCl 30-50 mls/min) and is contraindicated in severe renal failure (CrCl below 30mls/min) (EMC 2012). For elevations of bilirubin levels of three times the upper limit of normal, capecitabine should be interrupted until bilirubin falls below this level. The effect of severe hepatic dysfunction on capecitabine is not known (EMC 2012). Likewise a dose reduction of 5-FU is required with impaired renal and hepatic function (EMC 2011).

An investigative model Gieschke et al (2002) of pharmacokinetics of capecitabine identified that a 50% decrease in CrCl was associated with a 30% reduction in the clearance of α-fluoro-β-alanine (FBAL), a metabolite of capecitabine. This is an unsurprising find given that the majority of FBAL is excreted via the kidneys. In addition, the study reported that this was a predictor of dose-limiting toxicities. A similar effect of CrCl values and FBAL

clearance was seen in a study by Poole et al (2002) who also found that those with moderate or severe renal impairment experienced an increased incidence of grade 3/4 toxicities. However, no relationship between FBAL and these toxicities was found. There was, however a strong association between severe toxicities and another metabolite of capecitabine, 5'-DFUR (5'-deoxy-5-fluorouridine) whose clearance is also affected by the kidneys. They recommend that capecitabine should not be given to patients with severe renal impairment. A study of pooled data from two large phase III trials using pre-treatment CrCl values determined that for every 10 millilitres/minute reduction in CrCl the risk of developing PPE increased by 7% (95% CI: 2 – 11) (Hénin et al 2009).

2.7.8 Genetics

Other factors that have been linked to increased incidence of toxicities from 5FU are genetic polymorphisms of the enzymes DPD (dihydropyrimidine dehydrogenase the rate limiting enzyme of 5FU catabolism) (Diasio & Johnson 1999) and TP (Thymidine Phosphorylase the main activating enzyme of capecitabine) (Caronia et al 2011).

DPD activity has been shown to be circadian dependent with increased activity in the evening which corresponds with findings that 5-FU is metabolised faster in the evening (Bjarnason et al 1993). Alteration in genes regulating drug transport and metabolism have been shown to play a significant role in the development of severe PPE. This has been seen particularly in 5-FU (Johnson et al 1999, Van Kuilenburg et al 2002) and capecitabine (Mattison et al 2006) containing regimes where there was mutation of the gene (DPYD) (Van Kuilenburg et al 2002, Loganayagam et al 2010). This gene encodes for the enzyme DPD and a mutation leads to complete or partial loss of DPD enzyme (Johnson et al 1999). This results in delayed or incomplete catabolism of the drug resulting in severe and sometimes fatal side effects (Johnson et al 1999, Johnson & Diasio 2001, Loganayagam et al 2010). African Americans with colorectal cancer had a high incidence of 5FU toxicities in one study (Mattison et al 2006), which

motivated them to evaluate DPD enzyme activity in healthy African Americans compared with Caucasians [*sic*]. DPD deficiency was found to be three times greater in African Americans ($p = 0.07$), and the women in this group were found to have a higher incidence of DPD deficiency than the men in the same ethnic group ($p \leq 0.001$). The opposite was seen in the Caucasian [*sic*] group with men having a higher rate of DPD deficiency than women ($p = \leq 0.003$) Testing for DPD activity prior to commencing treatment with 5-FU or capecitabine has been suggested (Lu et al 1993). Point mutation in the DPD gene, resulting in deficiency in gene production, has been seen in German, Finnish, Turkish and Taiwanese populations (in < 3%) but not seen in Japanese and African American populations (Van Kuilenburg 2004). Because of this low prevalence there is doubt as to the usefulness of pre-treatment genetic testing to individualise doses (Etienne et al 1994), although Loganayagam et al (2010) found that the UK population deficit in the DPD gene accounts for approximately 19% of severe toxicities from 5FU. A further study five years later demonstrated that there was a significant difference in DPD levels between patients with breast cancer and healthy females ($p < .01$) suggesting that patients with breast cancer have an increased risk of toxicity from 5-FU (Lu et al 1998). PPE is not mentioned specifically in any of the studies of DPD deficiency, as it is not considered a life threatening toxicity; therefore it is unclear whether PPE occurs more frequently or severely in these patients.

Park et al (2003) found a high incidence of grade 3 PPE (52%) in 23 patients receiving combination therapy of capecitabine and docetaxel for advanced gastric cancer, who also received pyridoxine in an attempt to reduce the incidence of PPE. They suspected that ethnicity may be a factor (details not given) and analysed the DPD gene in those that developed PPE grade 3, finding no evidence of DPD deficiency, therefore suggesting that severe PPE is not associated with gene mutation. This is contrary to the findings by Harris et al (1991) and Milano et al (1999) who suggest an association in patients receiving 5FU therapy. The testing for DPD deficiency in all the studies cited above appear to have been on serum. Interestingly, Ferrero et al (2006) took

biopsies from the palms of the hands and the back (control), finding increased expression of TP, but a relative absence of DPD in the skin. They concluded that capecitabine may be activated in the skin due to this high level of TP in conjunction with the absence of DPD explaining the specificity of PPE to the palms of the hands and soles of the feet. They also suggested that this may be an area for pharmacological research to limit the development of PPE.

Gender differences have been reported, with females having lower levels of DPD than males, which may partly explain the increase in toxicity of 5-FU in females. However, the DPYD mutation has an autosomal recessive pattern of inheritance; therefore, it is difficult to explain this phenomenon since it is not sex-linked (Milano et al 1999).

Gene mutation of TP has been associated with death due to severe toxicities of 5FU (Caronia et al 2011). The presence of mutated genes is twice as common in Chinese people as in Caucasian [*sic*] people. However, similar incidence is seen between Caucasians [sic] and south-west Asians. It is unclear whether this same link is made with capecitabine (Tan & McLeod 2005). A third gene that has been shown to be associated with PPE is the cytidine deaminase (CDD) gene (p = 0.04) and may gives new insights into discovering the mechanisms of PPE (Caronia et al 2011). Gonzales-Haba et al (2010) examined mutations in the ABCB1 gene and suggested this could be a biomarker for toxicity in colorectal cancer, particularly for neutropenia, diarrhoea and PPE. However, the study appears to suggest that a mutation in this gene is significantly associated with a reduced risk of these toxicities.

2.7.9 Patient activities

Since PPE may result from increased vascularity, pressure and temperature (Arias et al 1997) in the hands and feet, patient risk factors may include strenuous physical activity (Lassere & Hoff 2004), trauma and friction (Baer et al 1985) caused by normal activities such as walking or grasping objects, and long-term alcohol intake (Lassere & Hoff 2004).

Some studies, predominantly with patients receiving PLD, have suggested that active cooling reduces the risk of developing PPE (Baer et al 1985, Zimmerman et al 1994, Molpus et al 2004, Scotte et al 2005, Sayer et al 2006, Mangili et al 2008). Others have found the opposite with an increased incidence of PPE in those who used active cooling measures (Tanyi et al 2009).

As previously alluded to (section 2.6), chemotherapy has been isolated in the sweat glands of patients who developed PPE. It would, therefore, seem logical that individual sweat patterns may play a role in the development of PPE. In a small study (n = 10) of patients receiving PLD, 5 patients had hyperhydrosis and all 5 developed PPE (Jacobi et al 2005). PLD presence in sweat was confirmed by spectroscopy in 12 patients in a study to understand the pathogenesis of PPE (Lademann et al 2005). Exposure to heat and sweating may be more prevalent during hot weather, which calls into question whether the time of year when chemotherapy is administered has any association with the development of PPE, although this notion was refuted by Tanyi et al (2009) who found no association between the incidence of PPE and time of the year treatment was given. Son et al (2009) however, stated that changes in the skin, due to environmental factors such as humidity and the increased use of central heating in the winter may make the skin more sensitive to PPE inducing agents. Regular exposure to the sun, even with sunscreen precautions has been linked to the development of PPE (Zimmerman et al 1995, Peramiquel et al 2006), with one report of a patient severely sunburnt during treatment who developed PPE despite resolution of the sun damage to the naked eye (Markman et al 2004).

Alcohol abuse has been associated with the development of PPE in patients receiving 5-FU or capecitabine with a suggestion that this group of patients should be prescribed pyridoxine from the start of treatment to reduce the severity of PPE (Vukelja et al 1989).

Whilst biographical, health status, organ function and genetics as risk factors for PPE have been tested as part of large phase III trials this has demonstrated contradictory findings for some factors. There is consistency in the literature to suggest that impaired renal function and DPD deficiency are risk factors for PPE. Potential risk factors related to patient activities that lead to increased trauma, pressure or temperature to the hands and feet have not been subjected to rigorous testing.

2.8 Strategies to manage or minimise the severity of PPE

Numerous approaches have been suggested to prevent and/or reduce the severity of PPE. Two universally accepted approaches to the management of PPE are, for moderate to severe symptoms, treatment delay with/without a reduction in the dose (EMC 2011 & 2012). The second accepted approach being supportive care in conjunction with patient education (Webster-Gandy 2007). Pharmacological and non-pharmacological supportive care strategies proposed in the literature will be presented in this section. Patient education strategies will be discussed in section 2.9.

2.8.1 Pyridoxine (Vitamin B6)

The interest in pyridoxine to prevent or treat PPE stems from its similarity to acrodynia (a condition observed in pyridoxine phosphate depleted rats) (Gyorgy & Eckardt 1939).

Early reports on the use of pyridoxine to treat PPE are based on single case reports or small uncontrolled studies, with a few examples given below.

Vukelja et al (1989) present a 63 year old man with metastatic pancreatic cancer who was given bolus 5-FU 900mg/week escalating to 1150mg/week. After 11 weeks of treatment he developed PPE with cracking to his finger tips, severe pain and difficulty holding objects. Pyridoxine 100mg daily was

prescribed with no change in the 5-FU dose resulting in complete resolution of his pain. To test whether this result was a coincidence, his skin was tested with topical 5-FU for 72 hours, during which time pyridoxine was stopped. Within 24 hours there was a recurrence of PPE with swelling and pain of the fingers. Pyridoxine was recommenced and within 24 hours the pain and swelling had resolved.

Vukelja et al (1993) reported two further cases, one male and one female, who received docetaxel monotherapy. Both patients developed PPE and were commenced on pyridoxine 50mg three times a day with an improvement in their pain within 24 hours. The female patient occasionally forgot to take the pyridoxine and when that happened she developed tingling of her fingers which prevented her from using her computer.

One patient with Kaposi's sarcoma who had previously been treated with PLD and which had been discontinued due to grade 3 PPE, presented with progression of the disease. She was retreated with PLD at a lower (50%) dose than previously given. She again developed PPE and was prescribed 100mg pyridoxine three times a day for one week, then reduced to 50mg three times a day. There was complete resolution of the symptoms of PPE and PLD treatment with pyridoxine was continued resulting in a good tumour response and no further PPE (Gordon et al 1995).

A 56 year old female with metastatic breast cancer was treated with a combination of capecitabine and docetaxel. She developed severe PPE and treatment was discontinued. Despite attempts to treat with other chemotherapy agents her disease progressed. Capecitabine and docetaxel were recommenced with pyridoxine (dose unknown) in an attempt to prevent the development of PPE. Her PPE was completely controlled and she was able to continue her treatment. Her liver metastases disappeared on scan images (Umeda et al 2010).

A controlled study of patients receiving continuous infusional 5-FU who were commenced on either 50mg or 150mg of pyridoxine per day once they developed moderate PPE showed a partial reversal of PPE and allowed continuation of treatment without delay in 4 out of the 5 patients who received pyridoxine. Based on this observation it was recommended that randomised trials be undertaken to evaluate whether pyridoxine reduces the incidence of PPE without affecting response (Fabian et al 1990).

Patients with multiple myeloma were administered a combination regime of vincristine, PLD and dexamethasone every 4 weeks. After a high incidence of grade 3 PPE in the first 9 patients pyridoxine 200mg/day was added to the regime. Following this addition of pyridoxine the incidence of grade 3 PPE reduced (Hussein et al 2002). The actual figures demonstrating the reduced incidence were not evident in their study nor was any statistical analysis. They stated that the result should be treated with caution since the decrease in PPE may be due to the medical teams' increased expertise with this regime particularly the detailed instructions given to patients to minimise the risk of PPE.

The cases reported above all suggest that pyridoxine does indeed play a role in treating PPE since all authors reported a reduction in the symptoms experienced by the patients enabling them to continue with their therapy. Several randomised trials have been carried out to assess the efficacy of pyridoxine to either prevent or treat PPE.

A preclinical randomised study in 41 dogs to establish the effectiveness of pyridoxine given with PLD to prevent the development of PPE found that the placebo group were over 4 times more likely to develop severe PPE than the pyridoxine group (p = .03). Although pyridoxine did not completely prevent PPE, it occurred later and with less severity resulting in fewer delays or discontinuation of treatment (Vail et al 1998).

During a phase II study of PLD in combination with paclitaxel, the first 15 patients developed grade 2 or 3 PPE. The next 20 patients were commenced on pyridoxine 300mg/day; however a reduction in the incidence of PPE was not seen demonstrating that high-dose pyridoxine has no effect on the frequency and severity of PLD-induced PPE (Rossi and Catalono 2007). Although a different dose of pyridoxine was used, another trial found similar results. A randomised controlled trial (n = 34) with 18 patients allocated to the pyridoxine group and 16 to the placebo group. Any patients who developed PPE grade 2/3 were unblinded and if taking the placebo they were changed to pyridoxine 100mg twice a day, if on pyridoxine they were removed from the trial. No statistical difference was found between the groups, indicating that pyridoxine was not effective in preventing or treating PPE (Von Gruenigen et al 2010).

The two studies above were carried out on patients receiving PLD therapy and it is possible that pyridoxine may be effective with different PPE-inducing agents. The following three trials report variable findings when pyridoxine is added to capecitabine.

A multicentre retrospective notes review was carried out to determine the incidence and severity of PPE in patients receiving capecitabine monotherapy and to assess the efficacy of pyridoxine as prophylaxis or treatment of PPE (Mortimer et al 2003). There were two groups of patients; those taking capecitabine alone (n = 99); and those who received pyridoxine (n = 99). Out of the 99 who received pyridoxine, 73 (74%) were prescribed this prophylactically with the remaining 26 receiving pyridoxine as treatment once PPE occurred. They found no statistically significant difference in the incidence of PPE between those who received capecitabine alone compared to those who received pyridoxine as prophylaxis. The conclusions drawn from this study were that the data did not support the use of pyridoxine as prophylaxis to prevent PPE. However, when used as treatment once PPE occurs, pyridoxine may provide some relief of symptoms ($p < .001$). Although, prospective randomised controlled trials to test this hypothesis would be

required. It is unclear from this study whether the patients who received pyridoxine once PPE occurred also had a delay in their treatment. It cannot therefore be established with any certainty if the positive effect seen was due to the pyridoxine or a delay in treatment.

A randomised controlled trial by Chalmerchai et al (2010) carried out in Thailand compared two doses of pyridoxine, 200mg versus 400mg daily to prevent capecitabine-induced PPE. A sample of 56 (28 in each group), found less grade 2 or 3 PPE in the high dose group 11 (39%) compared with 20 (71%) p = .03 with no cases of grade 3 in the high dose group compared with 3 (10.7%) in the lower dose group, but was not statistically different p = .24. A multivariate analysis demonstrated that 400mg of pyridoxine was the only independent factor for a reduction in the incidence of PPE. However, they found that the group receiving the higher dose of pyridoxine had worsened tumour response with an increased incidence of disease progression and a shorter time to progression. Limitations of their study include the lack of a placebo group, a small sample size and it did not meet the preplanned statistical power.

Another randomised double-blinded placebo controlled study (Kang et al 2010) was performed to examine the effectiveness of pyridoxine to prevent PPE. Chemo-naïve patients received capecitabine containing regimes and pyridoxine 200mg/day (n = 180) or a placebo (n = 180). If those in the placebo group developed PPE, they were further randomised to either the pyridoxine or the placebo group. The results showed no significant difference in the incidence of PPE between the two groups was found and concluding that pyridoxine is not effective to prevent or treat PPE associated with capecitabine containing regimes.

A final study (Yoshimoto et al 2010) to assess the impact of prophylactic pyridoxine (60mg/day) on the incidence of PPE with capecitabine monotherapy or in combination with cyclophosphamide (n = 38) compared historical data in 40 patients who had not received pyridoxine. The incidence

of PPE in the pyridoxine group was 52.6% compared with 82.8% in the capecitabine only group ($p < .01$). They suggest that pyridoxine is effective in reducing the rate of PPE. Limitations of this study include a small sample, gender biased (all women), and no data presented to show the difference between those who received capecitabine monotherapy and those who received a combination regime.

Pyridoxine has been reported anecdotally to be useful to both prevent and treat PPE induced by various anti-neoplastic agents. The trials that have been carried out, report findings on small samples and use different doses of pyridoxine making comparison difficult. As a safe nutritional supplement, its prophylactic use is attractive; however, its efficacy needs to be proven in large prospective randomised controlled trials (Lassere and Hoff 2004). These studies would also need to include data on the outcome of treatment comparing those who received pyridoxine with those who did not. Time to disease progression and overall survival data should be measured, particularly in the light of the worrying report by Chalmerchai et al (2010) mentioned above. The debate on the usefulness of pyridoxine in the prevention and management of PPE continues with further trials currently in progress.

2.8.2 Emollients

Moisturising creams are recommended for use before and during treatment to the hands and feet to reduce the severity of PPE (Bush & Smith 2001, Gressett et al 2006, Grenon & Chan 2009). Particular attention should be given to the creases of the hands and wearing cotton gloves and socks at night will aid absorption of the cream (Pike 2001, Von Moos et al 2008). Udderly smooth®, bag balm®, lanolin-containing creams, ammonium lactate (Lac-hydrin), have all been used and some patients have reported success with George's Special Dry Skin cream, hemp-based creams and Aquaphor (Gerbrecht 2003).

A case report of a 61 year old man receiving gemcitabine and vinorelbine combination every 3 weeks, developed PPE (hands only) three days after the start of cycle 2. He was treated with topical urea 10% and able to continue with his treatment. With his next cycle he developed PPE on his feet, again treated with topical urea. By cycle 4 the PPE had completely resolved on both his hands & feet and he continued with treatment with no recurrence of PPE (Laack et al 2001).

Urea & lactic acid are known to have keratolytic and hydrating properties and since hyperkeratosis is a feature of PPE, this provided support to study the role of a cream containing these substances (Gressett et al 2006, Grenon & Chan 2009). A Multicentre randomised controlled trial (n = 137) of cotaryl cream (12% urea and 6% lactic acid) compared with a placebo was carried out on patients taking capecitabine. From the start of treatment ½ - 1 teaspoon of the cream or placebo was applied to the palms of the hands and soles of the feet, twice a day. No statistically significant difference between the groups and grade 2 or 3 PPE was found. In fact there was an increased incidence of severe PPE in the cream group, concluding that there is no evidence to support the use of urea and lactic acid cream to prevent PPE. There was some concern that the cream itself may have caused some of the skin toxicity (Wolf et al 2010).

Bag Balm®, and Udderley Smooth cream® are petroleum-lanolin containing ointments intended for veterinary use to sooth cows udders. Bag Balm® also contains an antiseptic ingredient hydroxyquinoline sulphate (Bush and Smith 2001). A study by Chin et al (2001) described the effect of Bag Balm® as topical treatment for PPE caused by a variety of agents. 13 patients developed PPE with 9 assessed as grade 2 or 3. All 13 used Bag Balm® and 12 of the 13 reported improvement in their PPE. There were no discontinuations of treatment due to PPE, showing promising results for this emollient. To enhance the effectiveness of these creams Saif & Elfiky (2007) suggest soaking hands in lukewarm water for 10 minutes and then apply

petroleum jelly onto the wet skin, as this traps the water on the surface and also protects injured or blistered skin.

Topical antioxidant creams have also been shown to have promising results in the prevention and treatment of PPE. An observational study of 12 chemo-naïve patients who applied antioxidant cream to the hands and feet did not develop PPE of any grade. 4 patients who interrupted the application of the antioxidant ointment developed grade 1 or 2 PPE, which resolved with the re-application of the ointment. 3 other patients who had developed PPE with previous chemotherapy treatment developed very mild reactions while using the cream (Lademann et al 2006). The primary results of a pilot non-randomized study of 20 patients who received a specially designed topical antioxidant ointment for PPE was also very promising (Von Moos et al 2008).

2.8.3 Steroids

Since steroids are known to reduce inflammation, it is this property that has led to their use to prevent or treat PPE, although the known dangers of steroid use have to be considered (Lassere & Hoff 2004, Von Moos et al 2008).

Single or small group case reports have suggested that corticosteroids administered topically (Esteve et al 1995, Gordon et al 1995, Komamura et al 1995, Valkalis et al 1998) or systemically (Brown et al 1991, Hellier et al 1996, Titgan 1997, Hoff et al 1998b) are effective in the prevention and management of PPE induced by a range of agents but has yet to be proven with capecitabine (Lassere & Hoff 2004).

A 64 year old female received PLD with pre medications of intravenous dexamethasone 20mg, diphenhydramine 50mg, cimetidine 300mg and ondansetron 10mg. After cycle 3 she developed a general rash and severe desquamation and dermatitis in a stocking-glove distribution. She was started on oral dexamethasone 8mg twice a day starting 24 hours pre treatment and

for 5 days following treatment. This appeared to prevent further PPE without treatment delay or dose reduction (Titgan 1997).

A second case report of a 67 year old man with gliobastoma multiforme received temozolamide 200 mg/m^2 for 5 days every 4 weeks. After his fifth cycle he developed grade 3 PPE (WHO criteria) which was treated with intravenous dexamethasone (no dose and frequency given). The signs and symptoms of PPE disappeared within one week compared with the normal course of the side effect of 5-6 weeks (Kanat et al 2007).

In a phase I/II study of high-dose vinorelbine 8mg bolus followed by 96 hr continuous infusion of the same drug 7-14 mg/m^2 /day, 4 out of 60 patients developed PPE. One of these was given dexamethasone 8mg orally twice a day for 5 days starting prior to the vinorelbine bolus and resulted in no further PPE (Hoff et al 1998a).

Conversely in 12 patients with 5-FU induced PPE who were treated with topical steroids or systemic anti-inflammatory agents no significant activity was found. 5-FU was withheld in all the patients for up to 4 weeks with gradual relief, however, when 5-FU was restarted, PPE recurred. Of the 12, 6 tolerated the treatment without dose reduction, 4 required a dose reduction and 2 had to discontinue 5-FU due to PPE (Comandone et al 1993). In this small study no information was given about which steroids or anti-inflammatory agents were prescribed or the dose and frequency. The incidence of each grade of PPE or the toxicity criteria used was not included.

A prospective study (Drake et al 2004) of the effect of dexamethasone on PLD-induced PPE was carried out in 9 patients who developed grades 2-4 PPE. Of these 9 patients, 6 were given dexamethasone and were able to continue with treatment with no dose modification. The remaining 3 had no dexamethasone and required treatment delays and dose reduction. The conclusion was that dexamethasone is effective in managing PPE and has now become standard practice in one unit who have seen no dose reductions

due to PPE or any grade 3 or 4 PPE since introducing this practice. The findings from this study are limited by the small sample size, the lack of randomisation or statistical testing of the differences and are therefore inconclusive at this time.

2.8.4 Celecoxib

Celecoxib is a Cox-2 inhibitor used for the relief of acute pain and symptoms of chronic inflammatory conditions (Lassere & Hoff 2004). In a retrospective study of 67 patients receiving capecitabine monotherapy the addition of celecoxib appeared to reduce the incidence of PPE grade 2 or above from 34% with capecitabine alone to 13% when celecoxib was added (Lin et al 2002). This potential effect needs testing in a large prospective randomised trial to provide sufficient evidence to recommend its use for prophylaxis of PPE.

In a prospective randomised study, 16 patients were given capecitabine monotherapy and another 15 given capecitabine with celecoxib. The celecoxib group showed a significant reduction in the frequency of grade 1 PPE (29% versus 72%; $p < .001$) and for grade 2 PPE (11.76% versus 30%; $p = .02$), but no significant difference for grade 3 PPE. In the capecitabine only group, 5 patients refused to continue treatment and 1 required a dose reduction due to PPE, whereas, there were none in the celecoxib group (Zhang et al 2011). An earlier study by Lin et al (2002) also found a significant difference between the two groups for grade 1 PPE (12.5% versus 34.3%; $p = .04$), but not for grade 2 (3.1% versus 17.1%; $p = .11$). From this study they also suggested that the combination of celecoxib and capecitabine may enhance anti-tumour activity by inhibiting cox-2 expression, which they later confirmed (Lin et al 2006a). Survival and tumour response rates have not yet been identified in Kang et al's (2010) study, but may be published late 2012.

2.8.5 Other

Pyridoxine, emollients, corticosteroids and celecoxib have been the main areas of interest to prevent or treat PPE, although there have been reports of other substances that have shown some effect, although in most cases in only a single case report.

2.8.5.1 Cod Liver Oil (CLO)

A retrospective notes review (Kanis et al 2009) of 18 patients who had taken CLO (1 capsule three times a day) while receiving PLD (40mg/m^2 as monotherapy and 30mg/m^2 in combination regimes every 28 days), found no grade 2 PPE or above. There were no dose reductions, interruptions or discontinuations due to PPE. They suggest that CLO may alleviate PPE via reduced extravasation of PLD and/or by blunting of local inflammatory response since the active ingredients of CLO reduce the production of inflammatory cytokines.

2.8.5.2 Vitamin E

Vitamin E is added to many skin products and is known to be a major lipophilic antioxidant stabilising cell membranes. When administered systemically vitamin E promotes collagen synthesis and inhibits the inflammatory response, providing the basis for the following study (Kara et al 2006). Their study examined five patients with metastatic breast cancer who received docetaxel and capecitabine in combination, and were prescribed vitamin E 300mg per day when they developed PPE grade 2 or 3. Within 7-10 days the PPE resolved and they were all able to continue without a dose reduction of either docetaxel or capecitabine. They state that further studies are required to evaluate the use of vitamin E but initial findings suggest considering vitamin E as a preventive drug when receiving PPE-inducing drugs.

A retrospective multicentre study (Yamamoto et al 2010) examined the role of vitamin E in the management of capecitabine-induced PPE of 32 Her-2 negative patients with breast cancer. Capecitabine 828 mg/m^2 twice a day for 21 days every 4 weeks was prescribed. If a patient developed grade 2 PPE, they were prescribed vitamin E 100mg per day as a starting dose with no reduction in the capecitabine dose. A marked effect was seen within 7 days of commencing vitamin E with 17 patients requiring an increase of vitamin E to 400mg per day to reduce the pain of PPE, and 4 of these requiring a reduction in the dose of capecitabine. Their findings indicate that those taking vitamin E who managed to continue on the full dose of capecitabine had a longer time to progression than those who had a reduced dose of capecitabine.

2.8.5.3 Henna

Henna is a plant which is thought to have anti-inflammatory, antipyretic and analgesic properties. It is used as a topical medicine to treat seborrhoea (greasy skin) or fungal infections or for decorative purposes in some parts of the world (Yucel and Guzin 2008). These authors present the case of a female patient who develop grade 3 PPE on her feet only, had used henna on her hands and she was subsequently advised to use it on her feet as well. The symptoms resolved within 48 hours and completely disappeared after 1 week without any reduction in the dose of chemotherapy. This led on to an observational study on 10 Turkish women who after developing grade 2 or 3 PPE, applied henna to their hands and feet. They were instructed to wrap them in cloth and then wash them after 5-6 hours. They achieved a complete response in all 10 with no dose reduction. They conclude by stating that this coincidental discovery of henna dye for the treatment of PPE seems promising and is an area of future pharmacological research to identify the substance present in henna and develop it as a cream or lotion without the dying effect.

2.8.5.4 Nicotine patch

Kingsley (1994) reported a single case of a 65 year old female who received 5-FU and leucovorin continuous infusion over 24 hours every week. She presented with hyperpigmentation of the hands which progressed to desquamating erythema. A nicotine patch (7mg) was applied to the skin (location not stated) 1 hour pre infusion and removed 1 hour after completion resulting in complete resolution of the PPE. The effect of the nicotine may be due to vasoconstriction reducing the amount of 5-FU delivered to the skin.

2.8.5.5 Dimethyl Sulfoxide (DMSO)

First used as a solvent for chemical reactions, in medicine, DMSO is predominantly used as a topical analgesic; a vehicle for topical application of pharmaceuticals; an anti-inflammatory; and an antioxidant. It was there properties that led to a study by Lopez et al (1999). In their study, 10 (29%) out of 35 patients receiving PLD developed grade 3 PPE. Of these 10 patients, 2 patients developed grade 3 PPE after 3 cycles and applied topical DMSO 99% four times a day for 2 weeks. PPE resolved over a period of 1-3 weeks and shows promising results but requires prospective studies to definitively evaluate its therapeutic effectiveness. In the 2 cases mentioned above, treatment with PLD was interrupted during the time DMSO was applied which questions its effectiveness since the PPE could have resolved with an interruption in treatment. There are also some concerns about the toxicity of DMSO itself which need to be resolved before its use is considered for evaluation in the treatment of PPE (Von Moos et al 2008).

The interventions discussed above are predominately based on single case reports or small samples in uncontrolled trials. The safety and efficacy of these interventions have yet to be tested and proven in large randomised placebo controlled clinical trials for definitive recommendations to be made (Bush & Smith 2001).

2.9 The nurses' role in the assessment and recognition of PPE

The role of the oncology nurse is to educate the patient on how to recognise the signs and symptoms of PPE; when to report this to the hospital; dose modifications as required and strategies to reduce the risk and severity of PPE (Gerbrecht 2003).

Patient education strategies have developed from anecdotal evidence and are based on level 4 and 5 evidence (case series and expert opinion) and include the following advice;

- Use of emollient creams to hands and feet (Bush & Smith 2001) – but do not rub vigorously (Janusch et al 2006)
- Avoid skin irritants (Janusch et al 2006, Von Moos et al 2008)
- Wear cotton gloves and socks to aid absorption of the cream (Pike 2001, Von Moos et al 2008)
- Avoid tight fitting, clothes (Alza Pharmaceuticals 1999), jewellery and shoes (Bush & Smith 2001)
- Avoid adhesive dressings (Von Moos et al 2008)
- Avoid repetitive activity or remaining in the same position for long periods (Von Moos et al 2008)
- Avoid anything that causes sweating (Von Moos et al 2008)
- Pat the skin when drying do not rub (Von Moos et al 2008)
- Avoid extremes of temperature, pressure or friction (Alza Pharmaceuticals 1999, Gerbrecht 2003)
- Restrict the use of hot baths, hot showers, hot tubs and saunas (Alza Pharmaceuticals 1999, Pike 2001)
- Avoid hot foods and liquids (Mangili et al 2008)
- Avoid contact with hot water or steam such as seen in dishwashers or laundry (Alza Pharmaceuticals 1999)
- Avoid mechanical manual work (Janusch et al 2006)
- Avoid use of tools where squeezing of the hand onto a hard surface is required (DIY, gardening) (Von Moos et al 2008)

- Avoid excessive exercise (Alza Pharmaceuticals 1999) such as jogging, walking or aerobics (Von Moos et al 2008)
- Restrict exposure to strong sunlight (Pike 2001, Mangili et al 2008)

Signs and symptoms of PPE may resolve between cycles and some patients may be reluctant to report them. Patients sometimes believe that side effects of chemotherapy are inevitable and are to be tolerated. Others might hide symptoms as they fear that their cancer will grow and they may die if treatment is delayed or reduced (Mrozek-Orlowski & Sanborn 1999). To overcome these beliefs the nurse must emphasise that a dose reduction does not necessarily diminish the efficacy of treatment (particularly with capecitabine) (Gerbrecht 2003, Marse et al 2004). Tolerating side effects could compromise treatment, as allowing development of severe side effects will result in longer delays to allow them to resolve (Marse et al 2004). It is therefore important that the nurse questions the patient carefully, as subsequent episodes may be more severe and could be avoided with appropriate dose modification (Edwards 2003, Wood 2004). Figure 2.1 is a suggested PPE symptom assessment form which can be used by nurses during each consultation with a patient prior to each cycle of Capecitabine (Edwards 2003).

A prospective multicentre study (Grenier et al 2007) evaluated the impact of a nurse-led education and support programme on toxicity and adherence to treatment. The sample n = 112 consisted of women receiving PLD for recurrent ovarian cancer. All patients received education on the potential toxicities and how to manage them. They were issued with an education kit to take home which included; a patient booklet on PPE; a symptom diary; a list of hints to reduce the incidence or severity of PPE; and emollient creams to minimise the severity of PPE. At each visit the nurse reviewed the patient's symptom diary and re-emphasised actions to prevent, minimise or treat toxicities. Their findings suggested that the incidence of PPE (50%) was similar to phase III studies, however severe PPE and mucositis was substantially reduced with fewer discontinuations. There were however,

several limitations of this study, it lacked randomisation, and comparison was made with phase III studies rather than incidence of toxicities in the centres prior to the implementation of the programme. The patients in this study were receiving PLD as second, third, or fourth line treatment and may have had more advanced disease then those in other studies and some toxicities may still occur despite any interventions.

PPE SYMPTOM ASSESSMENT	
Routine examination	
Examine palms of the hands and soles of feet and toes, heels, bunion areas	
Examine tops of feet and toes, heels	
Examine skin exposed to pressure (waistline. Bra line, elbows, knees)	
Examine skin exposed to warmth/moisture (axilla, inner thigh, under breasts, perineum)	
Examine pressure points if patient is bed ridden	
Patient questionnaire	
Have you experienced any tingling, redness, rash, swelling, flaking, blisters, sores, cracks, or fissures in the palms of your hands or soles of your feet?	
Have any of these changes occurred in other parts of your body, such as your waistline, bra line, armpit, perineum, thighs, knees, heels, balls of feet etc?	
Have any of these changes to your skin been painful?	
Have any of these changes to your skin interfered with your normal activities?	
Have changes to the skin of your feet made walking uncomfortable or difficult?	
When did you first experience these symptoms and how did they develop?	
Have your symptoms resolved?	
How long did the symptoms take to resolve?	
Assessment and Plan:	
(Edwards 2003 p 29)	

Figure 2-1 PPE symptom assessment

The impact of PPE on the patient's quality of life is often underestimated. A valid and reliable tool to assess this impact would help health professionals to assess the effectiveness of treatments to relieve PPE and to make decisions on the appropriate actions to take when patients develop PPE. Sibaud et al

(2011) developed such a tool containing 14 items (HFS14) and tested its clinical validity by comparing its score to the NCI CTCAE criteria version 3 (2006). They also measured correlation with other know and validated tools which included the Dermatology Life Quality Index (DLQI); Skindex-16; short term 12 health-related questionnaires and pain measurement. They concluded that the HFS14 scale was easy to use and measured quality of life comparable to other tools, but needed further testing in longitudinal studies. Limitations of the study included small sample size (n = 43), gender imbalance (74% female) and lack of testing of other factors that may affect quality of life such as performance status and psychological well-being.

With the advent of more oral treatments, where the patient self administers the drugs and monitors their own side effects at home, assessing compliance and toxicity from a distance becomes a challenge. The role of the oncology nurse in ensuring the patient and their family understands how to take the drugs safely and the importance of recognising and reporting side effects immediately is more important than ever (Berg 2006).

2.10 Summary

In conclusion, although for most patients PPE is rarely serious, for a small number it can have serious consequences since it increases the risk of developing infection if neutropenic, amputation has been reported in a small number of cases and in circumstances such as DPD deficiency it can prove fatal. It is difficult to establish the true incidence of these serious consequences of PPE, since it relies on the reporting of single cases in the literature. Little attention in the literature was paid to this fairly common side effect until relatively recently and is generally only the subject of case reports, retrospective and small scale studies. The results of a few prospective trials are now emerging. While the theories of the pathophysiological mechanisms presented seem plausible, they are yet to be proven definitively. Age and gender as risk factors for PPE have been investigated in several large phase III studies of PPE causing agents and findings reported are contradictory.

Only small numbers of patients over 70 years old receiving 5FU or capecitabine have been studied thus far with no indication that this group has a higher incidence of PPE than younger patients. There is some evidence however that suggests that patients over the age of 80 receiving capecitabine have a high incidence of PPE and should be treated with caution. These older age groups require larger studies to establish the true incidence and impact of PPE. Another risk factor reported in a small number of studies is the association between performance status and PPE. This association is contradictory and has been reported in small samples only. Evidence is emerging to indicate that presentation of PPE varies between agents and ethnicity, particularly in people with dark skin. The incidence of PPE in people with dark skin may have been under reported in the past due to the symptoms not being diagnosed as PPE. The fact that severe PPE has been seen in patients following a reduction in dose would indicate that there are other factors rather than dose alone implicated in the development of PPE. The complexity in establishing these factors is that there is contradictory evidence; risk factors may vary for each family of anti-neoplastic agents; some are only subjectively reported and many have yet to be tested in patients receiving capecitabine. One factor that is gaining consensus in the use of capecitabine is the early onset of grade 1 PPE, which is associated with an increased risk of developing more severe PPE in later cycles. An interesting finding that has been reported in a few studies is that PPE may be a marker of efficacy of treatment. Larger studies of this finding are required to establish the reliability of this finding. Prevention and treatment of PPE is based on consensus, case reports and small scale studies and is often contradictory. There have been no large randomised controlled trials (RCTs) to test the effectiveness of emollients; steroids; celecoxib; cod liver oil; vitamin E; henna; nicotine patch or DMSO. Pyridoxine is the only preventative or treatment agent that has been subjected to analysis is several trials. The majority of these trials are case reports or small sample studies. However, the largest RCT of these studies reported no significant difference between the pyridoxine group and the placebo group to prevent or treat PPE. The one study that did show evidence in favour of high-dose pyridoxine also reported a poorer tumour

response. With the balance of the evidence and the unfavourable tumour response pyridoxine cannot be recommended to prevent or treat PPE.

There have been no studies to analyse patient activities such as exposure of the hands and feet to heat, friction and pressure as risk factors of PPE and there has yet been no attempt to develop and validate a PPE risk assessment tool. The advice given to patients receiving PPE causing agents is based on consensus rather than controlled trials. The current advice given to patients often results in them making changes to their lifestyle and temporary cessation of activities such as hobbies that they enjoy. These changes can impact on the patient's quality of life which may have already been affected by a diagnosis of cancer and the effects of treatment. Large trials to examine these activities rigorously would ensure that advice given is based on the best possible evidence.

The following chapter described the methodology used to collect and analyse data on these factors to make a unique contribution to the current body of knowledge on the subject of PPE.

CHAPTER 3 RESEARCH METHODOLOGY, STUDY DESIGN AND DATA COLLECTION METHODS

3.1 Introduction

The preceding chapter provided a systematic review of the literature. A deficit in knowledge, particularly related to the evidence to support advising patients to avoid certain activities to reduce the risk of PPE, was identified. This demonstrated a need to provide further insight into factors that increase the risk of developing PPE. This chapter describes how the research was conducted and presents the rationale for the choice of philosophical framework, study design and the analytical approach that was used throughout this systematic enquiry.

All research involving human subjects poses ethical dilemmas which must be considered during the research design and conduct of the study and these are clearly presented for the reader to examine. A note of importance is the tension that can occur when acting as researcher in ones own area of clinical practice. The chapter concludes by presenting limitations of the study design and methodology.

Research without theory does little to advance knowledge. Similarly, a study that lacks theoretical justification lacks substance. A theory is simply an interpretation of a phenomenon; it is not definitive and may be rejected or modified over time and there may even be competing theories to explain the same phenomenon (Parahoo 2006). A paradigm is a school of thought. Positivism is one such paradigm which has greatly influenced research in the health field. The most important characteristic of positivism is empiricism which implies that only what is observed can be called fact (Parahoo 2006). A theory must predict that each time the variables happen to be in the same relationship, the same results are obtained (Bowling 2002).

Quantitative research has its origins in positivism, maintaining that reality can be observed, measured and quantified in some way. This influences the questions posed, the type of data collected, how it is collected, analysed and interpreted (Seers & Critelton 2001). Although the purpose of quantitative research is to discover an answer to a particular problem, the link with previous knowledge is important to enable the researcher to learn from it and in return, contribute to it (Parahoo 2006). Without alluding to existing knowledge, the study and its findings will exist in isolation from other similar studies. A review of relevant literature and theories aided the decision of how to approach this study. The collection of data to support or refute hypotheses and data collection tools was based on existing literature. Analysis of the data collected in this study aimed to explain the relationship between variables that have been suggested in the literature to be linked with the development of PPE. This will result in the generation of a theoretical model containing risk factors for developing PPE. It is not possible within the confines of this study to test this theory as this would require further research. Since this study makes no attempt to intervene or change outcomes it can be defined as an observational or exploratory study. This is one of the two broad classes of quantitative research, the other being experimental studies which seek to intervene or alter care or treatment and consequently assess its effectiveness (Seers & Critelton 2001).

There was no intention in this study to qualitatively measure the impact of PPE on a participant's quality of life, physically or psychologically. Other studies have explored this and the primary intention in this study was to identify risk factors that predispose a patient to develop PPE.

In contrast to randomised controlled trials which can provide valid estimates of the underlying effect of the intervention being studied, surveys can only yield estimates of association, rather than whether one variable caused another, which may deviate from the true underlying relationships due to the effects of confounding variables (Bowling 2002). Methods to attempt to take into account these confounding variables will be discussed later.

Figure 3.1 summarises the research design applied to this study and is explained further in the following sections.

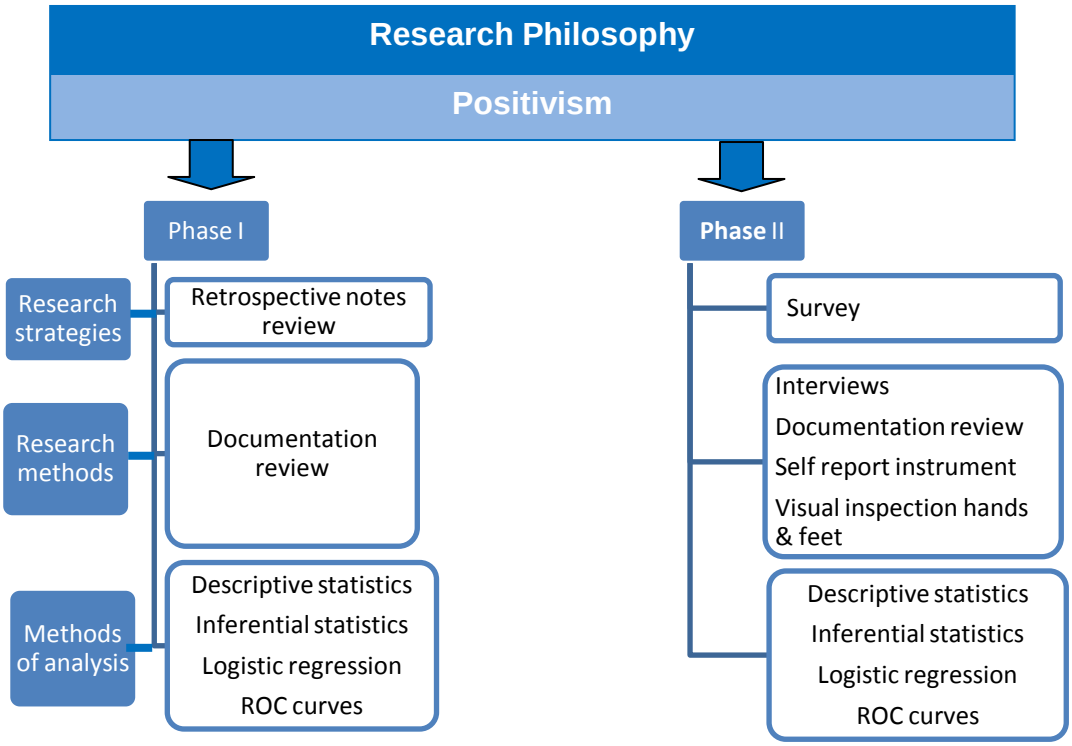


Figure 3-1 Research design

3.2 Research design

The study consists of two phases. Phase I is a retrospective notes review of patients who received infusional 5FU or capecitabine containing chemotherapy regimes over a one year period. The purpose was to establish which regime carried an increased risk of PPE to refine the sample selection for phase II. Participants in phase I were not included in the sample used in phase II thereby providing two independent samples to compare findings. The following sections will describe how the research was carried out in each phase followed by a rationale for the choice of data collection methods and statistical analysis.

3.2.1 Phase I - Retrospective notes review

A retrospective analysis of patients records, who had completed chemotherapy treatment (specified in the sample group) during the previous year formed the first phase of this study. Details of patients who had received the specified regimes were obtained from the oncology pharmacist. Data were collected using the medical notes data extraction form (Appendix 3.1) and included; tumour-related information; patient demographic and social data; co-morbidities; laboratory results; chemotherapy regime information and toxicities developed as a result of the chemotherapy. Toxicities were graded using the NCI CTCAE (version 3.0 2006) except for PPE which was graded according to the capecitabine clinical trial criteria (Blum et al 1999) (Figure 3.2).

Grade	Clinical domain	Functional domain
1	Numbness, dysesthesia/ paraesthesia, tingling, painless swelling or erythema	Discomfort that does not disrupt normal activities
2	Painful erythema, with swelling	Discomfort that affects activities of daily living
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living

Figure 3-2 Capecitabine Clinical Trials toxicity criteria (Blum et al 1999)

3.2.1.1 Sample selection and sample size estimation

The sample was taken from patients who had received oxaliplatin and infusional 5-FU (folfox) or capecitabine containing regimes, since infusional 5FU and capecitabine have been reported to have a high incidence of PPE. Details provided by the oncology pharmacist of patients who had received these regimes between April 2008 and March 2009 provided a potential sample of 415. However, due to difficulties locating several sets of notes and excluding those patients who received only 1 cycle of chemotherapy (unless stopped due to PPE) resulted in an actual sample size of 392 (n=145 folfox and n=247 capecitabine containing regimes).

As data were collected from participants receiving different chemotherapy regimes, the data were analysed as a whole sample and by chemotherapy agent (infusional 5FU, capecitabine containing regimes and capecitabine monotherapy) to ascertain whether there were any differences in risk factors between those regimes.

The widely accepted 80% power estimation (Munro 2005), an effect size of 0.3 (medium) and the significance level of 0.05 were used in this study and sample size estimated using G* Power version 3.1 priori analysis program (Faul et al 2007). A sample size of 108 participants was determined for a bivariate analysis. The actual size used was 392 in the retrospective sample as this represented all participants who received either capecitabine containing regimes or oxaliplatin and infusional 5FU and would enable a focus to be placed on one regime if this proved necessary. The capecitabine monotherapy sample from the retrospective data (n = 151) exceeded the 108 required to achieve 80% power in a bivariate analysis. Post hoc G* Power analysis of the capecitabine monotherapy sample from the retrospective data using the same parameters as above with n = 151 provided a power of 72% in a multivariate regression analysis.

3.2.1.2 Process of data analysis

To answer the research question;
Can risk factors of PPE be identified to predict the development of PPE?
The null hypothesis (H_0) for each variable was statistically tested. 31 variables were tested in this retrospective sample (table 3.1)

Variables tested in phase I retrospective sample			
Gender	Peripheral neuropathy	Aim of treatment	CrCl
Marital status	Skin conditions	Tumour type	ALT
Ethnicity	Inflammatory diseases	Recent weight loss	ALP
Employment	Previous cancer diagnosis	Start season	Bilirubin
Smoker	Metastatic spread	Age	Albumin
Alcohol	PPE with previous chemotherapy	BSA	Performance status
Diabetes	Previous radiotherapy	BMI	Other capecitabine-induced toxicities
PVD	Regime	Creatinine	

Table 3-1 Variables tested in phase I

Note: Inflammatory conditions are defined as a range of immune system disorders and include asthma; coeliac disease; rheumatoid arthritis; inflammatory bowel disorder; pelvic inflammatory disease and vasculitis.

Coding of data

The dependent variable being dichotomous was coded 0 and 1 with the category of most importance to the research question taking the coding of 1 (Marston 2010). In this study participants who developed PPE were coded 1 since the research question is to identify factors that may increase the risk of developing this condition. The Coding for all other variables is detailed in Appendix 3.2.

Data cleaning

The data were checked for errors following input into SPSS through examining frequencies for each variable and spurious data checked against the original forms and corrected if an error found. A random sample of 10% was subsequently generated in SPSS 16.0, 17.0 & 18.0 (IBM SPSS Chicago 2008, 2009 & 2010) and checked against the original forms and corrections made if necessary.

Statistical testing

Various statistic tests were applied to the data. Firstly each variable was tested in a bivariate analysis with the dependent factor PPE. Secondly the variables that reached statistical significance in the bivariate analysis were entered into a logistic regression model using various entry methods. Finally the various models from the logistic regression were entered into receiver operating characteristics (ROC) curves. Each of these stages will now be described further and the rationale for choice of the statistical tests will follow in section 3.5

Descriptive statistics were first employed to explain frequencies, measure of central tendency (mean, mode and median), dispersion of personal & demographic characteristics and to check for any skewness of the data. The distributions identified any variables that required recoding or collapsing into fewer categories and the variables that had sufficient spread of responses for them to be analysed with bivariate statistical tests (Bowling 2002).

Bivariate tests

Frequency, severity, clinical course and consequences of PPE were determined by descriptive statistics. Between group differences were assessed using the chi-square (χ^2) test for categorical data and independent-samples *t*-test for continuous data. The α value $p < .05$, 2-tailed for all tests was used throughout this bivariate analysis to answer the question of whether there is a difference between the groups and the outcome measure in either direction (Bland 1995).

Since the aim of this study is to identify factors other than the drug itself that may influence the development of PPE, the sample used for inferential statistical analysis was restricted to those who developed PPE within the first 3 cycles and those who did not develop it, based on the assumption that PPE developing in later cycles is more likely to be due to accumulation of the drug.

This assumption is supported by Lipworth et al (2009) who stated that studies show that nearly all cases of PPE occur within the first two or three cycles of capecitabine, thus suggesting that the total cumulative dose does not affect the incidence of PPE. Each grade of PPE was analysed separately because they carry a different clinical significance and treatment decision for subsequent doses, a recommendation made by Heo et al (2004).

Variables significant by bivariate analysis were further tested by multivariate logistic regression to seek to examine any relationship between variables and the nature of that relationship with the aim to make predictions (Parahoo 2006). The criteria for selection and retention of variables into the logistic regression are explained next.

Multivariate logistic regression - Modelling technique used

The following stages describe the method used for the manual purposeful selection of variables for inclusion and retention in the chosen model;

1. A bivariate model was fitted to each variable
2. Variables achieving $p < .25$ in the bivariate analysis were entered into the model and the logistic regression test applied
3. Variables achieving $p < .1$ were retained as significant and the variable with the largest p value above .1 then removed.

   Rather than removing all non-significant variables at once it is sensible to remove the variable with the largest p value and refit the model. This is because when one variable is removed from a model, the significance of those left in the model changes. This process is repeated until all variables in the model are significant at $p < .1$ (Marston 2010). For assessing whether a variable is significant overall in the model, the overall significance of the variable is more important than the significance of individual categories within the variable (Marston 2010). The reference category within each variable provides the overall significance of

the variable and it was this figure that was used to assess the significance level.

4. The β coefficient value for each variable was imported into excel and the percentage difference between the current step in the model and the previous one calculated
5. If this difference was greater than 20% for any variable remaining in the model, the *p* value of that variable was then examined and the following rules applied
    a. If the *p* value became < .1 when previously > .1 the variable that had been removed was returned to the model as a confounder
    b. If the *p* value remained < .1 the variable that had been removed was returned to the model as a confounder
    c. If the *p* value became > .1 when previously < .1the variable that had been removed was returned to the model as a confounder
    d. If the *p* value remained > .1 the variable that was removed was left out of the model
6. Stages 3 – 5 were repeated until only variables that had a *p* value of < .1 or confounders were left
7. This same model was then re-run using the forward and backward entry methods to make comparisons with the purposeful entry and retention model, to see if indeed the analyst selects a richer model compared with the computer which has no idea of the theory which determines the importance of each variable.
8. Variables that were not originally included into the model (*p* > .25 in the bivariate tests) were added one at a time and logistic regression applied. Any where the *p* value became < .25 were then entered into the model from stage 6 and the model reduced as before. Although these variables have no effect on PPE incidence they may have an effect with a group of variables, as logistic regression analysis shows those variables that best explain the occurrence of PPE (Marston 2010).

Figure 3.3 presents this model diagrammatically.

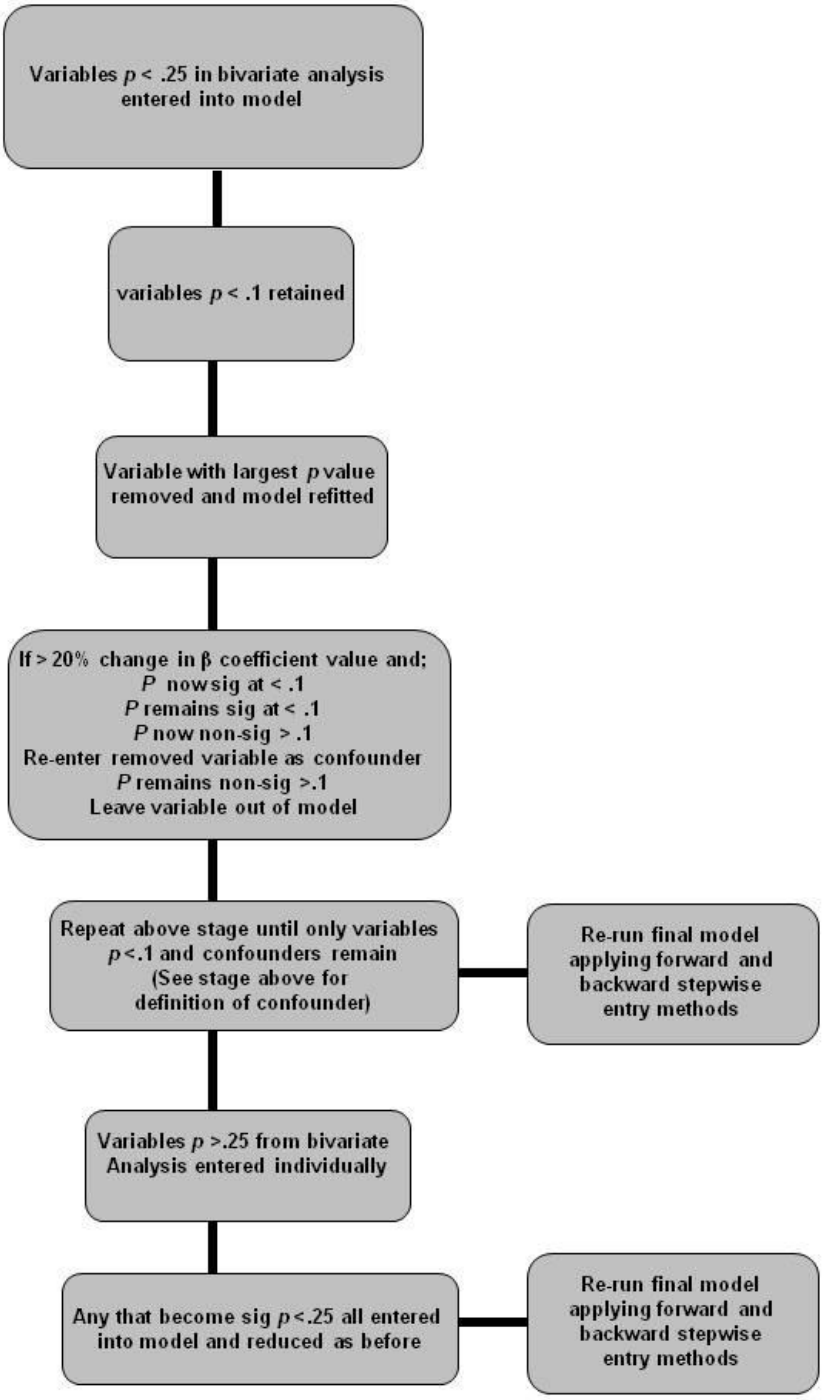


Figure 3-3 Algorithm for selection and retention of variables in logistic regression models

Once a model has been generated the question of whether it can be generalised to other samples is asked. If assumptions have been broken, accurate conclusions cannot be drawn from the model. However, even if the assumptions are met the belief that the model from the sample will be the same as the population from which the sample was drawn is questionable but the likelihood of this is increased. Cross-validation could be used to assess how well the model can predict the outcome in a different sample (Field 2005). In this study this was possible by comparing the model using cases from the retrospective notes review that had received capecitabine monotherapy with the prospective data. The results of this are presented in chapter 4.

Receiver operating characteristic (ROC) curve

Once all logistic regression models were completed the predictive values of each was calculated in SPSS. A ROC curve was created to compare the purposeful, forward and backward entry models and to compare the purposeful entry model with the same model containing additional variables as described in step 8 above. The area under the curve was examined to establish which model best predicted which combination of variables were more likely to increase the risk of developing PPE.

3.2.2 Phase II - Survey

Mixed strategies to collect data were used within the semi-structured interviews. These strategies included an interview schedule, documentation review, a self reporting instrument (symptom record) and visual inspection of the participant's hands and feet.

Pilot study

A pilot study is a smaller version of the study being proposed. Its purpose is to discover any problems with the data collection tools and the ability of the data to answer the research question(s) (Burns and Grove 1999). Any problems identified would enable the tools to be refined prior to undertaking the actual study.

Subjects used in the pilot study are not normally reused again in the actual study, since it may have an effect on these subjects during the study (Brink & Wood 1998). This is true in studies involving direct contact with participants; however, due to the retrospective nature of phase I, participants involved in the pilot study could also be included in the actual study without exerting any effect.

The data collection tool used in phase 2 was tested on 6 participants to assess ease and ability to collect the data required. No amendments were made following this pilot. The tool was tested on participants who received capecitabine monotherapy treatment prior to commencing treatment and when attending to receive cycle 2 of their treatment, to ensure the subjects chosen for the pilot test resembled the sample tested during phase 2 of the actual study (de Vaus 2002). In this phase, since direct contact was made with the participants, those used for the pilot study were not included in the actual study.

The symptom record and the participant information sheet were developed in conjunction with two patients who have received chemotherapy in the past to check that they were written in a patient friendly language. Interestingly, both of these patients contacted me at the hospital after reading about the planned research in the local newspaper.

Semi-structured interviews

Each participant was interviewed prior to commencement of their treatment and at each subsequent visit for 6 cycles of treatment. These participants attended for a planned hospital appointment at the time of each interview and much of the data collected are routinely asked as part of the usual chemotherapy process. Every attempt was made to ask the additional questions while the patient was waiting either to see their doctor or to receive their treatment, thereby keeping any inconvenience to a minimum.

The interviews were conducted in a private room in the clinical area to maintain privacy and confidentiality. The interview schedule (appendix 3.3) was designed to collect the same data as the data extraction form used in phase I. In addition other factors identified in the literature that may influence the development of PPE were included. These included patient characteristics such as skin type or activities such as those causing friction to the hands or feet. These factors could not be collected in phase I since they were not recorded nor routinely asked. Demographic, tumour-related information, chemotherapy regime and laboratory data were extracted from the patient's medical records and recorded on the interview schedule.

Attrition from this study due to drug toxicity or disease progression is unavoidable and details of this will be presented in chapter 4. There was the possibility of attrition if the participant was inconvenienced due to the interviews or if they felt uncomfortable in their relationship with the interviewer. This did not occur during the study, in fact, one patient who had initially declined to participate, later requested recruitment to the study once he developed PPE. Other patients recruited to the study went above and beyond what was asked of them; they rang the researcher between cycles to report symptoms of PPE and even photographed their own feet and/or hands and provided the researcher with copies at their next visit.

Self report instrument (symptom record)

A structured self report instrument (appendix 3.4) was designed to collect data between visits to hospital. The purpose of this instrument was to ascertain whether the participant developed PPE or other toxicities which had resolved prior to attending hospital to begin the next cycle of capecitabine. A few months after the start of phase II, the clinical area introduced the use of patient diaries produced by the drug manufacturer which collected the same data as the self report instrument designed for this study. The latter was therefore abandoned to avoid duplication and data were taken from the manufacturer's diary.

As with any diary, completion varied ranging from those that kept no records to those who kept very detailed accounts of what occurred between cycles. Approximately 50% of the participants maintained the symptom record or manufacturer's diary and although this did not affect collection of data about the incidence of toxicities, since participants were interviewed at each visit, the collection of the precise timing and frequency of some toxicities proved more difficult as it relied upon the participant's recall of the previous three weeks. This did not affect the findings of this study; rather it added a richness to the information provided by those who did maintain records.

Data obtained from these self report instruments or diaries was transferred to the interview schedule at each visit and therefore not reported separately in chapter 4. If a patient did not complete the self report instrument or diary they were questioned on the development of any toxicities between cycles.

Visual inspection of hands and feet

Participant's hands and feet were inspected at each visit to assess for signs of PPE. If any signs or symptoms were experienced they were grade according to the capecitabine clinical trials toxicity criteria (Blum et al 1999) and recorded on the interview schedule. Photographic evidence was taken with

the participant's permission for use to illustrate the variety of presentations of PPE.

3.2.2.1 Sample selection and sample size estimation

Based on the findings from phase I, the study design was refined and the prospective sample was restricted to participants receiving capecitabine monotherapy. This enabled comparison between the retrospective and prospective data and possible validation of the findings from the retrospective sample.

Population sampling was the method of choice for this phase of the study. All patients prior to commencing capecitabine monotherapy between 11th June 2009 and 31st December 2010, were offered recruitment into the study and followed for 6 cycles of treatment. The rationale for this sampling method is that each group should be representative of the total population in terms of age, gender and ethnicity. Since PPE most commonly occurs within the first 6 cycles of the treatment, it was not felt necessary to gather data beyond this point.

Details of patients commencing treatment were identified from the 'new case' diary (a diary of dates and times when a patient will attend for a nurse-led education and information session prior to commencing chemotherapy) or from the consultants clinic lists.

Patients attended a pre-chemotherapy nurse assessment clinic where they were provided with information and education about their proposed treatment. Each patient was given an information sheet, (appendix 3.5), by the chemotherapy nurse, about the study which also contained an invitation to participate. During the patient's visit to receive their first treatment cycle they were asked by the researcher if they wished to participate in the study and if they agreed, consent was taken (appendix 3.6), the first part of the interview schedule completed, and a symptom record booklet issued to participants.

Since individuals were now participants in the study, this term will be used from this point forward

Exclusion criteria included those participants who did not wish to participate and those who were unable to speak English where an interpreter was not available. Since the data being collected was not of a sensitive nature, family members could be used to interpret. Four patients declined but there were no patients excluded because of language difficulties. The reason for declining was that participants felt they had too much going on in their lives at present without an additional meeting with another health care professional.

The widely accepted 80% power estimation (Munro 2005), an effect size of 0.3 (medium) and the significance level of 0.05 were used in this study and sample size estimated using G* Power version 3.1 priori analysis program (Faul et al 2007). As in phase I the sample size of 108 participants was determined for a bivariate analysis. The actual size used was 125 in this sample. Post hoc G* Power analysis of the sample using the same parameters as above with n = 125 provided a power of 65% in a multivariate regression analysis.

Unfortunately due to changes in circumstances of the researcher's role within the trust it was not possible to collect further data to increase the size of the prospective sample.

3.2.2.2 Process of data analysis

To answer the research questions;
Can risk factors of PPE be identified to predict the development of PPE?
Do individual patient activities that cause friction or exposure to heat increase the risk of developing PPE?

The null hypothesis (H_0) for each variable was statistically tested. 41 variables were tested in this sample (table 3.2)

Variables tested in phase II retrospective sample			
Gender	Previous cancer diagnosis	BMI	Hot water
Marital status	Metastatic spread	Creatinine	Dry skin
Ethnicity	PPE with previous chemotherapy	CrCl	Cool hands
Employment	Previous radiotherapy	ALT	Cool feet
Smoker	Regime	ALP	Sweaty hands
Alcohol	Aim of treatment	Bilirubin	Sweaty feet
Diabetes	Tumour type	Albumin	Hand cream
PVD	Recent weight loss	Performance status	Skin type
Peripheral neuropathy	Start season	Other capecitabine-induced toxicities	
Skin conditions	Age	Sunburn	
Inflammatory diseases	BSA	Hobbies	

Table 3-2 Variables tested in phase II

Note: Inflammatory conditions are defined as a range of immune system disorders and include asthma; coeliac disease; rheumatoid arthritis; inflammatory bowel disorder; pelvic inflammatory disease and vasculitis.

The data gathered during phase II was subjected to the same coding and data cleaning process as described in section 3.2.1.2 for phase I of this study.

The various statistic tests applied to the data from phase I were repeated in phase II. Firstly each variable was tested in a bivariate analysis with the dependent factor PPE. Secondly the variables that reached statistical significance in the bivariate analysis were entered into a logistic regression model using various entry methods. Finally the various models from the logistic regression were entered into receiver operating characteristics (ROC) curves. Each of these stages was described in section 3.2.1.2

Data storage

A patient identification sticker was placed on the front sheet of the interview schedule to ensure the correct patient record was used at each visit to

prevent any patient data being mixed up. This front sheet was shredded after the data collection phase. Each patient was allocated a trial number which was used to anonymise data during the analysis stage. No identifiable data was accessed by individuals outside of the direct healthcare team during the study.

Data was stored on both a computer within the trust and on a memory stick as backup. The computer and memory stick that was used to store identifiable data have been encrypted and are therefore password protected and only accessible by the principal investigator. All identifiable material will be destroyed at the end of the study and only unidentifiable data will be archived in a secure office at the trust.

3.3 Issues of the researcher and clinician in practice

There are potential tensions that may exist when acting as a researcher in ones own area of clinical practice (Orb et al 2001). Since this is important in the context of phase II of this study this issue will be addressed here separately. The researcher as service provider is referred to as insider-research and has unique challenges and ethical dilemmas to consider.

The identification of the researcher as a nurse may influence the researcher-participant interaction and quality of data shared. This may depend upon the participant's perception of a nurse and previous experiences (Jack 2008). It could be argued that it is important for a nurse to become close to research participants to extract rich data (Wilkes & Beale 2005). Conversely one may elicit less information as participants feel coerced to participate and may limit information given (Orb et al 2001).

Power imbalance can add an extra layer of complexity when the researcher interviews their own patients, who may feel compelled to participate or risk jeopardizing the care or treatment they are receiving (Jack 2008, Johnson & Long 2010). A noncoercive disclaimer would include the elements of voluntary

participation; confidentiality; freedom to withdraw (Fouka & Mantzorou 2011) and informed consent (Daugherty 1999). The invitation to participate in the study was administered by the chemotherapy nurse running the pre-chemotherapy assessment clinic and not the researcher to prevent any possible coercion. Participation was voluntary, confidentiality was explained in the patient information sheet and all participants were free to withdraw without giving a reason. Informed consent was taken by the researcher and participants were given the opportunity to decline any stage of the study design, for example having photographs taken of their hands or feet. Others suggest that to avoid coercion the researcher should avoid direct contact with the participants when recruiting or interviewing (Yanos & Ziedonis 2006). The process of recruitment has been described above, but the interviewing was carried out by the researcher since it was not possible for anyone else to carry this out due to funding and workload issues. Yanos & Ziedonis (2006) equally state that it is possible to integrate the roles of clinician and researcher to develop a moral identity which promotes good ethical judgement. The key is to be aware of the possibility of exploitation and develop a relationship with participants that reduce the possibility of misconceptions of the role of researcher.

Intervention made during the interview may affect the validity an objectivity of the data (Jack 2008) and some authors suggest that intervention should only occur if the participant is in a state of anxiety or in life-threatening situations (Cartwright & Limandi 1997). Although, standing by and not providing care or interventions is incongruent with the culture of nursing, which is the ethic of caring (Fouka & Mantzorou 2011). The nurse as a researcher needs to consider their own and others expectations, of whether they should sometimes act as a nurse and provide care or always remain as the researcher (Wilkes & Beale 2005).

Strategies to address this include acknowledging requests for information but not addressing them until the end of the interview and referring to another health care professional if an intervention is required (Jack 2008).

An insider-researcher is in a prime position to investigate and encourage others to take the results of research seriously and to make changes in practice (Yanos & Ziedonis 2006). This type of researcher is in the unique situation of understanding the complexities of the work area, and how to navigate through these. Organisational, professional and personal contexts may influence the way a piece of research is undertaken. An additional dimension is the influence of the educational institute if undertaking the research as part of a programme of study (Costley et al 2010).

There is no absolute answer to the issue of the influence the clinician as researcher may have on participants. This should be reflected upon, rather than ignored (Jack 2008). It is not intrinsically unethical in finding oneself in a conflict of interest, the key question is whether the clinician/researcher recognizes this and how it is dealt with (Lemmens & Singer 1998).

It is a crucial role of the local research ethics committee to mediate between these conflicting interests (Kent 1997). The local ethics committee and the local R & D team at the trust were satisfied with the processes involved in conducting this research study. Neither of these bodies requested any guidelines prior to commencing the study to address any potential conflicts, therefore none were developed.

During the interviews there was no apparent evidence that any of the participants felt uncomfortable talking to the researcher. Many participants asked the receptionist of the chemotherapy suite to inform the researcher that they had arrived to ensure the opportunity was not missed to collect data. As a nurse some interventions were carried out, others were referred to more appropriate health care professionals. It was not apparent that this unduly influenced participation in the research, rather created a relationship which allowed rich data to be collected which occurs when the participant feels confident in the researcher.

3.4 Rationale for research design

Having described each stage of the data collection and analysis processes, the rationale for these is presented in this section.

3.4.1 Phase I. Retrospective notes review

Retrospective studies seek to understand the phenomenon as embedded in that particular period of history. It is a relatively inexpensive method of surveying a large number of people quickly and the data can be easily coded. The main disadvantages are that the researcher has to rely upon existing data that was not collected with the same rigor with which prospective research is carried out. Records may also be incomplete or difficult to decipher (Parahoo 2006, McKenna et al 2010). Despite these reservations it was felt that this method would provide a simple method to obtain a sample and data that would help to identify an appropriate sample for phase II and for comparison and validation of results between the two sample.

3.4.2 Phase II Survey

Prospective surveys occur over the forward passage of time, often with more than one episode of data collection and seek to explore what is likely to happen or the outcome of an event. Prospective studies can be expensive and consume a great deal of time and often have a high attrition rate (McKenna et al 2010). Other potential effects of a prospective survey that the researcher needed to consider were that participants may become ‘conditioned’ to the study. That is they learn the responses that they think are expected of them (McKenna et al 2010). In addition, there is the ‘Hawthorne effect’, a reactive effect of the study where people change their behaviour simply because they are being studied (Roethlisberger & Dickson 1939). It was not evident that responses were learned or that behaviour changed as a result of the research. Each participant openly revealed and described how they had felt between each cycle which was different for each individual and the only behaviours that changed were as a result of the discomfort caused by

the PPE or the treatment provided to relieve the symptoms, for example, the regular use of emollients. The strengths and weaknesses of face-to-face interviews are presented in table 3.3.

There are many factors to consider when conducting interviews; the development of an appropriate interview schedule; the environment where it occurs; the questioning and listening abilities of the interviewers; and managing the interview (Tod 2010). The interviews conducted within this study took place in a private room in the clinical area to maintain privacy and confidentiality. The interview schedule was formulated based on factors that may influence the development of PPE identified in the literature and from discussions with clinical experts. Since the qualities and training of interviewers are essential for the reliability and validity of the survey results, (Bowling 2002) training would have been provided to all data collection personnel by the principal investigator. However, due to staffing shortages and workload it was not possible for the specialist chemotherapy sisters to assist in the data collection as initially thought. Therefore the data were collected by a single interviewer, namely the principal investigator.

STRENGTHS	WEAKNESSES
➢ Can generate a large volume of data from a large sample (Tod 2010) ➢ Longer and more complex questions are possible (McKenna et al 2010, Tod 2010) ➢ High response rates (McKenna et al 2010) ➢ No literacy requirements for respondents (Tod 2010) ➢ Facilitates cooperation from research subject (McKenna et al 2010) ➢ Can use visual materials e.g. show cards (McKenna et al 2010) ➢ Provides additional opportunities to clarify questions and responses (Hughes 2002, McKenna et al 2010) ➢ Inconsistencies and misinterpretations can be checked (Bowling 2002) ➢ Ability to observe body language and have eye contact to aid in interpretation of what is being said (Hughes 2002) ➢ Enables the interviewer to ensure data are being collected from the correct sample (McKenna et al 2010)	➢ Costly due to time-intensive nature (McKenna et al 2010) ➢ Interviewee is not anonymous (McKenna et al 2010) ➢ Can be subject to interviewer bias (Bowling 2002) ➢ May be additional bias if interpreters are used (Tod 2010) ➢ Data are open to misinterpretation due to cultural differences (Hughes 2002) ➢ Difficult to replicate(Hughes 2002) ➢ Data are often subject to observer effect (Hughes 2002, Tod 2010) Many of the weaknesses are linked to accounts of people's subjective experiences

Table 3-3 Strengths and weaknesses of face-to-face interviews

3.4.2.1 Symptom record

The strength of self-report techniques is that they can yield information that would be difficult to obtain by other means such as feelings, retrospective activities and events. Their main weakness lies in the questionable validity and accuracy of self reports (Polit et al 2001, Parahoo 2006).

3.5 Rationale for data analysis methods

The research study generated a large amount of data which were analysed using parametric (χ^2) and nonparametric tests (*t* –test) to identify factors that are significant in patients who develop PPE. Data were initially analysed using bivariate descriptive and inferential statistical techniques. This gathered information on the frequency of occurrence of the categories of each single

variable for the purpose of description and testing of significance of each variable for the development PPE (Polit et al 2001, Parahoo 2006). Items which occurred at a specified significance level (as described in section 3.2.1.2 and figure 3.3) were then further analysed using multivariate statistical techniques (logistic regression and ROC curves) to analyse and infer relationships among three or more variables (Cormack 2000, Polit et al 2001, Parahoo 2006).

The descriptive part of the study obtained data from the sample regarding the incidence and distribution of variables, whereas the analytical/correlational part investigated associations between variables (Bowling 2002, Parahoo 2006). The rationale for multiple testing of data was firstly to test for any association between each individual variable and the development of PPE. This would allow comparison with findings in the literature. It would also establish those variables which achieved statistical significance to include in combination in the logistic regression model. Manual and automatic methods of entry and retention of variables into the regression model were employed to identify which method produced the most favourable model to predict the development of PPE (McNames 2005).

Caution should be used in the clinical importance placed on the meaning of the α value $p < .05$. A 'significant' value purely means that the results are not likely to be due to chance i.e. at $p < .05$, 5 times out of a 100 a true H_o would be rejected (type I error). Conversely a 'non-significant' value means that the difference is probably due to chance (Polit et al 2001, Munro 2005).

3.5.1 Sample size

The power of a statistical test is the probability that the null hypothesis (H_o) will be rejected given that it is in fact false. Significance tests that lack statistical power are questionable in their usefulness because they cannot reliably distinguish between (H_o) and the alternative hypothesis (H_1) of interest (Faul et al 2007). A priori power analysis is where the sample size (n) is

computed before the study begins using the 3 requirements for estimating sample size as defined by Cohen (1988); the power level required (1 – *β*); the prespecified significance level (*α* – the risk of type I error falsely rejecting a H_o when it is in fact true) and the population effect size.

Cohen's (1988) definition of effect size;
Small = 0.10
Medium = 0.30
Large = 0.50

3.5.2 Hypothesis testing

A scientific hypothesis (H_1) is one that states that there is a relationship between *X* and *Y*, conversely a null hypothesis (H_o) states that there is no relationship between *X* and *Y*. The process of testing the hypothesis statistically is one of disproof or rejection, since; proving that the H_1 is true is not possible. However, it is possible to demonstrate that the H_o has a high possibility of being incorrect, which provides evidence to lend support to the H_1. (Polit et al 2001). It is through statistical tests that the researcher then sets out to reject the H_o.

3.5.3 Bivariate analysis

3.5.3.1 Chi square (χ^2) test

Chi square (χ^2) test is used to make inferences about the existence of significant relationships between the group variable and the incidence of PPE. PPE was at the nominal level of 1 for the presence of PPE and 0 for its absence; this implies that the χ^2 test can be used to answer the core questions of this study concerning whether there is a significant effect for the group variable on PPE incidence. Of those nominal variables examined by the χ^2 test of independence, the association between variables was tested by

descriptive cross-tabulation. The group or incidence variable was entered in rows and the recorded variables were entered in columns, and expected and observed counts were indicated. Pearson (or Yates's correction for 2 x 2 tables) χ^2 value, *d.f* (degrees of freedom) and *p* value were calculated to decide the level of statistical significance of the association between variables.

The effect size (a measure of the strength and direction of the relationship between two variables) for variables with a statistically significant association with PPE is presented.

For two by two contingency tables in the χ^2 test, effect size is interpreted according to Cohen (1988) criteria where;
0.10 = small effect size
0.30 = medium effect size
0.50 = large effect size

For tables larger than two by two, Cramer's V is used and varies dependent on the degrees of freedom;

For 3 categories within a variable;
0.07 = small effect size
0.21 = medium effect size
0.35 = large effect size

For 4 or more categories within a variable;
0.06 = small effect size
0.17 = medium effect size
0.29 = large effect size

Assumptions;

1. Data are frequency data i.e. counts and categorical (nominal). Ordinal data will need to be categorized with a sound rationale for

doing so for example if the data are not normally distributed. An adequate sample for cross tabulation is one that ensures that no cell is empty and there should be > 5 participants in each expected count cell. If < 5 in any of these cells collapsing data to merge categories may be a solution.

2. Measures should be independent of each other. That is that a subject cannot appear in more than one cell or be used more than once.
3. There should be a theoretical reason for the categories

(Munro 2005)

These assumptions were met through categorizing some ordinal data or collapsing variables into fewer categories where there were counts of less than 5 in any cell. It is acknowledged that categorising a continuous variable may reduce the amount of information available, and that the statistical testing of this data may be less sensitive (less power). The choice of cut off points can lead to different conclusions about a set of data (Swinscow & Campbell 2002). The cut off points selected in this study reflect those used in other studies for example Creatinine clearance (CrClC1) was categorized using the same parameters as Poole et al (2002).

3.5.3.2 Independent-samples t-test for independent groups

Independent samples t-test for independent groups are used to compare the mean scores, of continuous variables for two different groups of people (Pallant 2007). In this study it is used to compare the mean scores of age and laboratory values (continuous dependent variables) in patients who developed PPE and those who did not (categorical independent variable).

The *t* value, *d.f* and *p* value were calculated to show any statistically significant differences in the mean scores of the two groups, and the mean

difference to show the magnitude of the differences in the means (Pallant 2007).

The effect size for continuous variables using eta-squared in the *t*-test is interpreted according to Cohen (1988);
0.01 = small effect size
0.06 = medium effect size
0.14 = large effect size

Assumptions

1. Data should be normally distributed, however, with larger samples; major problems will not occur if this assumption is violated.
2. The variances of the two groups are equal, although in reality this is not always possible and SPSS provides an alternative *t*-value that compensates for variances that are not equal
3. Data should be from different participants

(Pallant 2007, Marston 2010)

These assumptions were met with data close to normal distribution and with similar variances and from different participants. Normal distribution was tested by producing histograms of the frequencies with the normal distribution curve included for each set of data.

3.5.4 Multivariate analysis

Multivariate tests are used to understand the complex relationship between variables.

3.5.4.1 Logistic regression & Modelling

When a result from previous statistical tests is accepted as significant, it does not mean a causal relationship has been established. There is still more to do to make the argument secure. Establishing whether an apparently causal or

predictive relationship is statistically significant is only the first stage of the argument. The researcher still has to ascertain that it is this independent variable and not some other which is also associated, that produces the effect. To do this the following information is required;

1. Which of the influences are strong and which are weak
2. To what extent the different independent variables are 'independent' influences (or on the other hand, how much their influence overlaps)
3. Whether there are interaction effects (whether the influence of two or more variables together is different from what would be predicted by any one alone)

In the real world we are often comparing groups which differ in a number of elements. When design controls are not used, multivariate analysis techniques are employed for statistical control of these 'unwanted' differences and to show;

1. Whether the effects of extraneous variables are larger than those of the influence(s) being studied
2. Whether they are confounded by them (examined later)
3. Whether they interact with them

(Sapsford & Jupp 2006)

Logistic regression is a statistical modelling technique to investigate relationships between independent variables and a dichotomous dependent variable (in this study PPE) from which to produce a predictive model containing variables that best explain the occurrence of PPE. The goal being to ascertain if the variables used were important in the population being served by the clinical area from which the data were collected. Results are presented as a series of summary statistics including, for each individual predictor; its significance; coefficient estimation (β); and odds ratio (OR). The Beta coefficient is an estimate of the nature of the relationship of each variable to the prediction, controlling the overlap with all the other variables in the model. The larger this is, the larger the effect of that particular

independent variable on the dependent variable. The odds ratio lends interpretability to the data and is a factor by which the ratio of odds of an event for those with a given characteristic is measured against the odds of an event for those without. It approximates how much more likely (or unlikely) it is for the outcome to be present given certain conditions and used to determine which variables affect the probability of a particular outcome. For continuous independent variables the OR is given for a 1 unit of change in the predictor variable. Unlike the mean the OR does not fall in the middle of the confidence interval. (Munro 2005, Sapsford & Jupp 2006, Marston 2010).

Assessing the 'goodness of fit' of the model describes how well it fits a set of observations (variables). It is important to test the extent to which the model fits the data, since if a model is a poor fit of the observed data then it follows that predictions made from the model will also be poor (Field 2005). The Hosmer-Lemeshow test can be applied to any number of variables whether they are continuous or categorical and compares the values predicted (expected) by the model with those actually observed (Bewick et al 2005). Since the Hosmer-Lemeshow statistic is a test of the null hypothesis that the model is good, a *p* value of > .05 indicates a good fit and the null hypothesis that there is no difference between the observed and predicted (by the model) values can be accepted (Brake et al 2006). Caution should be applied when using this test as it is dependent on sample size and is not recommended for small samples (Chan 2004).

Cox and Snell and Nagelkerke (an adjusted version of Cox & Snell R^2) R square are used not to measure the goodness of fit but to measure usefulness of the predictor variables in predicting the response variable or as a measure of effect size (Bewick et al 2005). Or put another way it is the proportion of variability in a data set that is accounted for by the statistical model. It provides a measure of how well future outcomes are likely to be predicted by the model. R squared is the relative predictive power of a model with a descriptive measure between 0 and 1. The closer the value is to 1, the greater the ability of the model to predict the values of the variables within the

model. These are pseudo correlations, that is, not actual correlations but measures designed to emulate correlations. There is no agreed best measure and can be difficult to interpret. They may, however, be helpful in the model building state as a statistic to evaluate competing models. Hence the reason for reporting them (Hosmer & Lemeshow 2000). Since there is no agreed best method, the Nagelkerke figure will be reported within this study.

The classification table in the logistic regression helps to measure the ability of the model to correctly predict which category each case fits into by cross tabulation of the observed response categories with the predicted response categories.

Assumptions used in multivariate modelling procedures are more restrictive than bivariate analysis and if any of these assumptions are incorrect, the results may be seriously compromised. One solution to this problem is to fit a whole family of models to compare the conclusions or to validate the model results (Greenland 1989). Hence, the rationale for applying different entry methods to the same variables to establish whether different conclusions are reached with different modelling approaches.

Assumptions

1. Sample size and number of predictors must be considered. A large number of predictors, particularly if categorical with a small sample size can be problematic.
2. There should be no correlation between variables. Multicollinearity diagnostic tests can be applied to data to check for high intercorrelations among the predictor variables and if found one of the variables should be removed.
3. Outliers may affect the goodness of fit of the model and should be inspected for any where the model predicts that a case fits into one category where in reality it should be classified in the other.

(Pallant 2007)

To ensure these assumptions were met, the problem of categorical predictors was addressed during the bivariate analysis by collapsing categories within variables. Collinearity diagnostics were carried out for all categorical predictors using the Coefficients table from a linear regression test and one of the intercorrelated variables removed if the tolerance value was less than 0.1 Intercorrelation was evident between two variables, previous chemotherapy and PPE with previous chemotherapy therefore the variable previous chemotherapy was deleted from the data. On reflection this intercorrelation should have been blatantly obvious without running diagnostics since a patient could only have had PPE with previous chemotherapy if they had indeed had previous chemotherapy. However, running the diagnostic test confirmed this and provided a useful learning experience to increase knowledge of statistical testing. All outliers were checked against their original data to seek any obvious reasons why they did not fit the model well or if any error in data inputting had been made. As no obvious reason was found the outliers were not excluded from the analysis.

There were certain considerations to make prior to executing logistic regression, these included; identifying the reference category; how missing data will be dealt with and recognizing confounders. Unlike linear regression, dummy variables do not have to be created explicitly, since SPSS creates these from nominal variables. However, thought should be given to the most appropriate category to be the reference category against which the other categories are compared (Marston 2010). The reference category was chosen as the one that appeared, following the bivariate analysis, to be the least likely to increase the risk of PPE which should provide a positive value for the odds ratio (OR), thus easing the interpretation of the data.

There is always the problem of missing data and how it should be handled. A few missing observations are a minor nuisance, but a large amount of missing data are a major threat to a study's reliability. Missing data are much more common in retrospective studies. Information sought from patient's medical notes does not always provide certain life style information for example,

smoking habits. The simplest (but naïve) method is to use the complete cases only. However, this raises two important problems of its own; information is lost as the sample size is reduced and the results may be biased. In general it is advisable not to include in an analysis any variable that is not available for a large population of the sample (Altman & Bland 2007, Consentino & Claeskens 2011). One solution to this problem is to code the missing data as a category within the variable. However this code must not be used as a reference category since it has no influence on the dependent variable or take action on the resulting values for that category. This solution allows all the other data belonging to that case to be used in the analysis and avoids the problem of reducing the sample size.

Confounding can be a major concern in causal studies. Anticipating the role of confounding variables, as positive or negative, on effect measures is important in interpreting results because it can lead to bias in the estimation of exposure effects (Mehio-Sibai et al 2005). In the extreme, this can mean that a causal effect is suggested where none exists, or that a true effect is hidden. Confounding commonly occurs when there are differences between the exposed and unexposed groups in respect of independent risk factors for the disease. Confounding can be reduced by matching in the study design but this can be difficult and/or wasteful of resources. In the past statistical correction methods have been applied but more recently this is being replaced by methods based on regression models (McNames 2005). It is widely accepted that there are multiple risk factors for any disease/condition of interest, and the question is often asked whether the apparent association may be due in whole or in part to a variable which was not measured or controlled in the study design or analysis. Epidemiologists usually want to focus on the causal effect of one factor (exposure), although other factors may be considered only because they might be confounders rather than being of direct interest. The goal is to study the effect of the exposure on the disease/condition, ‘controlling’ or ‘adjusting’ for the others. The final choice of model form should be dictated by the need to eliminate confounding not parsimony (thriftiness in the number of variables in the final model). However

automated selection procedures should not be relied on to make decisions about confounders as they may result in inappropriate exclusions or inclusions in a model (Schlesselman 1978, McNames 2005).

There is often a temptation to reduce the model in a stepwise fashion until all the remaining terms have “significant” coefficients. However this defeats the purpose of multivariate control of confounding, since “non-significance” does not mean lack of confounding. The deletion of many “non-significant variables from the model may lead to substantial confounding by the aggregate of the deleted factors (Miettinen 1976). Since stepwise regression, can easily lead to invalid estimates and tests of effect, variable selection is better approached by direct estimation of the degree of confounding produced by each variable than by significance-testing algorithms (Greenland 1989).

How badly a covariable confounds the association between a disease and a primary trait depends on the strength of two other associations: between covariable and disease, and between covariable and primary trait. To assess the confounding potential by testing one of these associations for statistical significance, using a ‘traditional’ critical level of 0.05 or 0.01, is inadequate. Such a preliminary test places the burden of proof in the wrong direction, avoiding type I errors (True H_o incorrectly rejected). In evaluating confounding potential, the burden of proof should be in the opposite direction, type II error (fail to reject a false Ho) being more important. To identify any confounding effect of covariables with this backward burden of proof direction the significance level should be 0.25 or 0.50, possibly even higher (Dales & Ury 1978) Mickey & Greenland’s (1989) study of several different models confirmed these findings. Hosmer & Lemeshow (1989), while supporting this approach do offer a word of caution in that variables of questionable importance might be included in the model and that it is important to critically review all variables added to the model before a decision is reached regarding the final model.

If one wishes to conduct a statistical test of a confounder, a logically sound approach would employ equivalence testing in place of significance testing. The most commonly proposed alternative to conventional algorithms is to base variable selection on a "proportional change-in-estimate" method at some arbitrary level such as 10% or 20% (Miettinen 1976, Greenland 1989, Hosmer & Lemeshow 1989, Mickey & Greenland 1989).

3.5.4.2 Selection of variables for regression

The purpose is to select a subset of variables that does the best job of predicting a particular outcome. We usually want to find the smallest group of variables that will account for the greatest proportion of variance in the dependent variable known as a parsimonious model (Munro 2005, Miles & Shelving 2008), which should also be biologically reasonable (Hosmer & Lemeshow 1989). Predictors included and the way they are entered into a model can have a great impact on the results. Ideally predictors should be selected based on statistical or clinical significance. Clinical significance based on previous studies can prove difficult due to the contradictory nature of the findings. For example, Jansman et al (2000), Schellens et al (2005), Tan & McLeod (2005) and Chabner & Longo (2006) suggest that age and gender were significant in relation to PPE occurrence, while others found no significant difference in age and gender (Comandone et al 1993, Chiara et al 1997, Heo et al 2004, Gressett et al 2006, Janusch et al 2006, Webster-Gandy et al 2007). If the predictors were uncorrelated the order of entry would have little effect on the results. However since this is a rarity the method of entry chosen in crucial (Field 2005, Bursac et al 2007). The Backward, forward, stepwise techniques of entering variables into the model presents a problem, in that we are asking the computer to make decisions regarding which variables are important, when the computer has no idea about the theory that may determine which variables are important (Miles & Shevlin 2008). The analyst not the computer is ultimately responsible for the review and evaluation of the model (Hosmer & Lemeshow 1989).

3.5.4.3 Modelling technique used;

Binary logistic regression was chosen as it suits models where the dependent variable is dichotomous. Parameters for inclusion and retention in the model were based on a model presented by Bursac et al (2007) and described by Hosmer and Lemeshow (2000). This modelling technique uses purposeful selection of variables and is advantageous when interested in risk factor modelling, rather than simply prediction. This modelling method allows confounding variables in addition to significant variables to be included resulting in a potentially richer model (Bursac et al 2008). Assumptions used in modelling procedures are more restrictive than bivariate analysis and if any of these assumptions are incorrect, the results may be seriously compromised. One solution to this problem is to fit a whole family of models to compare the conclusions or to validate the model results (Greenland 1989). Comparison of models using different variable entry methods (forward, backward and purposeful) was made using the area under the curve figure obtained by applying Receiver Operator Characteristics (ROC) tests to establish which method proved to be the better predictor of PPE.

3.5.5 Receiver Operating Characteristic (ROC) Curves

ROC is used in classification analysis either to compare two or more assessors, scales or techniques or to establish the accuracy of (the sensitivity and specificity) a model to predict, in this case PPE. The value of this statistical test is to assist healthcare professionals to decide an optimal threshold for making decisions in a given situation (Anthony 2011). Caution should be applied when using thresholds, since they do not state with absolute certainty that a person will develop a condition, but usually indicate that it is fairly confident/quite likely. The level that the threshold is set at depends on the merits of specificity and sensitivity. If it is important to get the diagnosis right and false positives are not problematic then the threshold is set low so that as the score increases the risk of getting the condition

increases (figure 3.4). This means the test is set to be more sensitive but with poorer specificity (Anthony 1999).

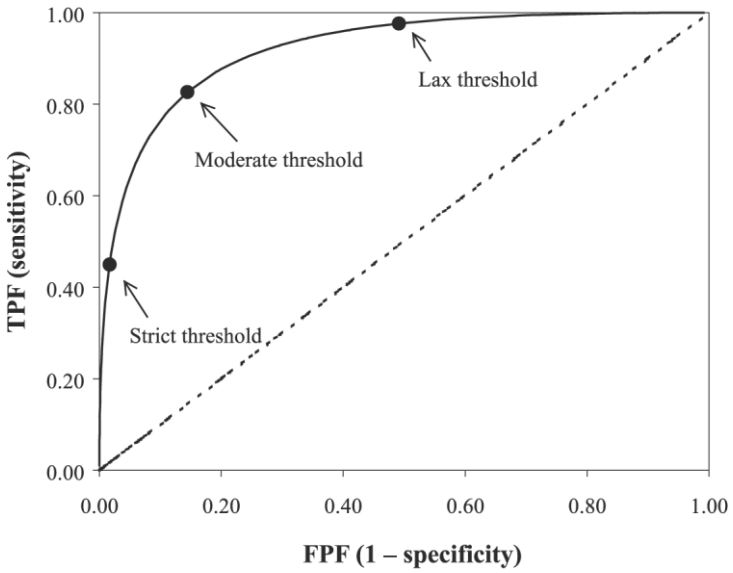


Figure 3-4 ROC curve demonstrating effect of threshold levels

(Braga & Oliveira 2003)

A ROC plot is obtained by calculating the sensitivity (true positive) and 1-specificity (false positive) of each observed data value. A model to perfectly discriminate between the two groups would produce a curve that coincided with the left and top sides of the plot (1.00) (Altman & Bland 1994). In practice, however, there is usually overlap between the values of the group with the condition (in this case PPE) and those without, meaning that the curve usually falls between the random diagonal line (left bottom to top right) and the perfect fit. The further the curve is from the diagonal line the better the classification. The area under the curve (AUC) indicates the probability that a random person with PPE has a higher value than a random person who does not develop PPE and is used to assess the performance of the model (Bowling 2002). AUC ranges from 0 to 1, thus AUC = 1 means all cases with PPE are higher than all without, and AUC = 0.5 means that half are higher and half are lower, or put another way, a model that is no better than guessing the outcome (Chan 2004). When comparing two or more curves, as with the comparison of the logistic regression models described above, the curve

above and to the left of the other(s) indicates a more accurate model (Anthony 2011).

3.6 Ethical considerations

Since I (the researcher) am an employee of the acute NHS trust where the study took place and working clinically within the chemotherapy suite is a normal part of my role, access to the population and their records does not present the problems that would be faced by a researcher external to the organisation. Each NHS trust has a Caldecott guardian responsible for the safekeeping of patient's records to protect their rights. Anyone (whether an insider researcher or external to the trust) wishing to carry out research requiring access to patients records, must gain approval from this guardian (Gelling 2010). Approval was given for the researcher to access patients notes for the purpose of this study. This did not, however, mean that the study could proceed without gaining formal ethical committee and Research and Development (R & D) approval. Application for ethical approval was submitted on 17th October 2008 to the University Faculty Ethics Committee and approved on 13th November 2008 with no amendments required (appendix 3.7). Application for ethical approval was submitted to the NHS ethics committee on 21st January 2009 and was considered at their meeting on 19th February 2009, I attended to answer any questions they had. Approval was granted following minor amendments on 27th March 2009 (appendix 3.8). Research governance approval from the trust's R & D lead was sought on 9th March 2009 and approved 29th May 2009 (appendix 3.9). Lengthy discussions have been held with a member of the R & D team to assist in the ethical approval process and to identify requirements for research governance approval which included curriculum vitae of the principal investigator and attendance on Good Clinical Practice (GCP) and consent training. Support for the study was sought and agreed by key managers of the chemotherapy suite and included the general manager, clinical director, head of nursing, matron, lead chemotherapy clinician, and senior sister.

An amendment was submitted to the ethics committee on 17th February 2010 requesting agreement to restrict the prospective sample to capecitabine monotherapy (Appendix 3.10), which was approved 1st March 2010

This research study was carried out in adherence with the Nursing Professional Code of conduct (NMC 2008), the Nuremberg Code of 1947 (National Institute for Health 2009), the Declaration of Helsinki 1964; 2002 (WMA) and the Research Governance Framework for Health and Social Care (DH 2001; 2003).

The ethical principles of beneficence and justice charges researchers to ensure that benefits outweigh risk (Polit et al 2001). The potential risk during the collection of data from these participants is one of emotional distress. If patients became distressed during an interview, the interview was terminated at once. If the patient wished to continue with the interview following recovery from their distress the interview was re-commenced. The chemotherapy specialist sister caring for the patient was informed of the patient's distress and asked to assist if necessary. The researcher made referrals (based on clinical need and not as a result of participation in the study) to the palliative care team, counselling or psycho-oncology services when appropriate following discussion with the specialist sister. This occurred on 5 occasions. Other assistance was given to individual participants and included helping one participant to complete an application for financial benefits, one to apply for funding to have a special weekend away for herself and her partner after being given a poor prognosis, one participant with Reynaud's disease to seek an appointment with a rheumatologist and another to seek information for his erectile dysfunction following colorectal surgery and radiotherapy.

The participant's right of self-determination is an essential ethical consideration and the researcher ensured that informed consent was given. Each participant was issued with an information sheet explaining the study and the right to refuse or withdraw at any time. Each participant was given the

opportunity to have any questions answered prior to giving or declining consent.

Methods to protect the participant's right to privacy included all data collected being treated with confidentiality and anonymity (McHaffie 2000). Information on the handling, use and storage of data were included in the participant information sheet.

During the retrospective notes review, if information was found that indicated a breach of codes of professional practice e.g. unsafe practice, the trust's policies would be followed and reported to the appropriate professional lead within the acute NHS Trust. During the collection of data in this phase this proved to be unnecessary.

Participants were informed that if they disclosed any information that indicated someone was at risk of harm, was against the law, unprofessional behaviour or unsafe practice, this would have to be reported to the appropriate authorities.

3.7 Research issues

Strengths and weaknesses of the study design and methodology will be presented in this section and limitations of the data collected, analysis and findings will be discussed in chapter 6 along with identification of the contribution of the study to the current body of knowledge.

3.7.1 Limitations of study design

The aspiration of objectivity in quantitative research is used to keep the participants and the researcher at a distance (Topping 2006). This is often achieved by using a researcher to collect data rather than someone directly involved in the clinical care of the patient. As previously mentioned due to

staff shortages and workload the specialist chemotherapy sisters were unable to assist with the data collection and the researcher became the soul data collector.

The strength of a single data collector lies in the consistency in the interpretation of the questions asked. However, the burden placed on one person to collect all of the data may limit the sample size that can be interviewed.

Despite the inexpensive method of surveying a large number of people relatively quickly, the main limitation of a retrospective analysis is the reliability of the data which may not be collected with the rigor expected in a research study. For some variables, data were unavailable in the participant's medical notes particularly performance status, history of weight loss, social history and ethnicity. Other difficulties included the inconsistency in the reporting method of toxicities of the treatment, with some doctors using the NCI CTCAE criteria v 3.0 (2006), others using terms such as mild, moderate or severe and a few only making reference to the presence of a toxicity with no history of its onset or severity.

The data were collected from a single centre with the sample drawn from that geographical area which may introduce an element of bias and influence the generalisability of the findings to other populations.

The size of the whole retrospective sample was sufficient to power the statistical tests to give a greater than 80% chance that a statistically significant effect would be detected. However, when this sample was restricted to those participants that received capecitabine monotherapy only the power was reduced to 72% and the power of the prospective data were 65%. With 80% being the conventional level of power required to detect an effect as it actually exists, the lower power seen in the capecitabine monotherapy samples may call the study results into question, in that the study might have been too small to detect any differences.

3.7.2 Validity and reliability of the proposed study

The variables entered and purposefully reduced in the logistic regression model applied to the retrospective capecitabine monotherapy sample were applied to the prospective data for the purpose of demonstrating validity and reliability of the findings. The result of this analysis is presented in chapter 4 and discussed further in chapter 5.

3.8 Summary

The methodological approach to conducting this study is based on the positivist paradigm drawing on a quantitative approach of survey design. Details of each phase of the study using a multi-strategy approach to data collection in phase two were explained. Sample selection for both phases of this study was described including estimation of the statistical power achieved. This was followed by an explanation of the process applied to the analysis of the data including details of the statistical tests used and the rationale for the use of the special algorithm employed for the selection and retention of variables in the multivariate modelling technique. The theoretical basis and subsequent research design used for this study has been presented. The issue of the potential role conflict when the researcher is also a clinician were discussed and ethical dilemmas were examined. Strategies to overcome these conflicts and challenges were identified. The chapter concluded by discussing limitations of the study design and methodology.
The following chapter presents the findings from the two phases of the study.

CHAPTER 4 FINDINGS

4.1 Introduction

This chapter presents the findings from data collected from the two samples (retrospective and prospective). The findings are presented in three sections; the whole sample from the retrospective notes review, followed by the findings from the participants within this sample who received capecitabine monotherapy only. Capecitabine monotherapy was the focus for the prospective data collection phase of the study, the findings of which are presented in the third and final section of this chapter. The descriptive statistics are presented for the whole of each sample. The inferential statistics are restricted to those who developed PPE prior to cycle 4 versus those who did not so that risk factors for early development of PPE could be identified. A detailed description of each model applied to the three samples is given with a summary table (table 4.45) of the statistics from these models at the end of the chapter. Individual case reports are presented to illustrate previously unreported or unusual features of PPE.

4.2 Retrospective data

4.2.1 Descriptive statistics

4.2.1.1 Sample characteristics

The sample was drawn from patients who had received oxaliplatin and infusional 5-FU (folfox) or capecitabine containing regimes between April 2008 and March 2009. A total of 392 participants of which men totalled 229 (58.4%) and women 163 (41.6%), were included in the analysis. The median age across the sample was 66 (range 30-85 yrs), with men slightly older than women with a median age of 67yrs (range 30-84 yrs) versus a median age of

63 yrs (35-85 yrs). The sample characteristics are presented in table 4.1. All participants received more than one cycle of chemotherapy, unless the treatment was stopped following the first cycle due to severe toxicities including PPE (n = 6), the incidence of these toxicities follows in the next section.

Description	Sample n (%)	With PPE[a] n (%)	PPE pre cycle 4[a] n (%)	PPE after cycle 4[a] n (%)	No PPE[b] N (%)
Frequency n (%)	392 (100)	109 (27.8)	82 (20.9)	27 (6.9)	283 (72.2)
Age median	66	68	69	62	65
Range	30-85	(39-85)	40-85	(39-82)	(30-84)
Gender M	229 (58.4)	68 (62.4)	52 (63.4)	16 (59.3)	161 (56.9)
F	163 (41.6)	41 (37.6)	30 (36.6)	11 (40.7)	122 (43.1)
Ethnicity					
White	273 (69.6)	67 (61.5)	47 (57.3)	20 (74.1)	206 (72.8)
Other	18 (4.6)	9 (8.2)	6 (7.3)	3 (11.1)	9 (3.2)
Not known	101 (25.8)	33 (30.3)	29 (35.4)	4 (14.8)	68 (24.0)
Marital status					
In a relationship	291 (74.2)	84 (77.1)	62 (75.6)	22 (81.5)	207 (73.1)
Not in a relationship	81 (20.7)	20 (18.3)	16 (19.5)	4 (14.8)	61 (21.6)
Not known	20 (5.1)	5 (4.6)	4 (4.9)	1 (3.7)	15 (5.3)
Employment					
Working	172 (43.9)	42 (38.5)	31 (37.8)	11 (40.5)	130 (45.9)
Not working	132 (33.7)	37 (34.0)	26 (31.7)	11 (40.5)	95 (33.6)
Not known	88 (22.4)	30 (27.5)	25 (30.5)	5 (18.5)	58 (20.5)
Tumour site					
Colorectal	275 (70.2)	79 (72.5)	63 (76.8)	16 (59.3)	196 (69.3)
Breast	33 (8.4)	13 (11.9)	10 (12.2)	3 (11.1)	20 (7.1)
Other[c]	84 (21.4)	17 (15.6)	9 (11.0)	8 (29.6)	67 (23.7)
Metastatic spread					
Y	202 (51.5)	44.0 (48)	37.8 (31)	63.0 (17)	54.4 (154)
N	188 (48.0)	56.0 (61)	62.2 (51)	37.0 (10)	44.9 (127)
PPE with previous chemo Y	12 (3.1)	9 (8.3)	7 (8.5)	2 (7.4)	3 (1.06)
N	134 (34.2)	42 (38.5)	36 (43.9)	6 (22.2)	92 (32.5)
No prev chemo	237 (60.4)	56 (51.4)	38 (46.3)	18 (66.7)	181 (64.0)
Not known	9 (2.3)	2 (1.8)	1 (1.3)	1 (3.7)	7 (2.4)
Regime					
capecitabine SA	151 (38.5)	76 (69.7)	63 (76.8)	13 (48.2)	75 (26.5)
Other cap[d]	96 (24.5)	22 (20.2)	14 (17.1)	8 (29.6)	74 (26.1)
Inf 5 FU	145 (37.0)	11 (10.1)	5 (6.1)	6 (22.2)	134 (47.4)
Season start					
Summer	157 (40.1)	33 (30.3)	25 (30.5)	8 (29.6)	124 (43.8)
Winter	235 (59.9)	76 (69.7)	57 (69.5)	19 (70.4)	159 (56.2)

[a] patients who developed PPE of any grade
[b] patients who did not develop PPE during treatment
[c] other tumour sites = Oesophageal; Gastric; Unknown primary; Cholangiocarcinoma; Pancreas; Pseudomyxoma peritonei; Neuroendocrine; Ovary
d other cap = capecitabine/RTD; ECX; capox; Cisp/Cap/RTD; Cap/docetaxel; Bev/Cap; Gem/Cap; EOX = 12

Table 4-1 Participant characteristics retrospective data

4.2.1.2 Toxicity

In relation to toxicity from both capecitabine containing regimes and infusional 5FU, mild to severe adverse events were reported for 284 (72.4%) of the 392 participants. Diarrhoea was the most common adverse side effect. The incidence of toxicity is listed in table 4.2; the figures reflect the development of multiple toxicities in many participants.

Toxicity	Sample	With PPE[a] n (%)	PPE pre cycle 4[a] n (%)	PPE after cycle 4[a] n (%)	No PPE[b] n (%)
Number (%)	392 (100)	109 (27.8)	82 (20.9)	27 (6.9)	283 (72.2)
Diarrhoea	152 (38.8)	57 (52.3)	50 (61.0)	7 (25.9)	95 (33.6)
Mucositis	107 (27.3)	37 (33.9)	30 (36.6)	7 (25.9)	70 (24.7)
N & V[c]	112 (28.6)	35 (32.1)	25(30.5)	10 (37.0)	77 (27.2)
Rash	17 (4.3)	3 (2.8)	2 (2.4)	1 (3.7)	14 (4.9)
Fatigue	101 (25.8)	32 (29.4)	21 (25.6)	11 (40.7)	69 (24.4)

[a] participants who developed PPE of any grade
[b] participants who did not develop PPE during treatment
[c] Nausea and vomiting

Table 4-2 Incidence of toxicity N (%) retrospective data

Gastrointestinal adverse events were observed most frequently. 152 participants reported diarrhoea (38.8%) and nausea and/or vomiting was recorded in 112 participants (28.6%). PPE developed in 109 participants (27.8%). The incidence of PPE was higher in those who received capecitabine monotherapy 50.3% (76 out of 151 participants) than in those receiving either other capecitabine containing regimes (22.9%) or infusional 5FU (7.6%). Diarrhoea and mucositis had a higher incidence in participants receiving infusional 5FU (40% for each toxicity). However, nausea and/or vomiting had a higher incidence in those who received other capecitabine containing regimes 35.4% (34 out of 96 participants). These results are presented in table 4.3.

Toxicity	Cap SA[a] n (%)	Other cap[b] n (%)	Inf 5FU[c] n (%)
Number (%)	151 (38.5)	96 (24.5)	145 (37.0)
PPE	76 (50.3)	22 (22.9)	11 (7.6)
Diarrhoea	37 (24.5)	27 (28.1)	58 (40.0)
Mucositis	34 (22.5)	15 (15.6)	58 (40.0)
N & V[d]	36 (23.8)	34 (35.4)	42 (29.0)
Rash	4 (2.6)	4 (4.2)	9 (6.2)
Fatigue	29 (19.2)	24 (25.0)	48 (33.1)

[a]capecitabine monotherapy
[b]Other capecitabine containing regimes = capecitabine/RTD; ECX; capox; Cisp/Cap/RTD; Cap/docetaxel; Bev/Cap; Gem/Cap; EOX = 12
[c]Infusional 5FU
[d]Nausea and vomiting

Table 4-3 Incidence of toxicity by regime (n = 392) retrospective data

Table 4.4 presents an examination of any association between these toxicities and the incidence of PPE at any cycle. A chi-square test for independence (with Yates continuity correction) indicated an association between diarrhoea and PPE, χ^2 (1, n = 392) = 10.85 p = .001. This significant association between diarrhoea and PPE showed that for those with diarrhoea, there were more cases of PPE than would have been expected (observed cases = 57 versus expected = 42) (table 4.5). However, only a small effect size was detected with phi = .17. The test showed no association between mucositis, nausea and vomiting, rash or fatigue and development of PPE at any cycle.

Variable	χ^{2a}	df[b]	p	phi[c]
Diarrhoea	10.85	1	.001	.17
Mucositis	2.92	1	.09	.09
N & V[d]	.70	1	.40	.05
Rash	.46	1	.50a	-.04
Fatigue	.78	1	.38	.05

[a] χ^2 differences between observed and expected frequencies
[b] *df* extent to which values are free to vary given a specific number of subjects and a total score (in 2 x 2 table always 1)
[c] phi strength of any association (effect size or risk) 0-1 higher values indicate a stronger association (small effect = .10, medium effect = .30, large effect = .50 (Cohen 1988)) Can be +ve or -ve
[d]Nausea and vomiting

Table 4-4 Chi-square other toxicity effects with PPE any cycle (n = 392) retrospective data

Crosstab

***p* = .001**			Diarrhoea		
			No	Yes	Total
PPE	No	Count	188	95	283
		Expected Count	173.3	109.7	283.0
	Yes	Count	52	57	109
		Expected Count	66.7	42.3	109.0
		% of Total	61.2%	38.8%	100.0%

Table 4-5 Cross tabulation of Chi-square test diarrhoea

Since PPE is the toxicity of interest in this study a more detailed description of the severity of PPE will now be presented.

4.2.1.3 Severity and time course of PPE

For analysis of the severity of PPE, the grade (previously stated in figure 3.2 page 65) and cycle at first presentation of PPE was recorded and the most severe episode of PPE experienced. The grade distribution, cycle of presentation and the worst episode are presented in table 4.6. Of the 109 participants who developed PPE at any cycle, 82 (75.2%) presented with PPE before starting cycle 4 and 27 (24.8%) after starting cycle 4 of their treatment. PPE was evaluated at the time of the development of the first episode. Of the 109 participants who had PPE, 20 participants (18.3%) had their first episode after the first cycle, 41 (37.6%) after the second cycle, 21 (19.3%) after the third cycle and 27 participants (24.8%) had their first episode following the fourth or more cycles. More participants presented with grade 1 PPE as their first episode for all regimes. Of the 59 (54.1%) participants whose first presentation at any cycle of PPE was grade 1, 25 developed grade 2 (9 participants) or grade 3 (16 participants) following subsequent cycles. 34 participants (31.2%) had grade 1 PPE, 35 participants (32.1%) had grade 2 PPE and 40 participants (36.7%) had grade 3 PPE as their most severe episode. There were differences in the incidence of PPE prior to cycle 4 between the different regimes. Out of those who developed PPE prior to cycle 4, 82.9% of those who received capecitabine monotherapy did so compared

with 63.6% of other capecitabine containing regimes and 45.4% for infusional 5-FU.

SEVERITY AND TIME COURSE OF PPE RETROSPECTIVE DATA FOR WHOLE SAMPLE AND BY REGIME										
Description	**All Data n (%)**	**capecitabine monotherapy n (%)**			**Other cap regimes n (%)**			**Infusional 5FU n (%)**		
		All	Pre C4	Post C4	All	Pre C4	Post C4	All	Pre C4	Post C4
Number	392 (100)	151 (100)			96 (100)			145 (100)		
No with PPE	109 (28.0)	76 (50.3)	63 (82.9)	13 (17.1)	22 (22.9)	14 (63.6)	8 (36.4)	11 (7.6)	5 (45.5)	6 (54.5)
1st episode of PPE[a]										
1	20 (18.3)	15 (19.7)	15 (23.8)	N/A	4 (18.2)	4 (28.6)	N/A	1 (9.1)	1 (20.0)	N/A
2	41 (37.6)	34 (44.8)	34 (54.0)	N/A	5 (22.7)	5 (35.7)	N/A	2 (18.2)	2 (40.0)	N/A
3	21 (19.3)	14 (18.4)	14 (22.2)	N/A	5 (22.7)	5 (35.7)	N/A	2 (18.2)	2 (40.0)	N/A
4 or later	27 (24.8)	13 (17.1)	N/A	13 (100)	8 (36.4)	N/A	8 (100)	6 (54.5)	N/A	6 (100)
Grade at 1st episode[b]										
1	59 (54.1)	43 (56.6)	36 (57.2)	7 (53.8)	9 (40.9)	6 (42.9)	3 (37.5)	7 (63.6)	2 (40.0)	5 (83.3)
2	26 (23.8)	17 (22.4)	14 (22.2)	3 (23.1)	6 (27.3)	5 (35.7)	1 (12.5)	3 (27.3)	2 (40.0)	1 (16.7)
3	24 (22.1)	16 (21.0)	13 (20.6)	3 (23.1)	7 (31.8)	3 (21.4)	4 (50.0)	1 (9.1)	1 (20.0)	0 (0.0)
Severity of PPE[c]										
1	34 (31.2)	24 (31.6)	18 (28.5)	6 (46.1)	5 (22.7)	2 (14.2)	3 (37.5)	5 (45.5)	1 (20.0)	4 (66.7)
2	35 (32.1)	23 (30.3)	19 (30.2)	4 (30.8)	7 (31.8)	6 (42.9)	1 (12.5)	5 (45.5)	3 (60.0)	2 (33.3)
3	40 (36.7)	29 (38.1)	26 (41.3)	3 (23.1)	10 (45.5)	6 (42.9)	4 (50.0)	1 (9.0)	1 (20.0)	0 (0.0)

[a] cycle in which the first episode of PPE developed number and percentage of those with PPE
[b] grade that participants presented with at first episode of PPE number and percentage of those with PPE
[c] worst grade for each participant developing PPE number and percentage of those with PPE

Table 4-6 Severity and time course of PPE retrospective data for whole sample and by regime

4.2.1.4 Treatment outcome.

231 of the 392 (58.9%) participants completed all planned cycles. Details of completion rates including deferral of treatment and dose reductions are provided in Table 4.7.

Outcome	Sample
Number (%)	**392 (100)**
Completed all cycles	231 (58.9)
Discontinued treatment	161 (41.1)
due to PPE[a]	17 (10.6)
due to other toxicities/adverse events[a]	71 (44.1)
Dis prog/poor PS[a]	38 (23.6)
Patient request[a]	10 (6.2)
Died[a]	15 (9.3)
No reason given[a]	10 (6.2)
Deferred due to PPE	47 (11.9)
Deferred due to other toxicities	17 (4.3)
Dose reduction at cycle 1	49 (12.5)
Dose reduction due to PPE	49 (12.5)
Dose reduction due to other toxicities	113 (28.8)
[a] % of total number who discontinued treatment	

Table 4-7 Completion rates n (%) retrospective data

161 participants (41.1%) discontinued treatment before completion of 6 cycles. Of these 161 participants, the reasons for the discontinuation of treatment were PPE 17 (10.6%), other toxicities or adverse events 71 (44.1%), disease progression or deteriorating performance status 38 (23.6%), patient request 10 (6.2%), died during treatment 15 (9.3%) or no reason given 10 (6.2%).

Of the 10 participants who chose to discontinue their treatment, 5 received capecitabine monotherapy, 2 received other capecitabine containing regimes and 3 infusional 5FU. Only 2 of these developed PPE, grade 1 (1) and grade 3 (1). 9 of the 10 chose to discontinue treatment as they were feeling generally unwell due to the effects of the treatment and 1 due to psychological distress. None of the participants met the usual threshold to stop based on the manufacturer's recommendations (Appendix 4.1). These 10 participants were

included in the analysis as they chose to discontinue their treatment after receiving at least 3 cycles of treatment.

Participants (49) who had a dose reduction at the start of their treatment did so for a variety of reasons; 19 due to moderate renal failure (creatinine clearance (CrCl) 30-50); 8 who had severe toxicities with previous chemotherapy; 1 receiving concurrent radiotherapy; 2 with delayed wound healing; 2 because of their age (80yrs); 3 with poor performance status (2-3) and 14 reason unknown. All of the 14 participants where the reason was unknown were female with metastatic breast cancer and the dose reduction consisted of a reduced length of administration time e.g. for 7 days with 2 weeks rest rather than the usual regime of 14 days administration and 1 week rest. Although these participants had received previous chemotherapy they had not suffered from severe toxicities and their ages ranged from 46 – 70 years. The only common feature of this group was that they were all under the care of one particular consultant. 64 participants had a delay between cycles due to the presence of toxicities, 47 of these was due to PPE (43.1% of the 109 who developed PPE) and 17 due to other toxicities.

Since the aim of this study is to identify factors other than the drug itself that may influence the development of PPE, the sample used for inferential statistical analysis was restricted to those who developed PPE within the first 3 cycles and those who did not develop it, based on the assumption that PPE developing in later cycles is more likely to be due to accumulation of the drug.

4.2.2 Inferential statistics

4.2.2.1 Bivariate analysis (Chi-square)

A chi-square test was applied to each individual variable and PPE and the findings of this are shown in table 4.8.

Variable	X^2	df	*P* value	Phi/Cramer's V
Gender	.86[b]	1	.35	-.05
Maritalstatus2gps	.07[b]	1	.79	.02
Ethnic2gps	2.86[b]	1	.09[a]	-.12
Job2gps	.10[b]	1	.75	.03
Smoker	.79[b]	1	.37	.07
Alcohol	.72[b]	1	.39	-.07
Recent wt loss	2.44[b]	1	.12	-.16
BMI2gpsM	.09[b]	1	.73	.02
BMI2gpsF	.12[b]	1	.77	.02
Diabetes	.34[b]	1	.56	.04
PVD	.00[b]	1	1.0[a]	-.01
Periph neuro	.18[b]	1	.67[a]	.04
Skin complaints	.56[b]	1	.45[a]	.07
Inflamm cond	.01[b]	1	.91	-.02
Previous Ca Δ	.57[b]	1	.45	.33
Prev DXT	3.53[b]	1	.06	.11
Performance status 3gps	5.02	2	.08	.15
Tumoursite3gps	7.47	2	.02	.14
Met spread	6.68[b]	1	.01	-.14
PPE with prev chemo	18.47	2	<.001[a]	.23
Regime3gps	73.17	2	<.001	.45
Aim of Rx2gps	3.64[b]	1	.06	-.11
Start season	4.14[b]	1	.03	.11
CrClC13gps	4.34	2	.11	.11
[a]at least 1 cell has expected count of less than 5 [b]yate's correction for 2 x 2 table				
	Indicates variables $p < .05$ and included in multivariate regression			
	Indicates additional variables $p < .25$ included in multivariate regression			

Table 4-8 Chi-square test for association between variables and development of PPE before cycle 4 retrospective data

A chi-square test for independence (with Yate's correction for 2 x 2 tables) indicated a significant association between;

- the development of PPE prior to cycle 4 and metastatic spread χ^2 (1, n = 265) = 6.68 p = .01.

The association between metastatic spread and PPE showed that for those whose cancer had not metastasised there were more cases of PPE than would have been expected (observed = 51 cases versus expected = 40.2) (table 4.9)

Crosstab

***p* = .01**			Metastatic spread		
			No	Yes	Total
PPE prior to Cycle 4	No	Count	127	154	281
		Expected Count	137.8	143.2	281.0
	Yes	Count	51	31	82
		Expected Count	40.2	41.8	82.0
		% of Total	49.0%	51.0%	100.0%

Table 4-9 Crosstabulation Chi-square metastatic spread

- PPE with previous chemotherapy χ^2 (1, n = 265) = 18.47 *p* = <.001.

The association between PPE with previous chemotherapy and PPE with current treatment showed that for those who did not develop PPE with previous treatment there were more cases of PPE than would have been expected (observed = 36 cases versus expected = 29). Participants who developed PPE with previous treatment there were more case of PPE than would have been expected (observed = 7 cases versus expected = 2.3) (table 4.10). The accuracy of this finding may be unreliable since the expected count in the latter is less than 5 breaching one of the assumptions of a chi square test.

Crosstab

***p* < .001**			PPE with previous			
			No previous chemo	No PPE with previous chemo	PPE with previous chemo	Total
PPE prior to Cycle 4	No	Count	181	92	3	276
		Expected Count	169.3	99.0	7.7	276.0
	Yes	Count	38	36	7	81
		Expected Count	49.7	29.0	2.3	81.0
		% of Total	61.3%	35.9%	2.8%	100.0%

Table 4-10 Cross tabulation Chi square PPE with previous chemotherapy

- Regime divided into 3 groups (capecitabine monotherapy; other capecitabine containing agents; infusional 5FU) χ^2 (1, n = 265) = 73.17 *p* = <.001.

The association between the regime and PPE showed that for those receiving capecitabine monotherapy there were more cases of PPE than would have been expected (observed = 63 cases versus expected = 31). Interestingly for those receiving infusional 5FU there were far less cases of PPE than would have been expected (observed = 5 cases versus expected = 31.2) (figure 4.11).

Crosstab

***p* = < .001**			regime3gp			
			Other Cap	Cap SA	Inf 5FU	Total
PPE prior to Cycle 4	No	Count	74	75	134	283
		Expected Count	68.2	107.0	107.8	283.0
	Yes	Count	14	63	5	82
		Expected Count	19.8	31.0	31.2	82.0
		% of Total	24.1%	37.8%	38.1%	100.0%

Table 4-11 Cross tabulation Chi square regime

- Tumour site divided into 3 groups (Colorectal cancer; Breast cancer; other) χ^2 (1, n = 265) = 7.47 *p* = .02

The association between tumour site and PPE showed that for those who had breast or colorectal cancer there were more cases of PPE than would have been expected (observed = 10 cases versus expected = 6.7 and observed = 63 cases versus expected = 58.2 respectively) (figure 4.12).

Crosstab

***p* = .02**			tumour site 3 gps			
			Other	Breast	Colorectal	Total
PPE prior to Cycle 4	No	Count	67	20	196	283
		Expected Count	58.9	23.3	200.8	283.0
	Yes	Count	9	10	63	82
		Expected Count	17.1	6.7	58.2	82.0
		% of Total	20.8%	8.2%	71.0%	100.0%

Table 4-12 Cross tabulation Chi square Tumour site

- The season during which the treatment commenced χ^2 (1, n = 265) = 4.14 *p* = .03

The association between the season at the start of treatment and PPE showed that for those whose started their treatment in the winter months there were more cases of PPE than would have been expected (observed = 57 cases versus expected = 48.5) (figure 4.13)

Crosstab

***p* = .03**			Seasonstart		
			Summer	Winter	Total
PPE prior to Cycle 4	No	Count	124	159	283
		Expected Count	115.5	167.5	283.0
	Yes	Count	25	57	82
		Expected Count	33.5	48.5	82.0
		% of Total	40.8%	59.2%	100.0%

Table 4-13 Cross tabulation Chi square season when treatment started

A small effect was detected for tumour site 3gps, Cramer's V = .14, start season, phi = .11 and metastatic spread, phi = -.14. A medium effect was detected for PPE with previous chemotherapy, Cramer's V = .23 and a large effect for regime 3gps, Cramer's V = .45.

4.2.2.2 Summary of findings from Chi-square tests

Findings from the chi-square tests ($p < .05$) show that those more likely to develop PPE within the first 3 cycles are participants;

- Whose tumour had not metastasised
- Who had been previously treated with chemotherapy but not necessarily had previous episodes of PPE
- Who received capecitabine monotherapy for breast or colorectal cancer
- Who commenced their treatment during the winter months

The results of the comparison of the means from the independent samples *t*-test for age and laboratory values (continuous data) prior to treatment commencing are shown in table 4.14. Independent-samples *t*-test were conducted to compare PPE incidence prior to commencing cycle 4 of the treatment for Body Surface Area (BSA), Body Mass Index (BMI), creatinine, creatinine clearance, Alanine Aminotransferase (ALT) and Bilirubin. No significant differences were observed in any of these variables between those who developed PPE and those who did not. The same test applied to age showed a significant difference between those who did not develop PPE ($\bar{X}$ = 64.18, SD = 10.66) and those that did ($\bar{X}$ = 67.13, SD = 11.54); t (363) = -2.17, *p* = .03 and applied to Alkaline Phosphatase (ALP) showed a significant difference between those who did not develop PPE ($\bar{X}$ = 163.03, SD = 174.68) and those that did ($\bar{X}$ = 111.75, SD = 102.39); t (226) = 3.31, *p* = .001 The magnitude in the difference of the means ($\bar{X}$) (mean difference) for age = -2.96 (95% CI, -5.64 to -.27) was small (eta squared = 0.01) and ALP = 51.28 (95% CI, 20.77 to 81.78) was large (eta squared = 0.99).

4.2.2.3 Summary of the findings from the t-tests

The mean of each group in the *t*-tests ($p < .05$) was examined, with the higher mean indicating the direction of association. Older participants and those with a lower pre treatment ALP level were more likely to develop PPE within the first 3 cycles.

Although this analysis is useful in showing any association of individual variables with the development of PPE, clinically, variables are not present in isolation and it is therefore more useful to apply multivariate tests to the data to establish the performance of the variables when in combination with each other. A multivariate analysis using logistic regression will now be described.

Variable	M[a] PPE Y[b]	SD	M[a] PPE N[c]	SD[d]	t	p	Mean diff[e]	CI[f]	ETA[2g]
Age	67.13	11.54	64.18	10.66	-2.17	.03	-2.96	-5.64 to -.27	0.01
BSA	1.82	.19	1.82	.22	.16	.87	.004	-.05 to .06	0.00
BMI	25.81	4.15	25.65	5.05	-.26	.79	-.16	-1.36 to 1.04	0.001
Creatinine	76.51	17.99	74.89	21.33	-.62	.53	-1.62	-6.71 to 3.47	1.00
CrCl	85.20	29.88	91.52	31.66	1.61	.11	6.32	-1.39 to 14.04	1.00
ALT	29.96	43.47	30.32	32.12	.082	.93	.36	-8.33 to 9.05	1.00
ALP	111.75	102.39	163.03	174.68	3.31	.001	51.28	20.77 to 81.78	0.99
Bilirubin	7.96	4.77	4.77	9.12	1.42	.15	1.50	-.56 to 3.57	1.00

[a] M = mean ($\bar{X}$)
[b] PPE Y = subjects who developed PPE prior to commencing cycle 4
[c] PPE N = subjects who did not develop PPE at any cycle
[d] SD = standard deviation
[e] Mean diff = Mean difference between the groups
[f] CI = 95% confidence interval
[g] ETA^2 = effect size

	Indicates variables $p < .05$ included in multivariate regression
	Indicates variables $p < .25$ included in multivariate regression

Table 4-14 Effects within PPE incidence pre cycle 4 (n = 265) retrospective data

4.2.2.4 Multivariate analysis

Variables that had a *p* value of < .25 but had less than 5 cases in any cell in the chi-square test were not included in the logistic regression as there were insufficient cases in such variables to reliably estimate odds ratios in the logistic regression. The two variables that this applied to were PPE with previous chemotherapy and tumour3gps (Colorectal cancer, Breast cancer and other). Tumour 3gps had been collapsed to reduce the number of categories within the variable, leaving both tumour3gps and PPE with previous chemotherapy with the minimum number of categories felt to be clinically relevant.

A multicollinearity diagnostics test was applied to the selected variables to identify any correlation between them. All variables had a tolerance value of > 0.1 indicating that there was no high correlation between any of the variables. However, clinically there may be an association between variables. From the variables tested for correlation a further chi-square test was applied to two variables thought to be clinically associated; metastatic spread and aim of treatment χ^2 (2, n = 390) = 229.04 *p* = < .001. Based on this result only one of these two variables, metastatic spread, was included in the logistic regression based on its significance in the bivariate analysis; *p* = .01 versus *p* = .06 for the variable aim of treatment. These two variables are clinically associated since participants with metastatic spread most frequently receive palliative treatment which is given without curative intent, but to decrease tumour load and increase life expectancy.

Table 4.15 provides a summary of variables that were significant in the bivariate analyses. It shows those variables significant at both the conventional alpha level of *p* < .05 and the relaxed level *p* < .25 included in the regression model. It excludes those variables with insufficient numbers to be included in the regression model or those that are clinically associated.

Variable	*P* < .05	*P* < .25
Age	.03	
Recent weight loss		.12
Previous radiotherapy		.06
PS 3 groups		.08
Metastatic spread	.01	
Regime 3 groups	< .001	
Start season	.03	
CrCl 3 groups		.11
Bilirubin		.15
ALP	.001	

Table 4-15 Variables from bivariate analysis entered into regression model

4.2.2.5 Purposeful entry and model reduction

10 variables (table 4.15) were entered into the logistic regression analysis and 5 removed. Logistic regression, which consisted of 8 steps, was performed for the research sample (n = 392) with 40 missing cases not included in the model. 27 of these were participants who developed PPE after commencing cycle 4 and the remaining 13 consisted of small numbers from several other predictor variables (appendix 4.2).

The omnibus tests of model coefficients revealed a Chi-square statistic of 111.16 (df, 9) $p < .001$ indicating that the model performs well compared to the baseline model before the variables were added. The Hosmer-Lemeshow statistic was applied to the data revealing a Chi-square statistic of 5.68 (df, 8) $p = 0.68$ which indicates that the observed numbers who develop PPE are not significantly different from those expected by the model and that the overall fit of the model is good. The Nagelkerke R^2 (.41) value shows about 41% of the variation in the outcome variable (PPE) is explained by the logistic regression model. This model correctly predicted 84.6% of the cases.

As illustrated in table 4.16 the outcome of the logistic regression analysis produced a model containing 3 predictors which were significantly related to PPE development; the regime the patient received, ALP level prior to commencing treatment and the season in which the treatment commenced.

There were a further 2 confounding predictors, performance status and metastatic spread. Performance status and metastatic spread were considered confounders since their removal, at different steps in the model building strategy, caused a greater than 20% change in the beta value of the variable ALP in both instances. It is possible that this effect could be explained by the fact that metastatic spread to the bones causes a raise in serum ALP and participants with metastatic spread are more likely to have poor performance status. Therefore it follows that those with poor performance status are more likely to have a raised ALP level. Factors had variable ability to predict the development of PPE. Participants who had received capecitabine monotherapy were nearly 6 times more likely to develop PPE than those who had received other capecitabine containing regimes (OR = 5.88; 95% CI 2.87 – 12.03, $p < .001$). The risk of PPE in those who commenced their treatment in the winter was just over twice as great compared to those who commenced in the summer (OR = 2.24; 95% CI 1.19 – 4.18, $p = .01$). In participants receiving infusional 5FU, they were less likely to develop PPE compared to those receiving other capecitabine containing agents (OR = .18; 95% CI .06 - .54, $p = .002$). For every unit increase in the ALP level taken prior to commencing treatment (OR = .99; 95% CI .99 – 1.0, $p = .05$) the risk of developing PPE was reduced. Performance status although a confounding variable and not achieving statistical significance showed a trend that as performance status worsened, the risk of developing PPE was reduced (OR = .97; 95% CI .44 – 2.14, $p = .95$). The other confounding variable, metastatic spread, again although not achieving statistical significance showed a trend that participants who did not have metastatic spread were one and a half times more likely to develop PPE than those who had metastatic spread (OR = 1.53; 95% CI .81 – 2.92, $p = .19$).

A logistic regression test was applied to regime3gps with infusional 5FU as the reference category to establish the odds ratio for capecitabine in combination regimes (other cap) when compared with 5FU, as this was not possible when the variable other cap was the reference category. For categorical variables with three or more categories, each category is

compared with the one selected as the reference category, hence the rationale for the change in reference category (the output for both models with the different reference categories are presented in table 4.16).

Predictor variable (n = 356)	B	Wald χ^2	*p** value	OR (exp β)	95% CI
Regime3gps					
Other cap (ref cat) (85)		58.78	<.001		
Cap SA (133)	1.77	23.49	<.001	5.88	2.87-12.03
Inf 5FU (138)	-1.69	9.43	.002	.18	.06-.54
Regime3gps					
Inf 5FU (ref cat) (138)		58.78	<.001		
Other cap (85)	1.69	9.44	.002	5.47	1.85 -16.15
Cap SA (133)	3.47	47.26	<.001	32.12	11.95-86.38
ALPC1 (356)	-.003	3.79	.05	.99	.99-1.0
Seasonstart					
Summer (143) (ref cat)					
Winter (213)	.81	6.38	.01	2.24	1.19-4.18
Metastatic spread[a]					
Yes (181) (ref cat)					
No (175)	.43	1.69	.19	1.53	.81-2.92
Performance status[a]					
PS 0 (112)		4.72	.32		
PS 1 (80)	-.03	.005	.95	.97	.44-2.14
PS 2 (25)	-1.75	4.41	.04	.17	.03-.88
Notes					
* significant at $p < .1$ (2-tailed)		[a] Confounder			

Table 4-16 Logistic regression output purposeful entry model retrospective data

Participants who received capecitabine monotherapy were 32 times more likely to develop PPE compared to those who received infusional 5FU (OR = 32.12, 95% CI 11.95 - 86.37, $p < .001$) and those who received other capecitabine containing regimes were over 5 times more likely to develop PPE than those who received infusional 5FU (OR = 5.47; 95% CI 1.85 - 16.15, $p = .002$). These findings added strength to the decision to focus on participants receiving capecitabine monotherapy only during the prospective data collection phase.

Variables that were not included in the original model containing the 10 variables were added one at a time and logistic regression applied. Out of the 11 variables that had $p > .25$ in the bivariate tests, 3 became significant at $p <$

.25 therefore these were added to the final model and reduced as before. Diabetes was removed leaving alcohol and gender, both of which achieved significance (using an alpha level of $p < .1$). Men were nearly twice as likely to develop PPE than women (OR = 1.83; 95% CI .95 – 3.53, $p = .07$) and participants that drank alcohol regularly were less likely to develop PPE than those that did not drink or only drank occasionally (OR = .53; 95% CI .23 – 1.23, $p = .05$) (table 4.17).

Predictor variable (n = 356)	B	Wald X^2	*p** value	OR (exp β)	95% CI
Regime3gps					
Inf 5FU (ref cat) (138)		58.83	< .001		
Other cap (85)	1.81	10.36	.001	6.12	2.03-18.42
Cap SA (133)	3.59	48.40	< .001	36.28	13.19-99.79
ALPC1	-.003	3.69	.05	.99	.99-1.00
Seasonstart					
Summer (143) (ref cat)					
Winter (213)	.83	6.46	.01	2.30	1.21-4.38
Metastatic spread[a]					
Yes (181) (ref cat)					
No (175)	-.39	1.35	.24	.68	.35-1.31
Performance status[a]					
PS 0 (ref cat) (112)		4.74	.31		
PS 1 (80)	-.09	.05	.82	.91	.41-2.05
PS 2 (25)	-1.74	4.28	.04	.18	.03-.91
Alcohol					
No (ref cat) (78)					
Yes (135)	-.63	2.16	.05	.53	.23-1.23
Gender					
Female (ref cat) (148)					
Male (208)	.61	3.31	.07	1.83	.95-3.53
Notes * significant at $p < .1$ (2-tailed) [a] Confounder					

Table 4-17 Logistic regression output purposeful entry model plus additional non-significant variables

4.2.2.6 Forward and backward conditional entry model

The same 10 variables included in the purposeful reduction model were entered into the logistic regression analysis and 6 removed in 4 steps in the

forward entry method and 7 removed in 8 steps in the backward entry method.

The assessment of the 'goodness of fit' is shown in table 4.18 demonstrating a good fit in both entry methods with the 38% variance explained by the model in both the forward entry and backward entry methods. The ability of the model to correctly predict which category each case fits into was 82.4% in both stepwise entry methods.

Test	Forward entry	Backward entry
Omnibus tests of Model Coefficients		
Chi-square	105.06	101.82
df	6	4
p	< .001	< .001
Nagelkerke R^2	.39	.38
Hosmer & Lemeshow		
Chi-square	3.63	10.21
df	8	8
p	.89	.25

Table 4-18 Goodness of fit automated entry method retrospective data

As shown in table 4.19 the outcomes of the automated entry methods of the logistic regression analysis showed predictive models containing 4 variables in the forward entry strategy and 3 variables in the backward entry strategy. Variables that were significantly related to PPE development; the regime the patient received, the season during which the participant commenced their treatment in and ALP level prior to commencing treatment were common in both models with weight loss an additional variable in the forward entry model. Factors had variable ability to predict the development of PPE but were similar in the forward and backward entry methods. The risk of developing PPE was more than 5 times greater in participants who received capecitabine containing regimes compared to those who had received infusional 5FU (OR = 5.75; 95% CI 1.93-17.10, p = .002 OR = 5.31; 95% CI 1.82-15.55, p =.002 respectively) and over 30 times greater in those who received capecitabine monotherapy compared with infusional 5FU (OR = 30.19; 11.29-80.69, p < .001 OR = 30.32; 95% CI 11.39-80.68, p < .001). Participants who

commenced their treatment in the winter were more than twice as likely to develop PPE than those who commenced in the summer (OR = 2.25; 95% CI 1.21-4.18, *p* = .01 OR = 2.25; 95% CI 1.18-4.05, *p* = .01) and for each unit increase in the ALP level taken prior to commencing treatment there was a reduced risk of developing PPE (OR = .99; 95% CI .99-.99 in both forward and backward entry models *p* = .006 and *p* = .003 respectively). In the forward entry model participants who had recently lost weight were less likely to develop PPE than those who had not lost weight recently (OR = .61; 95% CI .20-1.79, *p* = .21) although did not achieve statistical significance.

Predictor variable (n = 352)	B	Wald X^2	P* value	OR (exp β)	95% CI
Forward entry method					
Regime3gps					
Inf 5FU (137) (ref cat)		56.44	<.001		
Other cap (85)	1.75	9.91	.002	5.75	1.93-17.10
Cap SA (130)	3.41	46.13	<.001	30.19	11.29-80.69
ALPC1	-.004	7.62	.006	.99	.99-.99
Seasonstart					
Summer (140) (ref cat)					
Winter (212)	.81	6.56	.01	2.25	1.21-4.18
Weight loss					
No (34) (ref cat)					
Yes (98)	-.49	.81	.21	.61	.20-1.79
Backward entry method					
Regime3gps					
Inf 5FU (137) (ref cat)		58.72	<.001		
Other cap (85)	1.67	9.29	.002	5.31	1.82-15.55
Cap SA (130)	3.41	46.68	<.001	30.32	11.39-80.68
ALPC1	-.005	8.71	.003	.99	.99-.99
Seasonstart					
Summer (140) (ref cat)					
Winter (212)	.78	6.26	.012	2.20	1.18-4.05
Notes * significant at *p* < .1 (2-tailed)					

Table 4-19 Logistic regression output automated entry methods retrospective data

The differences in the odds ratios for each variable between the different entry strategy building models is probably because of the number of different

variables in each model, thereby reflecting the influence exerted on each variable when in combination with different variables.

Comparison of models using different variable entry methods (forward, backward and purposeful) was made using the area under the curve figure obtained by applying Receiver Operator Characteristics (ROC) tests to establish which method proved to be the better predictor of PPE.

4.2.2.7 Receiver operating characteristic (ROC) curves

ROC curves were applied to the predicted probabilities created in each of the logistic regression entry methods to compare the accuracy of the models in terms of their sensitivity and specificity in predicting participants who developed PPE within the first 3 cycles and those that did not develop PPE.

The model with 5 variables remaining following purposeful entry and retention provides a slightly more accurate prediction of participants who are likely to develop PPE and those who will not AUC = .85 (95% CI .81-.90) than the models with 4 and 3 variables remaining using the forward and backward entry methods respectively AUC = .84 (95% CI .80-.89) (figure 4.1). From the ROC curve applied to the purposeful entry model, the most favourable values for sensitivity and specificity are 82% and 76% respectively. The positive and negative predictive values calculated from the logistic regression output were 69.0% and 88.2% respectively.

A comparison of the final model with the same model including the two variables that were non-significant in the bivariate analysis (figure 4.2) showed that the latter model provided a more favourable ability to predict the development of PPE AUC = .87 (95% CI; .83 - .92) with a sensitivity = 78% and specificity 1 - 0.22 = 78% The positive and negative predictive values calculated from the logistic regression output were 70.6% and 88.5% respectively. The positive predictive value is the proportion of subjects with

PPE correctly diagnosed. The negative predictive value is the proportion of subjects without PPE who are correctly diagnosed.

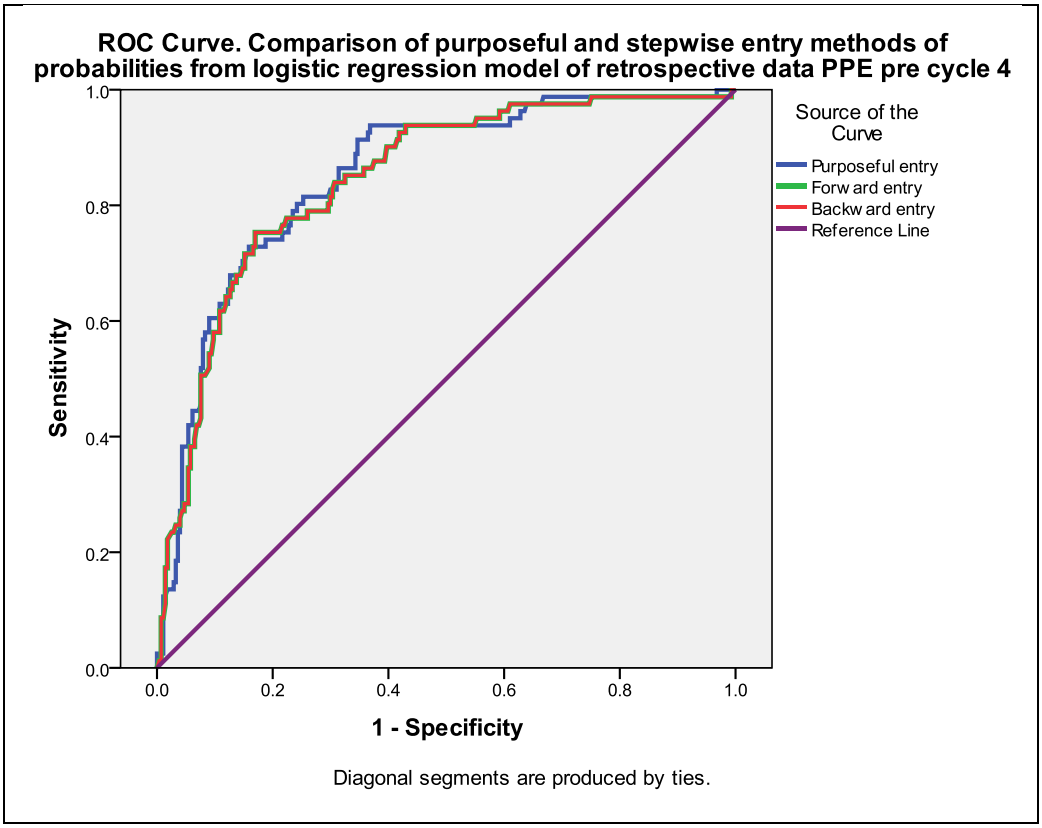


Figure 4-1 ROC curves comparing entry methods retrospective data

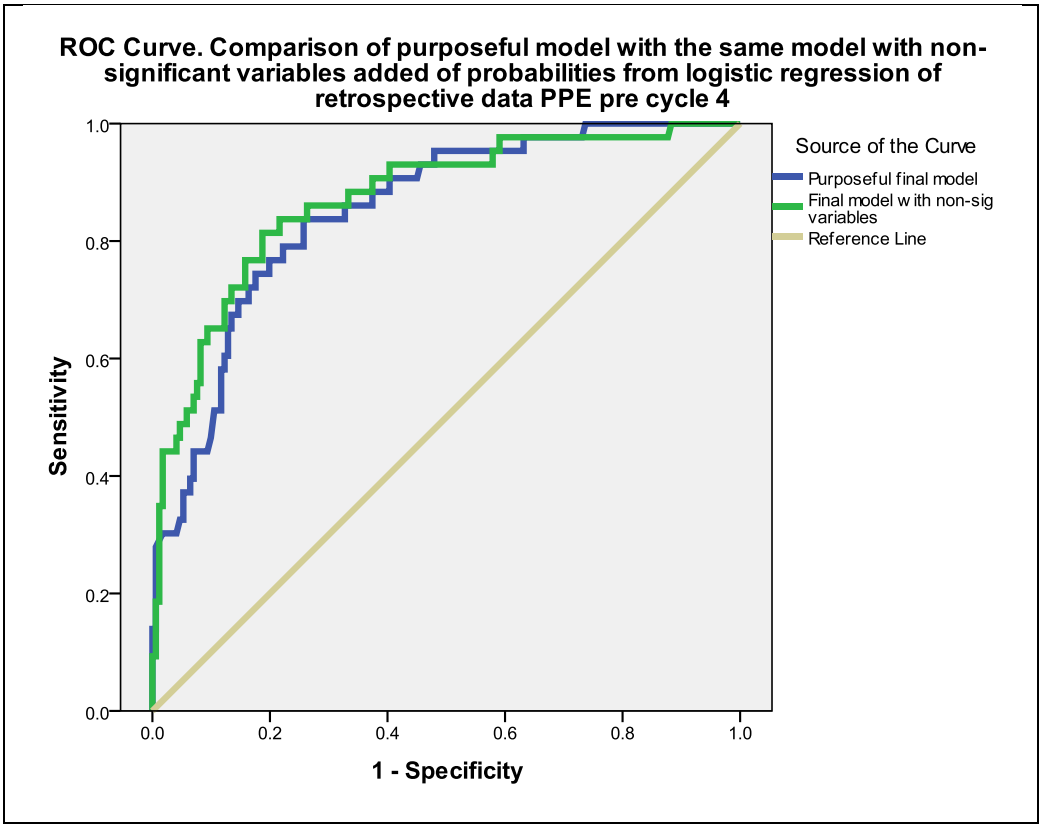


Figure 4-2 ROC curves comparing purposeful entry models retrospective data

Test Result Variable(s) from figure 4.7	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
Purposeful entry	.852	.806	.898
Forward entry	.845	.798	.892
Backward entry	.845	.798	.892
Test Result Variable(s) from figure 4.8	**Area**	**Asymptotic 95% Confidence Interval**	
		Lower Bound	**Upper Bound**
Purposeful entry final model	.851	.805	.897
Final model with non-sig variables	.872	.827	.917

Since the confidence intervals are wide and overlap between the models, this would indicate that there is very little difference between the models and that the automated entry methods produce a model that is not significantly different in predicting development of PPE within the first 3 cycles of treatment compared to the purposeful entry methods. Purposeful selection and retention of variables is however, worthwhile to produce a richer model, including

confounders. This is particularly so if one is interested in risk factors modelling rather than simply prediction.

4.2.2.8 Summary of findings from logistic regression

To summarise the findings from the richer purposeful model (final model with non-significant variables added), those most at risk of developing PPE were participants;

- Who were male
- Who did not drink alcohol regularly
- With good performance status
- Whose tumour had not metastasised
- Who received capecitabine monotherapy
- With a lower pre treatment ALP level
- Who commenced their treatment during the winter months

4.3 Retrospective data capecitabine monotherapy sample

As previously stated, the data analysis of the retrospective sample showed that participants who received capecitabine monotherapy had a higher incidence of PPE than those who received capecitabine in combination regimes or infusional 5-FU. The results of the analysis of the 151 subjects who received capecitabine monotherapy are presented in this section.

4.3.1 Descriptive statistics

4.3.1.1 Sample characteristics

A total of 151 participants of which men totalled 80 (53.0%) and women 71 (47.0%), were included in the analysis. The median age across the sample was 69 (range 39-85 yrs) with men slightly older than women with a median age of 71yrs (range 47-84 yrs) compared to a median age of 65 yrs (39-85 yrs). The sample characteristics are presented in table 4.20.

All participants received more than one cycle of chemotherapy, unless the treatment was stopped following the first cycle due to severe toxicities including PPE (n = 25).

Description	Sample	With PPE[a] n (%)	PPE pre cycle 4[a] n (%)	PPE after cycle 4[a] n (%)	No PPE[b] n (%)
Frequency no (%)	151 (100)	76 (50.3)	63 (82.9)	13 (17.1)	75 (49.7)
Age median	69	69.5	71	61	69
Range	39-85	39-85	40-85	39-75	43-84
Gender M	80 (53.0)	47 (61.8)	40 (63.5)	7 (53.8)	33 (44.0)
F	71 (47.0)	29 (38.2)	23 (36.5)	6 (46.2)	42 (56.0)
Ethnicity					
White	95 (62.9)	41 (54.0)	32 (50.8)	9 (69.2)	54 (72.0)
Other	8 (5.3)	7 (9.2)	5 (7.9)	2 (15.4)	1 (1.3)
Not known	48 (31.8)	28 (36.8)	26 (41.3)	2 (15.4)	20 (26.7)
Marital status					
In a relationship	107 (70.9)	57 (75.0)	46 (73.0)	11 (84.6)	50 (66.7)
Not in a relationship	35 (23.2)	16 (21.1)	14 (22.2)	2 (15.4)	19 (25.3)
Employment					
Working	61 (40.4)	30 (39.5)	23 (36.5)	7 (53.8)	31 (41.3)
Not working	44 (29.1)	21 (27.6)	18 (28.6)	3 (23.1)	23 (30.7)
Not known	46 (30.5)	25 (32.9)	22 (34.9)	3 (23.1)	21 (28.0)
Tumour site					
Colorectal	110 (72.8)	62 (81.6)	54 (85.7)	8 (61.5)	48 (64.0)
Breast	30 (19.9)	11 (14.5)	8 (12.7)	3 (23.1)	19 (25.3)
Other[c]	11 (7.3)	3 (3.9)	1 (1.6)	2 (15.4)	8 (10.7)
Metastatic spread					
Y	74 (49.0)	27 (35.5)	20 (31.7)	7 (53.8)	47 (62.7)
N	76 (50.3)	49 (64.5)	43 (68.3)	6 (46.2)	27 (36.0)
PPE with previous chemo Y	6 (4.0)	5 (6.6)	5 (7.9)	0	1 (1.3)
N	82 (54.3)	35 (46.1)	30 (47.6)	5 (38.5)	47 (62.7)
No prev chemo	58 (38.4)	35 (46.1)	28 (44.4)	7 (53.8)	23 (30.7)
Season start					
Summer	61 (40.4)	23 (30.3)	19 (30.2)	4 (30.8)	38 (50.7)
Winter	90 (59.6)	53 (69.7)	44 (69.8)	9 (69.2)	37 (49.3)

[a] patients who developed PPE of any grade
[b] patients who did not develop PPE during treatment
[c] other tumour sites = Pancreas; Ovary

Table 4-20 Patient characteristics retrospective sample capecitabine monotherapy data

4.3.1.2 Toxicity

In relation to toxicity from capecitabine monotherapy, mild to severe adverse events were reported for 102 of the 151 (67.5%) participants. Diarrhoea was the most common adverse effect. The incidence of each toxicity is listed in table 4.21, the figures reflecting the development of multiple toxicities in many participants.

Toxicity	Sample	With PPE[a] n (%)	PPE pre cycle 4 n (%)	PPE after cycle 4 n (%)	No PPE[b] n (%)
Number (%)	151 (100)	76 (50.3)	63 (82.9)	13 (17.1)	75 (49.7)
Diarrhoea	67 (44.4)	43 (56.6)	39 (61.9)	4 (30.8)	24 (32.0)
Mucositis	34 (22.5)	22 (28.9)	20 (31.7)	2 (15.4)	12 (16.0)
N & V[c]	36 (23.8)	23 (30.3)	18 (28.6)	5 (38.5)	13 (17.3)
Rash	4 (2.6)	2 (2.6)	1 (1.6)	1 (7.7)	2 (2.7)
Fatigue	29 (19.2)	22 (28.9)	17 (27.0)	5 (38.5)	7 (9.3)

[a] patients who developed PPE of any grade
[b] patients who did not develop PPE during treatment
[c] Nausea and vomiting

Table 4-21 Incidence of toxicity retrospective data capecitabine monotherapy

Gastrointestinal adverse events were observed most frequently. 67 participants reported diarrhoea (44.4%) and nausea and/or vomiting were observed in 36 participants (23.8%). PPE developed in 76 participants (50.3%) with 63 (82.9%) of these developing PPE during the first three cycles of their treatment.

A chi-square test for independence (with Yates continuity correction) indicated an association between diarrhoea and PPE, χ^2 (1, n = 151) = 8.27 p = .004, showing that for those who did not develop diarrhoea there were more cases of PPE than would have been expected (observed = 20 cases versus expected = 18.1) (table 4.22).

Crosstab

***p* = .004**			Diarrhoea		
			No	Yes	Total
PPE before Cycle 4	No	Count	188	95	283
		Expected Count	189.9	93.1	283.0
	Yes	Count	20	7	27
		Expected Count	18.1	8.9	27.0
Total		Count	208	102	310
		Expected Count	208.0	102.0	310.0
		% of Total	67.1%	32.9%	100.0%

Table 4-22 Cross tabulation Chi square diarrhoea

There was a statistically significant association between fatigue and PPE, χ^2 (1, n = 151) = 8.14 *p* = .004, showing that for those who reported fatigue there were more cases of PPE than would have been expected (observed = 11 cases versus expected = 7) (figure 4.23).

Crosstab

***p* = .004**			Fatigue		
			No	Yes	Total
PPE before Cycle 4	No	Count	214	69	283
		Expected Count	210.0	73.0	283.0
	Yes	Count	16	11	27
		Expected Count	20.0	7.0	27.0
Total		Count	230	80	310
		Expected Count	230.0	80.0	310.0
		% of Total	74.2%	25.8%	100.0%

Table 4-23 Cross tabulation Chi square fatigue

There was a small to moderate effect size detected with phi = .25 in both instances. The test showed no association between mucositis, nausea and vomiting or rash and development of PPE at any cycle (table 4.24).

Variable	**χ^{2a}**	**df[b]**	**p**	**Phi[c]**
Diarrhoea	8.27	1	.004	.25
Mucositis	2.92	1	.087	.15
N & V[d]	2.80	1	.094	.15
Rash	.00	1	1.00a	-.001
Fatigue	8.14	1	.004	.25

[a] χ^2 differences between observed and expected frequencies
[b] df extent to which values are free to vary given a specific number of subjects and a total score (in 2 x 2 table always 1)
[c] phi strength of any association (effect size or risk) 0-1 higher values indicate a stronger association (small effect = .10, medium effect = .30, large effect = .50 (Cohen 1988)) Can be +ve or -ve
[d] Nausea and vomiting

Table 4-24 Other toxicity effects with PPE incidence any cycle (n = 151) retrospective data capecitabine monotherapy

Since PPE is the toxicity of interest in this study, a more detailed description of the severity of PPE will now be presented.

4.3.1.3 Severity and time course of PPE

For analysis of the severity of PPE, the grade and cycle at first presentation of PPE was recorded and the most severe episode of PPE experienced. The grade distribution, cycle of presentation and the worst episode is presented in table 4.25. Of the 151 participants who received capecitabine monotherapy 76 (50.3%) developed PPE at any cycle, 63 (82.9%) presented with PPE before starting cycle 4 and 13 (17.1%) after starting cycle 4 of their treatment. PPE was evaluated at the time of the development of the first episode. Of the 76 participants who had PPE, 15 participants (19.7%) had their first episode after the first cycle, 34 (44.8%) after the second cycle, 14 (18.4%) after the third cycle and 13 participants (17.1%) had their first episode following the fourth or more cycles. Of the 43 participants whose first presentation of PPE at any cycle of PPE was grade 1, 20 developed grade 2 (11 participants) or grade 3 (9 participants) following subsequent cycles. 24 participants (31.6%) had grade 1 PPE, 23 participants (30.3%) had grade 2 PPE and 29 participants (38.1%) had grade 3 PPE as their most severe episode.

Toxicities of chemotherapy can impact on the patient's ability to continue with their normal activities and some can be life-threatening resulting in delays in treatment and sometimes a reduction in the dose prescribed. Some toxicities may influence the patient's tolerance of treatment, therefore, details of treatment outcome for this sample are given in the following section.

Description	Capecitabine monotherapy		
	All	Pre C4	Post C4
Number (%) No with PPE (%)	151 (100) 76 (50.3)	63 (82.9)	13 (17.1)
1st episode of PPE[a] 1 2 3 4 or later	 15 (19.7) 34 (44.8) 14 (18.4) 13 (17.1)	 15 (23.8) 34 (54.0) 14 (22.2) N/A	 N/A N/A N/A 13 (100)
Grade at 1st episode[b] 1 2 3	 43 (56.6) 17 (22.4) 16 (21.0)	 36 (57.2) 14 (22.2) 13 (20.6)	 7 (53.8) 3 (23.1) 3 (23.1)
Severity of PPE[c] 1 2 3	 24 (31.6) 23 (30.3) 29 (38.1)	 18 (28.5) 19 (30.2) 26 (41.3)	 6 (46.1) 4 (30.8) 3 (23.1)
[a]cycle in which the first episode of PPE developed number and percentage of those with PPE [b]grade that participants presented with at first episode of PPE number and percentage of those with PPE [c] worst grade for each participant developing PPE number and percentage of those with PPE			

Table 4-25 Severity and time course of PPE retrospective capecitabine monotherapy data

4.3.1.4 Treatment Outcome

81 (53.6%) out of 151 participants completed all planned cycles. Details of completion rates including deferral of treatment and dose reductions are provided in table 4.26.

70 participants (46.3%) among the 151 discontinued treatment before completion of 6 cycles. Of these 70 participants the reasons for the discontinuation of treatment were PPE in 11 (15.7%), other toxicities or adverse events 23 (32.9%), disease progression or deteriorating performance status 13 (18.6%), patient request 5 (7.1%), died during treatment 10 (14.3%) or no reason given 5 (7.1%). The remaining 3 (4.3%) were changed to alternative treatment due to toxicities from capecitabine; 2 of the 3 had PPE grade 3 as well as other toxicities.

The 5 participants who chose to discontinue their treatment did so as they were feeling generally unwell due to the effects of the treatment. None of the participants met the usual threshold to stop based on manufacturer's recommendations. Of the 10 that died during their treatment, 6 died following their first cycle of treatment, 2 of which suffered from severe multiple toxicities of capecitabine.

Outcome	Sample
Number (%)	151 (100)
Completed all cycles	81 (53.6)
Discontinued treatment	70 (46.3)
due to PPE[a]	11 (15.7)
due to other toxicities/adverse events[a]	23 (32.9)
Dis prog/poor PS[a]	13 (18.6)
Patient request[a]	5 (7.1)
Died[a]	10 (14.3)
No reason given[a]	5 (7.1)
Changed to other treatment	3 (4.3)
Deferred due to PPE	35 (23.2)
Deferred due to other toxicities	26 (17.2)
Dose reduction at cycle 1	41 (27.2)
Dose reduction due to PPE	34 (22.5)
Dose reduction due to other toxicities	30 (19.9)
[a]% of total no who discontinued treatment	

Table 4-26 Completion rates n(%) retrospective data capecitabine monotherapy

To enable comparison with studies in the literature a further analysis was performed comparing treatment outcome with treatment intent (table 4.27).

Outcome	Adjuvant/ neoadjuvant n (%)	Metastatic/ Palliative n (%)
Number (%)	79 (52.7)	71 (47.3)
Completed all cycles	54 (68.4)	27 (38.0)
Discontinued treatment due to PPE	6 (7.6)	5 (7.0)
Discontinued treatment due to other toxicities	9 (11.4)	4 (5.6)
Dose reduction at cycle 1	13 (16.5)	28 (39.4)
Dose reduction due to PPE	24 (30.4)	10 (14.1)
Dose reduction due to other toxicities	15 (19.0)	15 (21.1)

Table 4-27 Comparison of completion rates n(%) and treatment intent

There is similarity between the percentage of the sample receiving treatment with adjuvant/neoadjuvant intent compared with metastatic/palliative intent. A higher proportion completed all 6 cycles in the adjuvant group. More participants receiving treatment for palliative intent had a dose reduction at the start of treatment. There were similar percentages in each group who had treatment discontinued due to PPE or a dose reduction due to other toxicities. Dose reduction as a result of PPE occurred more frequently in the adjuvant group.

As in the model using the whole sample from the retrospective notes review, the sample used for inferential statistical analysis was restricted to participants who developed PPE within the first 3 cycles and those who did not develop it.

4.3.2 Inferential statistics

4.3.2.1 Bivariate analysis

The findings from the chi-square test for all variables are shown in table 4.34 (page 140). A chi-square test for independence (with Yate's correction for 2 x 2 tables) indicated a significant association between the development of PPE prior to cycle 4 and;

- Gender χ^2 (1, n = 138) = 4.47 p = .03.

The association between gender and PPE showed that for men there were more cases of PPE than would have been expected (observed = 40 cases versus expected = 33.3) (table 4.28).

Crosstab

***p* = .03**			Sex		
			Male	Female	Total
.=those with PPE C4 onwards	.00	Count	33	42	75
		Expected Count	39.7	35.3	75.0
	1.00	Count	40	23	63
		Expected Count	33.3	29.7	63.0
		% of Total	52.9%	47.1%	100.0%

Table 4-28 Cross tabulation Chi square gender

- Tumour site 2 groups (Colorectal and other) χ^2 (1, n = 138) = 7.28 p = .01

The association between tumour site and PPE showed that for those with colorectal cancer, there were more cases of PPE than would have been expected (observed = 54 cases versus expected = 46.6) (table 4.29).

Crosstab

***p* = .01**			tumour2gps		
			Other	Colorectal	Total
.=those with PPE C4 onwards	.00	Count	27	48	75
		Expected Count	19.6	55.4	75.0
	1.00	Count	9	54	63
		Expected Count	16.4	46.6	63.0
		% of Total	26.1%	73.9%	100.0%

Table 4-29 Cross tabulation Chi square tumour type

- Metastatic spread χ^2 (1, n = 138) = 12.50 p = <.001

The association between metastatic spread and PPE showed that for those whose cancer had not metastasised there were more cases of PPE than would have been expected (observed = 43 cases versus expected = 32.2) (table 4.30).

Crosstab

***p* < .001**			Metastatic spread		
			No	Yes	Total
.=those with PPE C4 onwards	.00	Count	27	47	74
		Expected Count	37.8	36.2	74.0
	1.00	Count	43	20	63
		Expected Count	32.2	30.8	63.0
		% of Total	51.1%	48.9%	100.0%

Table 4-30 Cross tabulation Chi square metastatic spread

- PPE with previous chemotherapy χ^2 (2, n = 138) = 6.46 p = .04

The association between PPE with previous chemotherapy and PPE showed that for those who had not had previous chemotherapy, and those who had PPE with previous chemotherapy there were more cases of PPE than would have been expected (observed = 28 cases versus expected = 24 and observed = 5 cases versus expected = 2.8). The accuracy of this finding may be unreliable since the expected count in the latter is less than 5 breaching one of the assumptions of a chi square test (table 4.31).

Crosstab

***p* = .04**			PPE with previous			
			No previous chemo	No PPE with previous chemo	PPE with previous chemo	Total
.=those with PPE C4 onwards	.00	Count	23	47	1	71
		Expected Count	27.0	40.8	3.2	71.0
	1.00	Count	28	30	5	63
		Expected Count	24.0	36.2	2.8	63.0
		% of Total	38.1%	57.5%	4.5%	100.0%

Table 4-31 Cross tabulation Chi square PPE with previous chemotherapy

- Treatment intent χ^2 (1, n = 138) = 15.29 *p* = <.001

The association between treatment intent and PPE showed that for those who were receiving adjuvant capecitabine, there were more cases of PPE than would have been expected (observed = 45 cases versus expected = 33.1) (table 4.32).

Crosstab

***p* < .001**			Aimofcurrentregime2gps		
			Adj or neoadj	metastatic or palliative	Total
.=those with PPE C4 onwards	.00	Count	27	47	74
		Expected Count	38.9	35.1	74.0
	1.00	Count	45	18	63
		Expected Count	33.1	29.9	63.0
		% of Total	52.6%	47.4%	100.0%

Table 4-32 Cross tabulation Chi square treatment intent

- The season during which the treatment commenced χ^2 (1, n = 138) = 5.12 *p* = .02

The association between the season in which treatment started and PPE showed that for those who commenced their treatment during the winter months, there were more cases of PPE than would have been expected (observed = 44 cases versus expected = 37) (table 4.33).

Crosstab

***p* = .02**			Seasonstart		
			Summer	Winter	Total
.=those with PPE C4 onwards	.00	Count	38	37	75
		Expected Count	31.0	44.0	75.0
	1.00	Count	19	44	63
		Expected Count	26.0	37.0	63.0
		% of Total	41.3%	58.7%	100.0%

Table 4-33 Cross tabulation Chi square season in which treatment started

A small to medium effect size was detected for gender, phi = .19; tumour site, phi = .25 and the season in which treatment was commenced, phi = .21.

Medium effects were seen for metastatic spread, phi = -.32, treatment intent, phi = .35 and PPE with previous chemotherapy cramer's V = .22.

Variable	X^2	df	*p* value	Phi/Cramer's V
Gender	4.47[b]	1	.03	-.19
Maritalstatus2gps	.12[b]	1	.73	.05
Ethnic2gps	3.23[b]	1	.07[a]	-.23
Job2gps	.00[b]	1	1.00	-.01
Smoker	.10[b]	1	.76	.06
Alcohol	.14[b]	1	.71	-.06
Recent wt loss	.68[b]	1	.41	-.18
BMI2gpsM	.00[b]	1	1.00	-.01
BMI2gpsF	.00[b]	1	1.00	-.01
Diabetes	.01[b]	1	.93	.03
PVD	.67[b]	1	.24[a]	-.10
Periph neuro	.01[b]	1	.93[a]	-.04
Skin complaints	.01[b]	1	.92[a]	.09
Inflamm cond	2.05[b]	1	.15	-.14
Previous Ca Δ	3.47[b]	1	.06[a]	.18
Prev DXT	.51[b]	1	.48	-.08
PPE with prev chemo	6.46	2	.04[a]	.22
Tumoursite2ps	7.28[b]	1	.01	.25
Met spread	12.50[b]	1	<.001	-.32
Aim of Rx2gps	15.29[b]	1	<.001	-.35
PS3gps	3.92	2	.14[a]	.27
Start season	5.12[b]	1	.02	.21
CrClC13gps	3.16	2	.21	.15
[a]at least 1 cell has expected count of less than 5 [b]yate's correction for 2 x 2 table				
	Indicates variables $p < .05$ and included in multivariate regression analysis			
	Indicates additional variables $p < .25$ and included in multivariate regression analysis			

Table 4-34 Chi-square test for association between variables and development of PPE before cycle 4 retrospective data capecitabine monotherapy

Other analyses were performed to allow comparison with findings in the literature and include;

- Treatment intent and treatment outcome
- Treatment intent and dose reduction
- PPE and age ≥ 65 years compared to > 65 years
- PPE and age > 79 years
- PPE and age and gender combined
- Age and gender combined and treatment intent

- Performance status and dose reductions
- PPE and hormone status of breast cancer
- Grade 3 PPE and creatinine clearance 3 groups
- PPE and gender and alcohol combined
- Metastatic spread and dose reduction

- Treatment intent and treatment outcome χ^2 (4, n = 150) = 32.35 p < .001

The association between treatment intent and treatment outcome showed that for those who received their treatment with adjuvant/neoadjuvant intent, there were more cases who completed all cycles than would have been expected (observed = 43 cases versus expected = 42.7). For those who received treatment with palliative intent, there were more cases who stopped treatment for other reasons than would be expected (observed = 35 cases versus expected = 19.9) (table 4.35). A large effect size was seen phi = .46.

	Outcome					
	Completed all planned cycles	Stopped due to PPE	Stopped due to other toxicity	Stopped for other reasons	Changed to other treatment due to PPE	Total
Adj or neoadj						
Count	54	6	9	7	3	79
Expected count	42.7	5.8	6.8	22.1	1.6	79
Met or pall						
Count	27	5	4	35	0	71
Expected count	38.3	5.2	6.2	19.9	1.4	71
% of total	54.0	7.3	8.7	28	2.0	100

Table 4-35 Cross tabulation treatment intent and treatment outcome

- Treatment intent and dose reduction
  - At start of treatment χ^2 (1, n = 150) = 8.82 p = .003

The association between treatment intent and dose reduction at the start of treatment showed there were more cases who received treatment for palliative intent than would have been expected (observed = 28 cases versus

expected = 19.4) (table 4.36). A medium to large effect size was seen phi = .26.

Dose reduction at cycle 1			
		No	**Yes**
Adj or neoadj	Count	66	13
	Expected count	57.4	21.6
Met or pall		43	28
	Count	51.6	19.4
	Expected count		
% of total		72.7	27.3

Table 4-36 Cross tabulation treatment intent and dose reduction cycle 1

- Due to PPE χ^2 (1, n = 150) = 4.77 *p* = .03

The association between treatment intent and dose reduction due to PPE showed there were more cases who received treatment for adjuvant/neoadjuvant intent than would have been expected (observed = 24 cases versus expected = 17.9) (table 4.37). A small effect size was seen phi = .19

Dose reduction due to PPE			
		No	**Yes**
Adj or neoadj	Count	55	24
	Expected count	61.1	17.9
Met or pall		61	10
	Count	54.9	16.1
	Expected count		
% of total		77.3	22.7

Table 4-37 Cross tabulation treatment intent and dose reduction due to PPE

- Due to other toxicities χ^2 (1, n = 150) = .12 *p* = .94

The association between treatment intent and dose reduction due to other toxicities showed that the proportion receiving treatment for adjuvant/neoadjuvant intent is not significantly different from the proportion receiving treatment for palliative intent.

- PPE and age ≤ 65 years compared to > 65 years χ^2 (1, n = 150) = < .001 *p* = 1.00

The association between the two age groups and PPE showed that the proportion of participants who were ≤ 65 years old who developed PPE of any

grade or grade 3 as their worse grade is not significantly different from the proportion of participants older than 65 years who developed PPE.

- PPE and age > 79 years

Since there were only 20 participants aged over 79 years a cross tabulation was not possible and therefore only frequency data are presented here (table 4.38)

Participants aged over 79 years n = 20 (100%)	
PPE within the first 3 cycles	12 (60)
Grade 2 or 3 at presentation (% of total with PPE)	8 (66.7)
Grade 3 PPE as the worst grade (% of total with PPE)	6 (50)
Completed all planned cycles	11 (55)
Stopped due to PPE	3 (15)
Deferred due to PPE	5 (25)
Deferred due to other toxicities	2 (10)
Dose reduction at cycle 1 (9 due to moderate renal failure, 6 of whom went on the develop PPE grade 2 or 3)	11 (55)
Dose reduction due to PPE	5 (25)
Dose reduction due to other toxicities	2 (10)

Table 4-38 Frequency data participants aged over 79 years (n = 20)

- PPE and age and gender combined χ^2 (3, n = 138) = 5.63 p = .13

Age and gender were combined into four groups; men < 65yrs; men > 64yrs; women < 65yrs; and women > 64yrs.

The association between the age and gender combined and PPE showed that the proportion of participants in any of the 4 groups who developed PPE of any grade is not significantly different from the proportion of participants who did not develop PPE.

When the same variable was entered into a regression analysis, older women were more likely to develop PPE compared with younger women (OR = 1.41, 95% CI .50 – 3.97 p = .51) with the opposite among males, younger men were more likely to develop PPE compared with older men (OR = 1.05, 95% CI .40 - 2.73 p = .92). However, neither achieved statistical significance. (table 4.39).

Variable Agesex	B	Wald	Sig	Exp (B)	95% C.I for Exp (B)	
					Lower	Upper
F < 65 (ref cat)		5.51	.14			
M < 65	1.02	3.35	.07	2.78	.93	8.29
F > 64	.35	.43	.51	1.41	.50	3.97
M > 64	.97	3.80	.05	2.65	.99	7.03
M > 64 (ref cat)		5.51	.14			
F < 65	.50	3.80	.05	.38	.14	1.00
M < 65	.49	.01	.92	1.05	.40	2.73
F > 64	.45	1.92	.17	.53	.22	1.230

Table 4-39 Logistic regression output age and gender combined and PPE retrospective sample

- Age and gender combined and treatment intent χ^2 (3, n = 150) = 20.04 $p < .001$

The association between treatment intent and age and gender combined showed there were more men aged < 65 or > 64 years who received treatment for adjuvant/neoadjuvant intent than would have been expected (observed = 21 and 31 cases versus expected = 15.3 and 26.9 respectively) and there were more women aged < 65 who received treatment for palliative intent than would be expected (observed = 27 cases versus expected = 16.1) (table 4.40). A large effect size was seen phi = .37.

		Treatment intent	
		Adj or neoadj	Met or pall
F < 65	Count	7	27
	Expected count	17.9	16.1
M < 65	Count	21	8
	Expected count	15.3	13.7
F > 64	Count	20	16
	Expected count	19.0	17.0
M > 64	Count	31	20
	Expected count	26.9	24.1
% of total		52.7	47.3

Table 4-40 Cross tabulation treatment intent and age and gender combined

- Performance status and dose reductions
  - At start of treatment χ^2 (2, n = 92) = .57 p = .75

The association between performance status and dose reduction at the start of treatment showed that the proportion that had a dose reduction at the start of treatment is not significantly different from the proportion that did not have a dose reduction at the start of treatment for any grade of performance status.

- Due to PPE χ^2 (2, n = 92) = 5.22 *p* = .07

The association between performance status and dose reduction due to PPE showed that the proportion that had a dose reduction due to PPE is not significantly different from the proportion that did not have a dose reduction due to PPE for any grade of performance status.

- Due to other toxicities χ^2 (2, n = 92) = 2.89 *p* = .24

The association between performance status and dose reduction due to other toxicities showed that the proportion that had a dose reduction due to other toxicities is not significantly different from the proportion that did not have a dose reduction due to other toxicities for any grade of performance status.

- PPE and hormone status of breast cancer

Of the 30 participants with breast cancer, 13 (43.3%) were oestrogen positive (ER) and 9 (30.0%) progesterone receptor (PR) positive. Due to this smaller number it was not possible to apply this data to a chi square test.

- Grade 3 PPE and creatinine clearance 3 groups χ^2 (4, n = 76) = 2.54 *p* = .64

The association between grade 3 PPE and creatinine clearance showed that the proportion that had mild renal impairment (CrCl 50.01 – 80.00) is not significantly different from the proportion that had moderate renal impairment (CrCl < 50.01) or normal renal function (CrCl > 80.00). Of the 76 participants who developed PPE, 29 developed grade 3 as their worst grade. 3 had moderate renal impairment; 12 mild renal impairment and 14 normal renal function.

A logistic regression applied to creatinine clearance and PPE any cycle or PPE within the first 3 cycles showed that the risk of developing PPE increases for every point decrease in CrCl (OR = .99, 95% CI .99 – 1.01).

A logistic regression applied to CrCl 3 groups showed that participants with mild renal impairment were twice as likely to develop PPE at any cycle and within the first 3 cycles compared with those with moderate renal impairment or normal renal function (table 4.41)

	OR	95% CI
Mild renal impairment compare with moderate renal impairment PPE any cycle	2.10	.72 – 6.10
Mild renal impairment compare with moderate renal impairment PPE within the first 3 cycles	1.77	.60 – 5.21
Mild renal impairment compare with normal renal function PPE any cycle	1.78	.88 – 3.61
Mild renal impairment compare with normal renal function PPE within the first 3 cycles	1.93	.92 – 4.06

Table 4-41 Logistic regression applied to creatinine clearance 3 groups

- PPE and gender and alcohol combined χ^2 (1, n = 51) = <.001 p = 1.00

The association between PPE and gender and alcohol combined showed that the proportion that developed PPE at any cycle is not significantly different from the proportion that did not develop PPE for both men and women who drank alcohol.

A chi square could not be applied to gender and alcohol combined and PPE within the first 3 cycles due to insufficient number of cases to meet the assumption that there is a minimum of 5 cases per cell.

- Metastatic spread and dose reductions
    - At start of treatment χ^2 (1, n = 150) = 5.28 p = .02

The association between metastatic spread and dose reduction at the start of treatment showed there were more participants whose tumour had metastasised and had a dose reduction at the start of treatment than would have been expected (observed = 27 cases versus expected = 20.2) (table 4.42). A small to medium effect size was seen phi = .20.

			Dose reduction at cycle 1	
			No	Yes
Metastatic spread	No	Count	62	14
		Expected count	55.2	20.8
Metastatic spread	Yes	Count	47	27
		Expected count	53.8	20.2
% of total			72.7	27.3

Table 4-42 Cross tabulation metastatic spread and dose reduction at start of treatment

- Due to PPE χ^2 (1, n = 150) = 4.23 *p* = .04

The association between metastatic spread and dose reduction due to PPE showed there were more participants whose tumour had not metastasised and had a dose reduction due to PPE than would have been expected (observed = 23 cases versus expected = 17.2) (table 4.43). A small effect size was seen phi = .18.

			Dose reduction due to PPE	
			No	**Yes**
Metastatic spread	No	Count	53	23
		Expected count	58.8	17.2
Metastatic spread	Yes	Count	63	11
		Expected count	57.2	16.8
% of total			77.3	22.7

Table 4-43 Cross tabulation metastatic spread and dose reduction due to PPE

- Due to other toxicities χ^2 (2, n = 150) = 2.14 *p* = .34

The association between metastatic spread and dose reduction due to other toxicities showed that the proportion that had a dose reduction due to other toxicities is not significantly different from the proportion that did not have a dose reduction due to other toxicities.

4.3.2.2

Summary of findings from chi-square

Findings from the χ^2 tests ($p < .05$) show that those more likely to develop PPE were participants;

- Who were male
- With colorectal cancer
- Whose tumour had not metastasised
- Who had PPE with previous chemotherapy or had not had previous chemotherapy
- Receiving capecitabine monotherapy as adjuvant therapy
- Who commenced their treatment during the winter months

The results of the comparison of the means from the independent samples *t*-test for age and laboratory values (continuous data) prior to treatment commencing are shown in table 4.44. Independent-samples *t*-tests were conducted to compare PPE incidence prior to commencing cycle 4 of the treatment for age, BSA, BMI, creatinine, creatinine clearance, and ALT and no significant differences were observed, in any of these variables, between those who developed PPE and those that did not. The same test applied to ALP, albumin and bilirubin (bili) showed a significant difference between those who did not develop PPE (ALP; $\bar{X}$ = 223.04, SD = 211.04, ALB; $\bar{X}$ = 40.15, SD = 4.38, bili; $\bar{X}$ = 10.01, SD = 10.77) and those that did (ALP; $\bar{X}$ = 105.45, SD = 58.80, ALB; $\bar{X}$ = 41.85, SD = 2.98, bili; $\bar{X}$ = 7.92, SD = 4.61) t (132) = 4.53, *p* = <.001 t (132) = 1.50, *p* = 0.01. The magnitude in the difference in the means ($\bar{X}$) (mean difference) for ALP = 117.59 (95% CI, 65.94 to 169.23) was small (eta squared = 0.13), for albumin = -1.70 (95% CI, -2.97 to -.43) and bilirubin = 2.90 (95% CI, -.68 tp -4.87) was very small (eta squared = 0.05 and 0.02 respectively).

Variable	M[a] PPE Y[b]	SD	M[a] PPE N[c]	SD[d]	t	p	Mean diff[e]	CI[f]	ETA[2g]
Age	67.98	11.03	65.84	11.54	-1.10	.27	-2.14	-5.96 to 1.68	0.008
BSA	1.79	.20	1.77	.20	-.58	.56	-.02	-.08 to .05	0.002
BMI	25.10	4.00	25.37	4.85	.35	.73	.27	-1.25 to 1.79	0.0009
Creat	76.51	17.33	76.00	25.01	-.14	.89	-.51	-7.89 to 6.87	0.0001
CrCl	80.79	27.63	85.86	31.08	1.00	.32	5.06	-4.95 to 15.08	0.007
ALT	32.89	49.02	38.39	49.38	.64	.52	5.50	-11.36 to 22.37	0.003
ALP	105.45	58.80	223.04	211.04	4.53	<.001	117.59	65.94 to 169.23	0.13
Bili	7.92	4.61	10.01	10.77	1.50	.009	2.90	-.68 to -4.87	0.02
ALB	41.85	2.98	40.15	4.38	-2.66	.009	-1.70	-2.97 to -.43	0.05

[a] M = mean $\bar{X}$
[b] PPE Y = subjects who developed PPE prior to commencing cycle 4
[c] PPE N = subjects who did not develop PPE at any cycle
[d] SD = standard deviation
[e] Mean diff = Mean difference between the groups
[f] CI = 95% confidence interval
[g] ETA^2 = effect size

Indicates variables $p < .05$ and included in multivariate regression analysis

Table 4-44 Effects within PPE incidence pre cycle 4 (n = 138) retrospective data capecitabine monotherapy

To enable comparison with findings in the literature, logistic regression was applied to BMI and showed that for every point increase in BMI the risk of PPE increased OR = 1.02, 95% CI .95 – 1.09 although this suggested an effect this was not confirmed statistically $p = .64$

A logistic regression applied to BSA showed that for every unit increase in BSA the risk of developing PPE increased OR = 2.37; 95% CI .48 – 11.57, $p = .28$ However this failed to achieve statistical significance.

4.3.2.3 Summary of findings of t-test

The mean of each group in the *t*-tests ($p < .05$) was examined, with the higher mean indicating the direction of association. Those with a lower pre treatment ALP level or bilirubin level or raised albumin level (only slightly) were more likely to develop PPE.

Although this analysis is useful in showing any association of individual variables with the development of PPE, clinically, variables are not present in isolation and it is therefore more useful to apply multivariate tests to the data to establish the performance of the variables when in combination with each other. A multivariate analysis using logistic regression will now be described.

4.3.2.4 Multivariate analysis

The modelling technique used with the whole of the retrospective notes sample was applied to the capecitabine monotherapy sample.

Variable	*P* < .05	*P* < .25
Gender	.03	
Inflammatory conditions		.15
Tumour site 2 groups	.01	
Metastatic spread	< .001	
Season start	.02	
CrCl 3 groups		.21
Bilirubin	.009	
ALP	< .001	
ALB	.009	

Table 4-45 Variables from bivariate analysis entered into regression model

Table 4.45 provides a summary of variables that were significant in the bivariate analysis. It shows those variables significant at both the conventional alpha level of $p < .05$ and the relaxed level $p < .25$ included in the regression model. It excludes those variables with insufficient numbers to be included in the regression model or those that are clinically associated.

4.3.2.5 Purposeful entry and model reduction

9 variables were entered into the logistic regression analysis and 4 removed. Logistic regression, which consisted of 5 steps, was performed for the research sample (n = 151) with 20 missing cases not included in the model. 13 of these were participants who developed PPE after commencing cycle 4 and the remaining 7 consisted of small numbers from several other predictor variables. (Appendix 4.2).

The omnibus tests of model coefficients revealed a Chi-square statistic of 36.05 (df, 4) $p < .001$ indicating that the model performs well compared to the baseline model before the variables were added. The Hosmer-Lemeshow statistic was applied to the data indicating a good fit ($p = > .05$) for all steps until the final step where gender was removed. As this test now showed a poor fit gender was put back into the final model to ensure a good fit, assuming that gender is a confounder and important to the model construction. The Nagelkerke R^2 (.34) value shows about 34% of the variation in the outcome variable (PPE) is explained by the logistic regression model and the percentage correctly predicted to have PPE in this model was 75.0%.

As illustrated in table 4.46 the outcome of the logistic regression analysis produced a model containing 4 predictor variables and 1 confounding variable (gender) which were significantly related to PPE development; absence of pre existing inflammatory conditions, ALP level prior to commencing treatment, the season in which the treatment commenced and metastatic spread. Factors had variable ability to predict the development of PPE. Participants who did not have a pre existing inflammatory condition such as arthritis were two and a half times more likely to develop PPE (OR = 2.59; 95% CI .80 – 8.85, $p = .10$). The risk of PPE in participants who commenced their treatment in the winter was just over two and a half times as great compared to those who commenced in the summer (OR = 2.75; 95% CI 1.21 – 6.24, $p = .02$). The absence of metastases made the chances of developing PPE over twice as likely than the presence of metastatic disease (OR = 2.25; 95% CI .95 –

5.31, *p* = .06) and for every unit increase in the ALP level taken prior to commencing treatment (OR = .99; 95% CI .98 - .99, *p* = .02) the risk of developing PPE was reduced. Men were almost twice as likely to develop PPE than women (OR = 1.91; 95% CI .85 – 4.32), however, this difference did not achieve statistical significance (*p* = .12) since this is a confounding variable.

Retrospective data capecitabine monotherapy					
Predictor variable	**B**	**Wald X^2**	**P* value**	**OR (exp β)**	**95% CI**
Gender Female (60) (ref cat) Male (72)	.65	2.44	.12	1.91	.85-4.32
Inflammatory conditions Yes (20) (ref cat) No (112)	.95	2.26	.10	2.59	.80-8.85
Seasonstart Summer (54) (ref cat) Winter (78)	1.01	5.85	.02	2.75	1.21-6.24
ALPC1	-.006	5.75	.02	.99	.98-.99
Metastatic spread Yes (64) (ref cat) No (68)	.81	3.39	.06	2.25	.95-5.31
Notes * significant at *p* < .1 (2-tailed)					

Table 4-46 Logistic regression output. Predictors of PPE development purposeful entry model

Variables that were not included in the original model were added one at a time and logistic regression applied. Out of the 16 variables that had *p* > .25 in the bivariate tests, 3 became significant at *p* < .25 and were added to the model and reduced as before. All 3 were retained in the model, 1 (smoker) became significant at *p* < .01, and the other 2 (alcohol and weight loss) were retained as confounding variables (table 4.47). Participants who smoked were nearly twice as likely to develop PPE as those who did not smoke (OR = 1.65; 95% CI .46-5.95, *p* = .08). Conversely participants who did not drink alcohol regularly were more likely to develop PPE (OR = .51; 95% CI .17-1.54, *p* = .17). Participants who had lost weight prior to commencing treatment were more likely to develop PPE than those who had not lost weight (OR = .36;

95% CI .07-1.95, p = .24). The latter two variables failed to achieve statistical significance but remained as confounders.

Retrospective data capecitabine monotherapy					
Predictor variable	**B**	**Wald X^2**	**P* value**	**OR (exp β)**	**95% CI**
Gender Female (60) (ref cat) Male (72)	.98	4.56	.03	2.67	1.08-6.56
Inflammatory conditions Yes (20) (ref cat) No (112)	.58	.85	.35	1.79	.52-6.14
Seasonstart Winter (78) (ref cat) Summer (54)	-.89	3.81	.05	.41	.16-1.00
ALPC1	-.006	3.82	.05	.99	.98-1.00
Metastatic spread Yes (64) (ref cat) No (68)	1.02	4.64	.03	2.79	1.09-7.09
Smoker No (68) (ref cat) Yes (18)	.50	.58	.08	1.65	.46-5.95
Alcohol No (31) (ref cat) Yes (47)	-.67	1.43	.17	.51	.17-1.54
Weight loss No (ref cat) (13) Yes	-1.01	1.39	.24	.36	.07-1.95
Notes * significant at $p < .1$ (2-tailed)					

Table 4-47 Logistic regression output purposeful entry model with additional non-significant variables

Different entry methods were applied to the same variables as those used in the purposeful entry model building process and the retention strategy was based on the same rationale as stated previously.

4.3.2.6 Forward and backward conditional entry model

The same 9 variables included in the purposeful reduction model were entered into the logistic regression analysis and 5 removed in 3 steps in the

forward entry method and 4 removed in 5 steps in the backward entry method.

The assessment of 'goodness of fit' is shown in table 4.48 demonstrating a good fit in both entry methods with 28% variance explained by the model in the forward entry method and 31% in the backward entry method. The ability of the model to correctly predict which category each case fits into was 68% in the forward and 70% in the backward stepwise entry methods.

Test	Forward entry	Backward entry
Omnibus tests of Model Coefficients		
Chi-square	31.47	34.84
df	3	4
p	< .001	< .001
Nagelkerke R^2	.28	.31
Hosmer & Lemeshow		
Chi-square	13.38	15.16
df	8	8
p	.09	.06

Table 4-48 Goodness of fit automated entry methods retrospective capecitabine monotherapy data

As shown in table 4.49 the outcomes of the automated entry methods of the logistic regression analysis showed predictive models containing 3 variables in the forward entry strategy and 4 variables in the backward entry strategy which were significantly related to PPE development. The season that the participant commenced their treatment in, metastatic spread and ALP level prior to commencing treatment were common in both models with inflammatory conditions an additional variable in the backward entry model. Factors had variable ability to predict the development of PPE but were identical in the forward and backward entry methods for the 3 common variables. The variables in both automated models showed similar odds ratios and alpha values as the purposeful entry and retention model

Retrospective data capecitabine monotherapy					
Predictor variable	**B**	**Wald X^2**	**P* value**	**OR (exp β)**	**95% CI**
Forward entry method					
Season start Summer (53) (ref cat) Winter (78)	.92	5.22	.02	2.51	1.14-5.35
ALPC1	-.006	5.31	.02	.99	.98-.99
Metastatic spread Yes (63) (ref cat) No (68)	.90	4.54	.03	2.47	1.07-5.68
Backward entry method					
Inflammatory conditions No (111) (ref cat) Yes (20)	-1.04	3.2	.07	.35	.11-1.10
Seasonstart Summer (53) (ref cat) Winter (78)	.97	5.54	.02	2.63	1.18-5.87
ALPC1	-.006	5.58	.02	.99	.98-.99
Metastatic spread Yes (63) (ref cat) No (68)	.90	4.39	.04	2.47	1.06-5.75
Notes * significant at $p < .1$ (2-tailed)					

Table 4-49 Logistic regression output predictors of PPE in the automated entry methods

4.3.2.7 Receiver operating characteristic (ROC) curves

ROC curves were applied to the predicted probabilities created in each of the logistic regression entry methods to compare the accuracy of the models in terms of their sensitivity and specificity in predicting those that develop PPE within the first 3 cycles and those that do not.

The model with 5 variables remaining following the purposeful entry and retention strategy provides a slightly more accurate prediction of those who are likely to develop PPE and those who will not AUC = .80 (95% CI .72-.88) than the models with 4 variables remaining in the backward entry method and 3 variables remaining using the forward entry method AUC = .77 (95% CI .70-.86) and AUC = .76 (95% CI .69-.84) respectively (figure 4.3). From the ROC

curve applied to the purposeful reduction model, the most favourable values for sensitivity and specificity were 75% and 65% respectively. The positive and negative predictive values calculated from the logistic regression output were 70.6% and 79.7% respectively. However, since the confidence intervals are wide and overlap between the models, this would indicate that there is no statistically significant difference between the models.

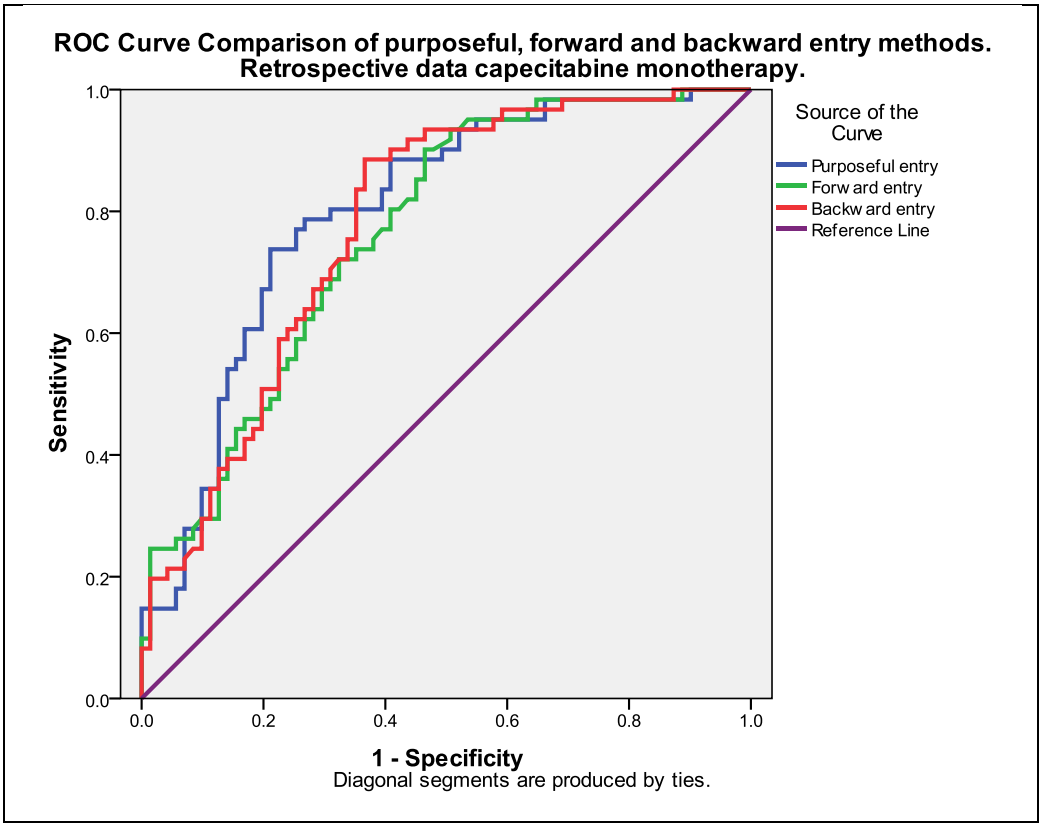


Figure 4-3 ROC curve comparison of purposeful and automated entry methods

Test Result Variable(s) from figure 4.24		Area	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
	Purposeful entry	.800	.724	.876
	Forward entry	.765	.686	.845
	Backward entry	.777	.699	.856

A comparison of the final model with the same model including the three variables that were non-significant in the bivariate analysis (figure 4.4) showed that the latter model provided a more favourable ability to predict the

development of PPE AUC = .84 (95% CI; .78 - .91) with a sensitivity = 79% and specificity 1-.29 = 71%. The positive and negative predictive values calculated from the logistic regression output were 68.6% and 69.0% respectively.

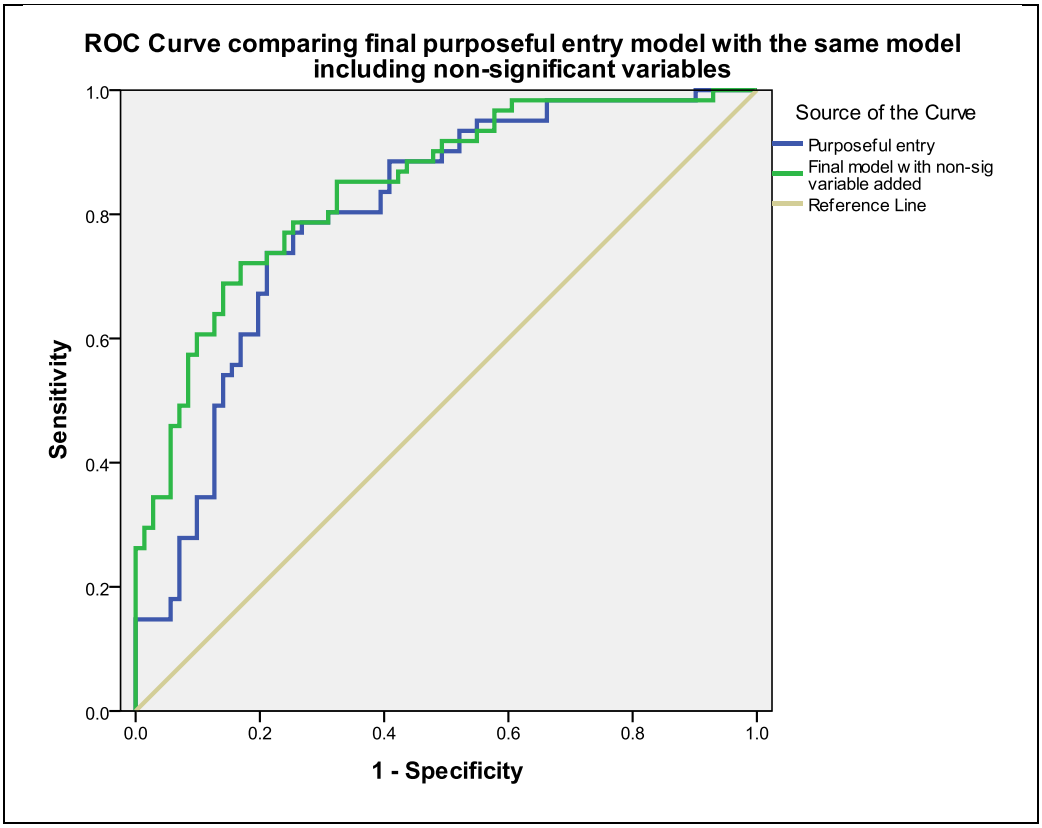


Figure 4-4 ROC curve comparing purposeful entry model with model containing non-significant variables

Test Result Variable(s) from figure 4.25	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
Purposeful entry	.800	.724	.876
With non-sig added	.843	.777	.909

As previously stated, the purposeful selection and retention of variables is, however, worthwhile to produce a richer model including confounders. This is particularly so if one is interested in risk factor modelling rather than simply prediction.

4.3.2.8 Summary of findings of logistic regression model

To summarise the findings from the purposeful selection and retention model, those most at risk of developing PPE were participants;

- Who were male
- Who smoked
- Who did not drink alcohol regularly (confounder)
- With no history of an inflammatory condition
- Who did not lose weight prior to commencing treatment (confounder)
- Whose tumour had not metastasised
- Who commenced their treatment during the winter months
- With a lower pre treatment ALP level

Four variables (smoking, alcohol, inflammatory conditions and weight loss) must be treated with some caution due to the large number of missing data for these variables, a weakness of retrospective data.

4.4 Prospective data

4.4.1 Descriptive statistics

4.4.1.1 Sample characteristics

The sample was drawn from patients commencing capecitabine monotherapy 11th June 2009 to 31st December 2010. A total of 125 participants of which men totalled 49 (39.2%) and women 76 (60.8%) were included in the analysis. The median age was 65 (range 36-83yrs) with no difference between men and women whose median ages were 65yrs (range 36-83yrs) and 64.5 yrs (44-83yrs) respectively.

The sample characteristics are presented in table 4.50. All participants received more than one cycle of chemotherapy, unless the treatment was stopped following the first cycle due to severe toxicities including PPE (n = 1).

Description	Sample	With PPE[a] n (%)	PPE pre cycle 4[a] n (%)	PPE after cycle 4[a] n (%)	No PPE[b] n (%)
Frequency n (%)	125 (100)	83 (66.40)	70 (84.33)	13 (15.66)	42 (33.60)
Age median	65	63	64	60	70.5
Range	36-83	38-81	38-81	41-80	36-83
Gender M	49 (39.2)	34 (41.0)	30 (42.9)	4 (30.8)	15 (35.7)
F	76 (60.8)	49 (59.0)	40 (57.1)	9 (69.2)	27 (64.3)
Ethnicity					
White	113 (90.4)	73 (88.0)	62 (88.6)	11 (84.6)	40 (95.2)
Other	9 (7.2)	8 (9.6)	6 (8.6)	2 (15.4)	1 (2.4)
Not known	3 (2.4)	2 (2.4)	2 (2.8)		1 (2.4)
Marital status					
In a relationship	98 (78.4)	65 (78.3)	55 (78.6)	10 (76.9)	33 (78.6)
Not in a relationship	27 (21.6)	18 (21.7)	15 (21.4)	3 (23.1)	9 (21.4)
Employment					
Working	45 (36.0)	35 (42.2)	28 (40.0)	7 (53.8)	10 (23.8)
Not working	77 (61.6)	46 (55.4)	40 (57.1)	6 (46.2)	31 (73.8)
Not known	3 (2.4)	2 (2.4)	2 (2.9)		1 (2.4)
Tumour site					
Colorectal	70 (56.0)	48 (57.8)	42 (60.0)	6 (46.2)	22 (52.4)
Breast	45 (36.0)	30 (36.1)	23 (32.9)	7 (53.8)	15 (35.7)
Other[c]	10 (8.0)	5 (6.1)	5 (7.1)	0	5 (11.9)
Metastatic spread					
Y	63 (50.4)	38 (45.8)	29 (41.4)	9 (69.2)	25 (59.5)
N	61 (48.8)	45 (54.2)	41 (58.6)	4 (30.8)	16 (38.1)
PPE with previous					
chemo Y	13 (10.4)	8 (9.7)	8 (11.4)	0	5 (11.9)
N	70 (56.0)	47 (56.6)	37 (52.9)	10 (76.9)	23 (54.8)
No prev chemo	42 (33.6)	28 (33.7)	25 (35.7)	3 (23.1)	14 (33.3)
Season start					
Summer	51 (40.8)	37 (44.6)	31 (44.3)	6 (46.2)	14 (33.3)
Winter	74 (59.2)	46 (55.4)	39 (55.7)	7 (53.8)	28 (66.7)

[a] patients who developed PPE of any grade
[b] patients who did not develop PPE during treatment
[c] other tumour sites = Pancreas; Cholangiocarcinoma, unknown primary

Table 4-50 Patient characteristics prospective data

4.4.1.2 Toxicity

Mild to severe adverse events were reported for 101 (80.8%) of the 125 participants. Fatigue and diarrhoea were the most common adverse side effects. The incidence of toxicity is listed in table 4.51, the figures reflecting the development of multiple toxicities in many participants. The incidence of

the toxicities was similar except for the development of a rash which was infrequent and seen in only 7 participants (5.6%). PPE developed in 83 participants (66.4%) with 70 (84.33%) of these developing PPE during the first three cycles of their treatment.

Toxicity	Sample	With PPE [a] n (% with PPE)	PPE pre cycle 4[a] n (% with PPE)	PPE after cycle 4[a] n (% with PPE)	No PPE[b] n (% without PPE)
Number (%)	**125 (100)**	**83 (66.4)**	**70 (84.3) [d]**	**13 (15.7)[d]**	**42 (33.6)**
Diarrhoea	55 (44.0)	41 (49.4)	36 (51.4)	5 (38.5)	14 (33.3)
Mucositis	43 (34.4)	34 (41.0)	31 (44.3)	3 (23.1)	9 (21.4)
N & V[c]	49 (39.2)	39 (47.0)	31 (44.3)	8 (61.5)	10 (23.8)
Rash	7 (5.6)	6 (7.2)	6 (8.6)	0	1 (2.4)
Fatigue	56 (44.8)	38 (45.8)	34 (48.6)	4 (30.8)	18 (42.9)

[a] patients who developed PPE of any grade
[b] patients who did not develop PPE during treatment
[c] Nausea and vomiting
[d] % of those who developed PPE

Table 4-51 Incidence of toxicity n (%) prospective data

A chi-square test for independence (with Yates continuity correction) indicated an association between mucositis and PPE, χ^2 (1, n = 125) = 3.89 p = .05, showing that for those with mucositis there were more cases of PPE than would be expected (observed = 41 cases versus expected = 36.5) (table 4.52).

Crosstab

***p* = .05**			Mucositis		
			No	Yes	Total
PPE	No	Count	33	9	42
		Expected Count	27.6	14.4	42.0
	Yes	Count	49	34	83
		Expected Count	54.4	28.6	83.0
		% of Total	65.6%	34.4%	100.0%

Table 4-52 Cross tabulation Chi Square Mucositis

The only other toxicity where an association was seen was between nausea and vomiting and PPE, χ^2 (1, n = 125) = 5.35 p = .02, showing that for those who reported nausea and vomiting there were more cases of PPE than would be expected (observed = 39 cases versus expected = 32.5) (table 4.53).

Crosstab

p = .02			Nausea or Vomiting		
			No	Yes	Total
PPE	No	Count	32	10	42
		Expected Count	25.5	16.5	42.0
	Yes	Count	44	39	83
		Expected Count	50.5	32.5	83.0
		% of Total	60.8%	39.2%	100.0%

Table 4-53 Cross tabulation Chi Square Nausea or Vomiting

A small to medium effect size was detected in both cases with phi = .19 and phi = .22 respectively. The test showed no association between diarrhoea, fatigue or rash and development of PPE at any cycle (table 4.54).

Variable	χ^{2b}	df[c]	p	phi[d]
Diarrhoea	2.30	1	.13	.15
Mucositis	3.89	1	.05	.19
N & V[e]	5.35	1	.02	.22
Rash	.49	1	.48[a]	.10
Fatigue	.01	1	.90	.03

[a] at least 1 cell contained less than 5 cases
[b] χ^2 differences between observed and expected frequencies
[c] df extent to which values are free to vary given a specific number of subjects and a total score (in 2 x 2 table always 1)
[d] phi strength of any association (effect size or risk) 0-1 higher values indicate a stronger association (small effect = .10, medium effect = .30, large effect = .50 (Cohen 1988)) Can be +ve or -ve
[e] Nausea and vomiting

Table 4-54 Other toxicity effects with PPE incidence any cycle (n = 125) prospective data

Since PPE is the toxicity of interest in this study, a more detailed description of the severity of PPE will now be presented.

4.4.1.3 Severity and time course of PPE

For analysis of the severity of PPE, the grade and cycle at first presentation of PPE was recorded as well as the most severe episode of PPE experienced. The grade distribution, cycle of presentation and the worst episode are presented in table 4.55. Of the 125 participants who received capecitabine monotherapy, 83 (66.4%) developed PPE at any cycle, 70 of these (84.33%)

presented with PPE before starting cycle 4 and 13 (15.66%) after starting cycle 4 of their treatment. PPE was evaluated at the time of the development of the first episode. Of the 83 participants who had PPE, 20 participants (24.1%) had their first episode after the first cycle, 32 (38.5%) after the second cycle, 18 (21.7%) after the third cycle and 13 participants (15.7%) had their first episode following the fourth or more cycles. Of the 56 participants whose first presentation of PPE at any cycle was grade 1, 23 went on to develop more severe PPE; grade 2 (17 participants) or grade 3 (6 participants) following subsequent cycles. 34 participants (40.96%) had grade 1, 34 (40.96%) grade 2, and 15 participants (18.1%) had grade 3 PPE as their most severe episode.

Description	Capecitabine monotherapy		
	All	Pre C4	Post C4
Number (%)	125 (100)		
No with PPE (%)	83 (66.40)	70 (84.33)	13 (15.66)
1st episode of PPE[a]			
1	20 (24.1)	20 (28.6)	N/A
2	32 (38.5)	32 (45.7)	N/A
3	18 (21.7)	18 (25.7)	N/A
4 or later	13 (15.7)	N/A	13 (100)
Grade at 1st episode[b]			
1	56 (67.5)	47 (67.1)	9 (69.2)
2	20 (24.1)	17 (24.3)	3 (23.1)
3	7 (8.4)	6 (8.6)	1 (7.7)
Severity of PPE[c]			
1	34 (40.96)	25 (35.7)	9 (69.2)
2	34 (40.96)	31 (44.3)	3 (23.1)
3	15 (18.1)	14 (20.0)	1 (7.7)

[a]cycle in which the first episode of PPE developed number and percentage of those with PPE
[b]grade that patients presented with at first episode of PPE number and percentage of those with PPE
[c]worst grade for each patient developing PPE number and percentage of those with PPE

Table 4-55 Summary data of PPE prospective data

An incidental finding during this phase was that some patients may not reveal that they have developed PPE unless specifically questioned. An example of this is a female participant in her 50s had a consultation with a doctor and was prescribed her fifth cycle of capecitabine. Prior to providing the patient with

the tablets, it is usual for the nurse or pharmacist to check that the patient is taking the tablets correctly, they have no toxicities and that they are aware of symptoms to report. It would be easy to assume, that as this was the patient's fifth cycle, she would have a full understanding of these. However, from observation of the patient's hands and further questioning, she revealed that both her hands and feet had been very painful and had developed open cracks in the folds of her fingers which had improved. She thought this was due to the cold weather even though she had not experienced this in past winters. On examination, there was erythema of the palms, the healed cracks were evident, and she also stated that her feet were still quite painful but with no broken areas of skin. The concern here was that her PPE had not resolved completely to grade 1 and that if she was to continue with her capecitabine she would rapidly present with grade 3 PPE which may require hospitalisation. This opportunity was used to emphasise to the patient the importance of reporting any symptoms and the implications if they are not reported. A doctor was asked to review the patient who agreed that the treatment should be deferred for one week to allow the PPE to resolve.

As mentioned in chapter 2 (page 24), presentation of PPE may differ in people with dark skin. An example seen in this study was a 61 year old lady from the Philippines with breast cancer who developed grade 3 PPE after cycle 2 of capecitabine treatment. She presented with hyperpigmentation particularly highlighting the creases on the palms of her hands, with blisters and desquamation causing pain and affecting her ability to carry out activities (figure 4.5). She had received previous chemotherapy regimes and had developed PPE at that time.

Figure 4-5 PPE with hyperpigmentation in a non-white participant

Toxicities of chemotherapy can impact on the patient's ability to continue with their normal activities and some can be life-threatening resulting in delays in treatment and sometimes a reduction in the dose prescribed. Some toxicities may influence the patient's tolerance of treatment, therefore, details of treatment outcome for this sample are presented in the following section.

4.4.1.4 Treatment Outcome

72 (57.6%) out of 125 participants completed all planned cycles. Details of completion rates including deferral of treatment and dose reductions are provided in table 4.56.

53 (42.4%) participants among the 125 discontinued treatment. Of these 53 participants the reasons for the discontinuation of treatment were PPE in 5 (9.4%), other toxicities or adverse events 29 (54.7%), disease progression or deteriorating performance status 17 (32.1%), patient request 2 (3.8%), and died during treatment 4 (7.5%). The 3 (5.7%) participants who had received FOLFOX regime and changed to capecitabine did not require 6 cycles of capecitabine and therefore stopped treatment before the sixth cycle. 3 (5.7%) participants developed other serious illnesses and 2 (3.8%) moved home to another location in the country and transferred their care to that region. The remaining participant was changed to alternative treatment due to toxicities from capecitabine, including PPE grade 1. The 2 participants who chose to discontinue their treatment did so as they were feeling generally unwell due to the effects of the treatment. Neither of these two participants met the usual threshold to stop based on the manufacturer's recommendations. The 4 participants who died during treatment were all receiving capecitabine for palliation, 3 for breast cancer and 1 for colorectal cancer. Three of these died following the second cycle and one after commencing the fourth cycle of capecitabine.

Outcome	Sample
Number	125 (100)
Completed all cycles	72 (57.6)
Discontinued treatment	53 (42.4)
due to PPE[a]	5 (9.4)
due to other toxicities/adverse events[a]	29 (54.7)
Dis prog/poor PS[a]	17 (32.1)
Patient request[a]	2 (3.8)
Died[a]	4 (7.5)
Had previous cycles of folfox[a]	3 (5.7)
Changed to other treatment[a]	1 (1.9)
Developed other illness[a]	3 (5.7)
Patient moved location[a]	2 (3.8)
Deferred due to PPE	35 (28.0)
Deferred due to other toxicities	32 (25.6)
Dose reduction at cycle 1	27 (21.6)
Dose reduction due to PPE	33 (26.4)
Dose reduction due to other toxicities	23 (18.4)
[a]% of total number who discontinued treatment	

Table 4-56 Completion rates n (%) prospective data

To enable comparison with studies in the literature a further analysis was performed comparing treatment outcome with treatment intent (table 4.57).

Outcome	Adjuvant/ neoadjuvant n (%)	Metastatic/ Palliative n (%)
Number (%)	60 (100)	65 (100)
Completed all cycles	40 (66.7)	32 (49.2)
Discontinued treatment due to PPE	3 (5.0)	2 (3.1)
Discontinued treatment due to other toxicities	8 (13.3)	2 (3.1)
Dose reduction at cycle 1	9 (15.0)	19 (29.2)
Dose reduction due to PPE	18 (30.0)	15 (23.1)
Dose reduction due to other toxicities	10 (16.7)	14 (21.5)

Table 4-57 Comparison of completion rates n(%) and treatment intent

There is similarity between the percentage of the sample receiving treatment with adjuvant/neoadjuvant intent compared with metastatic/palliative intent. A higher proportion completed all 6 cycles in the adjuvant group. More participants receiving treatment for palliative intent had a dose reduction at the start of treatment. There were similar percentages in each group who had

treatment discontinued due to PPE. dose reduction due to PPE or a dose reduction due to other toxicities.

As in the previous analysis of the retrospective sample and the participants receiving capecitabine monotherapy taken from that sample, inferential statistical tests were applied to those who developed PPE within the first 3 cycles and those who did not develop it.

4.4.2 Inferential statistics

4.4.2.1 Bivariate analysis

The findings from the chi-square test for all variables are shown in table 4.58

Variable	X^2	df	*P* value	Phi/Cramer's V
Gender	.58[b]	1	.45	-.08
Maritalstatus2gps	.00[b]	1	1.00	.005
Ethnic2gps	.13[b]	1	.72[a]	-.06
Job2gps	.83[b]	1	.36	-.1
Smoker	.01[b]	1	.90[a]	-.04
Alcohol	1.54[b]	1	.21	.13
Recent wt loss	.29[b]	1	.59	-.07
Diabetes	2.52[b]	1	.11	-.16
PVD	.57[b]	1	.45[a]	-.11
Periph neuro	.00[b]	1	.99[a]	.03
Skin complaints	.05[b]	1	.83	.04
Inflamm cond	3.87[b]	1	.05	.19
Previous Ca Δ	.14[b]	1	.71	.06
Prev DXT	.96[b]	1	.33	-.10
Perf status 3 gps	6.56	2	.04	.23
PPE with prev chemo	.65	2	.72	.07
Tumoursite3gps	1.04[b]	2	.59	.09
Met spread	4.83[b]	1	.03	-.21
Aim of Rx2gps	5.22[b]	1	.02	-.22
Start season	.51[b]	1	.48	-.08
CrClC13gps	2.85	2	.24	.15
Sunburn	.49[b]	1	.49	.09
Hobbies	.30[b]	1	.58	.07
Hot water	1.05[b]	1	.30	-.12
Dry skin	.65[b]	1	.42	.10
Cool hands	3.83[b]	1	.05	-.22
Cool feet	2.79[b]	1	.09	-.19
Sweaty hands	.02[b]	1	.89	-.04
Sweaty feet	.02[b]	1	.89	.04
Hand cream	.00[b]	1	1.00	-.002
Skin type 2gps	.00[b]	1	1.00	-.013
[a]at least 1 cell has expected count of less than 5 [b]yate's correction for 2 x 2 table				
	Indicates variables $p < .05$ and included in multivariate regression analysis			
	Indicates additional variables $p < .25$ included in multivariate regression analysis			

Table 4-58 Chi-square test for association between variables and development of PPE before cycle 4 prospective data

A chi-square test for independence (with Yate's correction for 2 x 2 tables) indicated a significant association between the development of PPE prior to cycle 4 and;

- Presence of a pre-existing inflammatory condition χ^2 (1, n = 125) = 3.87 *p* = .05

The association between inflammatory conditions and PPE showed that for those who had a pre-existing inflammatory condition there were more cases of PPE than would have been expected (observed = 25 cases versus expected = 19.6) (table 4.59).

Crosstab

***p* = .05**			Inflammatory conditions		Total
			No	Yes	
PPE before C4	No PPE or post C4	Count	45	10	55
		Expected Count	39.6	15.4	55.0
	PPE pre C4	Count	45	25	70
		Expected Count	50.4	19.6	70.0
		% of Total	72.0%	28.0%	100.0%

Table 4-59 Cross tabulation Chi Square Inflammatory conditions

- Treatment intent (aim of treatment 2gps) χ^2 (1, n = 125) = 5.22 *p* = .02

The association between treatment intent an PPE showed that for those who were receiving capecitabine as adjuvant therapy, there were more cases of PPE than would have been expected (observed = 41 cases versus expected = 34.2) (table 4.60).

Crosstab

***p* = .02**			Aim of current regime		Total
			Adjuvant or neoadjuvant	Metastatic or Palliative	
PPE before C4	No PPE or post C4	Count	20	35	55
		Expected Count	26.8	28.2	55.0
	PPE pre C4	Count	41	29	70
		Expected Count	34.2	35.8	70.0
		% of Total	48.8%	51.2%	100.0%

Table 4-60 Cross tabulation Chi Square Treatment Intent

- Metastatic spread χ^2 (1, n = 125) = 4.83 *p* = .03

The association between metastatic spread and PPE showed that for those whose cancer had not metastasised there were more cases of PPE than would have been expected (observed = 41 cases versus expected = 34.4) (table 4.61).

Crosstab

***p* = .03**			Metastatic spread		
			No	Yes	Total
PPE before C4	No PPE or post C4	Count	20	34	54
		Expected Count	26.6	27.4	54.0
	PPE pre C4	Count	41	29	70
		Expected Count	34.4	35.6	70.0
		% of Total	49.2%	50.8%	100.0%

Table 4-61 Cross Tabulation Chi Square Metastatic Spread

- Performance status χ^2 (2, n = 121) = 9.31 *p* = .05

The association between performance status and PPE showed that for those whose performance status was 0. There were more cases of PPE than would have been expected (observed = 33 cases versus expected = 26) (table 4.62).

***p* = .05**			Perfstatus3gps			Total
			0	1	2 & 3	
PPE before C4	No PPE	Count	14	34	6	54
		Expected Count	21.0	27.7	5.4	54.0
	PPE pre C4	Count	33	28	6	67
		Expected Count	26.0	34.3	6.6	67.0
Total		**% of total**	38.8%	51.2%	9.9%	**100%**

Table 4-62 Cross Tabulation Chi Square Performance Status

- Cool hands χ^2 (1, n = 125) = 3.83 *p* = .05

The association between cool hands and PPE showed that for those who had a tendency to have warm hands, there were more cases of PPE than would have been expected (observed = 42 cases versus expected = 21) (table 4.63).

Crosstab

***p* = .05**			Cool hands		
			No	Yes	Total
PPE before C4	No PPE or post C4	Count	17	21	38
		Expected Count	22.2	15.8	38.0
	PPE pre C4	Count	42	21	63
		Expected Count	36.8	26.2	63.0
		% of Total	58.4%	41.6%	100.0%

Table 4-63 Cross Tabulation Chi Square Cool Hands

A small effect size was detected for pre-existing inflammatory conditions, phi = .19 and a small to medium effect size for metastatic spread, treatment intent, performance status and a tendency to have warm hands (phi = .21, .22, .23 and .22 respectively).

A case from this prospective sample highlights the potential link between peripheral vascular disease and PPE. A 68 year old white skinned male commenced adjuvant capecitabine following a right hemicolectomy for colorectal cancer. The retired gentleman, who lives alone, stopped smoking 20 years ago and who drinks one and a half litres of whisky per week and has a past medical history of a previous high grade non-Hodgkin's lymphoma which had been treated with chemotherapy (CHOP). In addition he had received radiotherapy to his right eye 12 years previously. Co-morbidities include Rheumatoid Arthritis currently treated with methotrexate; Dermatomyocitis treated with prednisolone 7.5mg daily and Reynaud's Disease. Other medications taken were amlodipine and ibandronic acid. Folic acid was stopped prior to commencing capecitabine.

This gentleman was commenced on 75% of the standard capecitabine regime of 1250 mg/m^2 twice a day for 2 weeks with 1 weeks rest due to the concomitant methotrexate. He tolerated his first cycle well with PPE grade 1 as the sole toxicity and the capecitabine was increased to the full dose. Following cycle 2 he went on to present with grade 3 PPE with erythema, pain, swelling and sores on his fingers significantly affecting his daily activities (figure 4.6).

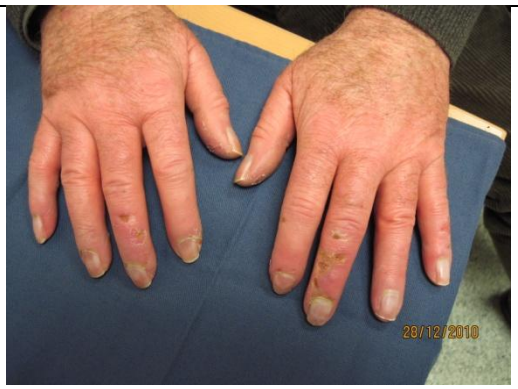


Figure 4-6 PPE grade 3 following cycle 2 of capecitabine monotherapy

His treatment was deferred for 2 weeks with improvement in some of the lesions. However, one lesion had become infected for which he was prescribed antibiotics. Two weeks later this lesion had shown no improvement (figure 4.7), and he was subsequently referred to a dermatologist who prescribed a further course of antibiotics. The capecitabine was stopped.

Figure 4-7 Infected lesion following a course of antibiotics

People commencing capecitabine in the presence of dermatological toxicities from previous chemotherapy treatment may experience a delay or even a deterioration in symptoms as was the case in a young female in the current study. This lady previously received docetaxel, but unfortunately her disease progressed during this treatment and she was changed to capecitabine. She had lost her finger nails due to the effect of docetaxel which failed to heal during treatment with capecitabine (figure 4.8).

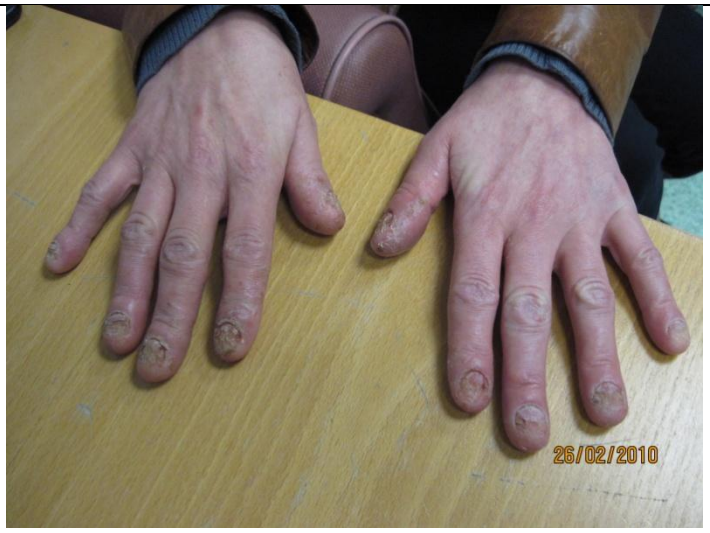


Figure 4-8 Nail toxicity from docetaxel

Other analyses were performed to allow comparison with findings in the literature and include;

- Treatment intent and treatment outcome
- Treatment intent and dose reduction
- PPE and age ≥ 65 years compared to > 65 years
- PPE and age > 79 years
- PPE and age and gender combined
- Age and gender combined and treatment intent
- Performance status and dose reductions
- Performance status and hobbies
- PPE and hormone status of breast cancer
- Grade 3 PPE and creatinine clearance 3 groups
- PPE and gender and alcohol combined
- Metastatic spread and dose reduction

- Treatment intent and treatment outcome χ^2 (3, n = 125) = 14.33 p < .002

The association between treatment intent and treatment outcome showed that for those who received their treatment with adjuvant/neoadjuvant intent, there were more cases who completed all cycles than would have been expected (observed = 40 cases versus expected = 34.8). For those who received treatment with palliative intent, there were more cases who stopped treatment for other reasons than would be expected (observed = 28 cases versus expected = 19.1) (figure 4.64). A large effect size was seen phi = .34.

	Treatment outcome				
	Completed all planned cycles	Stopped due to PPE	Stopped due to other toxicity	Stopped for other reasons	Total
Adj or neoadj					
Count	40	3	8	9	79
Expected count	34.8	2.4	4.8	17.9	79
Met or pall					
Count	32	2	2	28	71
Expected count	37.2	2.6	5.2	19.1	71
% of total	58.1	4.0	8.1	29.8	100

Table 4-64 Cross tabulation treatment intent and treatment outcome

- Treatment intent and dose reduction
  - At start of treatment χ^2 (1, n = 125) = 3 13 p = .08

The association between treatment intent and dose reduction at the start of treatment showed that the proportion receiving treatment for adjuvant/neoadjuvant intent is not significantly different from the proportion receiving treatment for palliative intent.

  - Due to PPE χ^2 (1, n = 125) = .39 p = .53

The association between treatment intent and dose reduction due to PPE showed that the proportion receiving treatment for adjuvant/neoadjuvant intent is not significantly different from the proportion receiving treatment for palliative intent.

  - Due to other toxicities χ^2 (3, n = 125) = 2.30 p = .51

The association between treatment intent and dose reduction due to other toxicities showed that the proportion receiving treatment for

adjuvant/neoadjuvant intent is not significantly different from the proportion receiving treatment for palliative intent.

- PPE and age ≤ 65 years compared to > 65 years χ^2 (1, n = 125) = 5 47 *p* = .02

The association between the two age groups and PPE showed there were more participants aged ≤ 65 years who developed PPE of any grade than would have been expected (observed = 47 versus expected = 40.3) (table 4.65). A small to medium effect size was seen phi = .23.

		PPE	
		No	**Yes**
Age ≤ 65	Count	14	47
	Expected count	20.7	40.3
Age > 65	Count	28	35
	Expected count	21.3	41.7
% of total		33.9	66.1

Table 4-65 Cross tabulation age 2 groups and PPE any grade

- PPE by grade and age ≤ 65 years compared to > 65 years χ^2 (3, n = 125) = 8 97 *p* = .03

The association between the two age groups and PPE showed that more participants aged ≤ 65 years old developed grade 1 PPE than would have been expected (observed 23 versus expected = 16.7) (table 4.66) A medium to large effect size was seen phi = .27

		Worst grade of PPE			
		1	**2**	**3**	**N/A**
Age ≤ 65	Count	23	17	7	14
	Expected count	16.7	16.2	7.4	20.7
Age > 65	Count	11	16	8	28
	Expected count	17.3	16.8	7.6	21.3
% of total		27.4	26.6	12.1	33.9

Table 4-66 Cross tabulation age 2 groups and worst grade of PPE

The proportion of participants who developed PPE grade 3 as their worse grade was similar between the two groups (11.5 and 12.7% respectively).

- PPE and age > 79 years

Since there were only 6 participants aged over 79 years a cross tabulation was not possible and therefore only frequency data are presented here (table 4.67)

Participants aged over 79 years n = 6 (100%)	
PPE within the first 3 cycles	2 (33.3)
Grade 3 PPE as the worst grade	1 (16.7)
Completed all planned cycles	3 (50)
Stopped due to PPE	1 (16.7)
Deferred due to PPE	2 (33.3)
Deferred due to other toxicities	1 (16.7)
Dose reduction at cycle 1 (1 due to moderate renal failure who did not subsequently develop PPE. 1 of the 4 developed PPE grade 1 and other toxicities requiring further dose reduction))	4 (66.7)
Dose reduction due to PPE	2 (33.3)
Dose reduction due to other toxicities	1 (16.7)

Table 4-67 Frequency data participants aged over 79 years (n = 6)

- PPE and age and gender combined χ^2 (3, n = 125) = 5.01 p = .17

Age and gender were combined into four groups; men < 65yrs; men > 64yrs; women < 65yrs; and women > 64yrs.

The association between the age and gender combined and PPE showed that the proportion of participants in any of the 4 groups who developed PPE of any grade is not significantly different from the proportion of participants who did not develop PPE.

When the same variable was entered into a regression analysis, younger women were more likely to develop PPE compared with older women (OR = 1.38, 95% CI .56 - 3.41 p = .48) with a similar finding among males, (OR = 3.55, 95% CI 1.04 – 12.06 p = .04). However, only the male sample achieved statistical significance. (table 4.68).

Variable	**B**	**Wald**	**Sig**	**Exp (B)**	**95% C.I for Exp (B)**	
Agesex					**Lower**	**Upper**
F < 65	.32	.49	.48	1.38	.56	3.41
M < 65	1.27	4.12	.04	3.55	1.04	12.06

Table 4-68 Logistic regression output age and gender combined and PPE prospective sample

- Age and gender combined and treatment intent χ^2 (3, n = 125) = 42.58 $p < .001$

The association between treatment intent and age and gender combined showed there were more men aged < 65 or > 64 years who received treatment for adjuvant/neoadjuvant intent than would have been expected (observed = 20 and 18 cases versus expected = 11.0 and 11.6 respectively) and there were more women aged < 65 who received treatment for palliative intent than would be expected (observed = 34 cases versus expected = 19.1) (table 4.69). A large effect size was seen phi = .59. However, since there are less than 5 cases in two cells this result may not be reliable.

		Treatment intent	
		Adj or neoadj	**Met or pall**
F < 65	Count	3	34
	Expected count	17.9	19.1
M < 65	Count	20	4
	Expected count	11.6	12.4
F > 64	Count	19	20
	Expected count	18.9	20.1
M > 64	Count	18	6
	Expected count	11.6	12.4
% of total		48.4	51.6

Table 4-69 Cross tabulation treatment intent and age and gender combined

- Performance status and dose reductions
    - At start of treatment χ^2 (2, n = 125) = 5.50 $p = .06$

The association between performance status and dose reduction at the start of treatment showed that the proportion that had a dose reduction at the start of treatment is not significantly different from the proportion that did not have a dose reduction at the start of treatment for any grade of performance status.

- Due to PPE χ^2 (2, n = 125) = 4.78 $p = .09$

The association between performance status and dose reduction due to PPE showed that the proportion that had a dose reduction due to PPE is not significantly different from the proportion that did not have a dose reduction due to PPE for any grade of performance status.

- Due to other toxicities χ^2 (6, n = 125) = 4.85 $p = .56$

The association between performance status and dose reduction due to other toxicities showed that the proportion that had a dose reduction due to other toxicities is not significantly different from the proportion that did not have a dose reduction due to other toxicities for any grade of performance status.

- Performance status and hobbies χ^2 (2, n = 125) = 6.22 *p* = .04

The association between performance status and hobbies showed that there were more cases of those with performance status 0 who had hobbies that could cause friction or pressure to the hands or feet than would be expected (observed = 25 versus expected = 20.9) (table 4.70). A medium effect size was seen phi = .25. Since there are less than 5 cases in one expected count cell the result may not be reliable.

		Hobbies	
		No	**Yes**
PS 0	Count	12	25
	Expected count	16.1	20.9
PS 1	Count	24	29
	Expected count	23.0	30.0
PS 2 & 3	Count	7	2
	Expected count	3.9	5.1
Total %		43.4	56.6

Table 4-70 Cross tabulation performance status and hobbies

- PPE and hormone status of breast cancer

Of the 45 participants with breast cancer, 23 (51.1%) were oestrogen positive (ER) and 13 (28.9%) progesterone receptor (PR) positive.

  - Oestrogen receptor status and PPE χ^2 (1, n = 40) = 7.37 *p* = .007

The association between oestrogen receptor status and PPE showed that there were more cases developing PPE that were oestrogen receptor positive than would be expected (observed = 20 versus expected = 15.5) (table 4.71). A medium to large effect size was seen phi = .48

		ER	
		Negative	**Positive**
PPE No	Count	10	3
	Expected count	5.5	7.5
PPE Yes	Count	7	20
	Expected count	11.5	15.5
Total %		42.5	57.5

Table 4-71 Cross tabulation oestrogen receptor status and PPE

- Progesterone status and PPE

The association between progesterone status and PPE showed that the proportion that were progesterone positive is not significantly different from the proportion that were progesterone negative.

- Grade 3 PPE and creatinine clearance 3 groups χ^2 (6, n = 83) = 14.40 p = .03

The association between grade 3 PPE and creatinine clearance showed that there were more cases that had mild renal impairment (CrCl 50.01 – 80.00) and grade 3 PPE than expected (observed = 10 versus expected = 6.4) (table 4.72). A medium to large effect size was seem phi = .34 However the assumption that there should be 5 cases in all expected count cells was violated, therefore the result may be unreliable.

CrCl		Worst grade of PPE		
		1	**2**	**3**
<50.00	Count	2	0	1
	Expected count	1.9	1.9	8
50.01-80.00	Count	10	11	10
	Expected count	14.4	14.4	6.4
>80.01	Count	22	23	47
	Expected count	17.7	17.7	7.8
Total %		41	41	18

Table 4-72 Cross tabulation CrCl 3 groups and worst grade of PPE

Of the 15 participants who developed PPE grade 3 as their worst grade; 1 had moderate renal impairment; 10 mild renal impairment and 4 normal renal function.

A logistic regression could not be applied to CrCl 3 groups since there were less than 10 cases in one category.

- PPE and gender and alcohol combined
    - Men and alcohol χ^2 (1, n = 45) = .65 *p* = .42

The association between men and alcohol and PPE showed that the proportion that drank alcohol regularly and developed PPE is not significantly different from the proportion that did not drink alcohol regularly and developed PPE.

- Women and alcohol χ^2 (1, n = 71) = .02 *p* = .89

- The association between women and alcohol and PPE showed that the proportion that drank alcohol regularly and developed PPE is not significantly different from the proportion that did not drink alcohol regularly and developed PPE.

- Metastatic spread and dose reductions
    - At start of treatment χ^2 (1, n = 125) = 3.30 *p* = .11

The association between metastatic spread and dose reduction at the start of treatment showed that the proportion whose tumour had metastasised was not significantly different from the proportion whose tumour had not metastasised.

- Due to PPE χ^2 (1, n = 125) = 4.82 *p* = .09

The association between metastatic spread and dose reduction due to PPE showed that the proportion whose tumour had metastasised was not significantly different from the proportion whose tumour had not metastasised.

- Due to other toxicities χ^2 (2, n = 123) = 2.35 *p* = .50

The association between metastatic spread and dose reduction due to other toxicities showed that the proportion whose tumour had metastasised was not significantly different from the proportion whose tumour had not metastasised.

4.4.2.2 Summary of findings from the chi-square tests

Findings from the chi-square tests ($p < .05$) show that those more likely to develop PPE were participants;

- Who had a history of inflammatory conditions
- Whose tumour had not metastasised
- Who received capecitabine monotherapy as adjuvant treatment
- With a good performance status
- Who reported having warm hands most of the time

The results of the comparison of the means from the independent samples *t*-test for age and laboratory values (continuous data) prior to treatment commencing are shown in table 4.73. Independent-samples *t*-tests were conducted to compare PPE incidence prior to commencing cycle 4 of the treatment for age, BSA, BMI, creatinine, creatinine clearance, ALT, ALP, Bilirubin and Albumin and no significant difference was observed in any of these variables between those who developed PPE and those that did not.

To allow comparison with findings in the literature, logistic regression was applied to BSA to establish any risk of developing PPE. This showed that for every unit increase in BSA the risk of developing PPE increased OR = 4.43; 95% CI .69 – 28.26, $p = .11$ However this did not achieve statistical significance

Variable	M[a] PPE Y[b]	SD	M[a] PPE N[c]	SD[d]	t	p	Mean diff[e]	CI[f]	ETA[2g]
Age	62.39	10.12	66.22	11.92	1.93	.06	3.83	-.09 to 7.75	.03
BSA	1.79	.21	1.72	.21	-1.70	.09	.27	-.14 to .01	.02
BMI	27.14	8.73	24.72	5.06	-1.82	.07	-2.41	-5.04 to .21	.02
Creat C1	73.61	17.64	70.47	16.37	-1.01	.31	-3.14	-9.25 to 2.98	.01
CrClC1	89.78	28.95	83.01	32.54	-1.22	.22	-6.77	-17.71 to 4.17	.01
ALTC1	29.54	24.38	29.44	22.21	-.02	.98	-.09	-8.63 to 8.45	<.001
ALPC1	139.92	151.52	160.83	140.38	.77	.44	20.91	-32.54 to 74.36	.005
BiliC1	7.38	3.22	8.19	5.00	1.05	.29	.80	-.70 to -2.30	.01
ALB C1	43.28	4.14	42.00	3.70	-1.72	.09	-1.28	-2.76 to .199	.02

[a] M = mean
[b] PPE Y = subjects who developed PPE prior to commencing cycle 4
[c] PPE N = subjects who did not develop PPE at any cycle
[d] SD = standard deviation
[e] Mean diff = Mean difference between the groups
[f] CI = 95% confidence interval
[g] ETA squared = effect size

Indicates variables with $p < .25$ included in multivariate regression analysis

Table 4-73 Effects within PPE incidence pre cycle 4 (n = 138) prospective data

4.4.2.3 Multivariate analysis

The modelling technique used is the same as that applied to the retrospective data.

Table 4.74 provides a summary of variables that were significant in the bivariate analysis. It shows those variables significant at both the conventional alpha level of $p < .05$ and the relaxed level $p < .25$ included in the regression model. It excludes those variables with insufficient numbers to be included in the regression model or those that are clinically associated.

Variable	*P* < .05	*P* < .25
Age		.06
Alcohol		.21
BMI		.07
Diabetes		.11
Inflammatory conditions	.05	
Performance status 3 groups	.04	
Metastatic spread	.03	
CrCl		.22
Albumin		.09
Cool hands	.05	

Table 4-74 Variables from bivariate analysis entered into regression model

4.4.2.4 Purposeful entry and model reduction

11 variables were entered into the logistic regression analysis and 3 removed. Logistic regression, which consisted of 6 steps, was performed for the research sample (n = 125) with 13 missing cases (those that developed PPE after the third cycle of treatment) not included in the model. (Appendix 4.2)

The omnibus tests of model coefficient revealed a Chi-square statistic of 35.29 (df, 10) $p < .001$ indicating that the model performs well compared to the baseline model before the variables were added. The Hosmer-Lemeshow statistic was applied to the data revealing a Chi-square statistic of 4.77 (df, 8) $p = .78$ which indicates that the observed numbers who develop PPE are not significantly different from those expected by the model and that the overall fit is good. The Nagelkerke R^2 (.36) value shows about 36% of the variation in the outcome variable (PPE) is explained by the logistic model and the percentage correctly predicted in this model was 72.6%

As illustrated in table 4.75 the outcome of the logistic regression analysis produced a model containing 6 predictors and 2 confounding variables. The predictors which were significantly related to PPE development included; pre existing inflammatory conditions, metastatic spread, cool hands, age, BMI and CrCl prior to commencing treatment. The 2 confounding variables were alcohol and performance status. Performance status and alcohol consumption

were considered confounders since their removal, at different steps in the model building strategy, caused a greater than 20% change in the beta value of other variables. The removal of alcohol from the model caused a change in the beta value of the variables performance status and creatinine clearance. The removal of performance status caused a change in the beta value of the variable alcohol. Factors had variable ability to predict the development of PPE. Participants who had a pre existing inflammatory condition such as arthritis were nearly 3 times more likely to develop PPE prior to cycle 4 (OR = 2.60; 95% CI .89 – 7.59, *p* = .08) The risk of PPE in participants who did not have metastatic spread was just over 3 times as great compared to those who had metastatic spread (OR = 3.18; 95% CI 1.17 – 8.61, *p* = .02). The tendency to have warm hands made the chances of developing PPE nearly twice as likely than those with a tendency to have cool hands (OR = 1.90; 95% CI .72 – 5.02, *p* =.06) and for every unit increase in age (OR = .93; 95% CI .88 - .99, *p* = .01) the risk of developing PPE was reduced. For every unit increase in BMI the risk of developing PPE increased (OR = 1.13; 95% CI 1.00 – 1.29. *p* = .04), conversely the risk of PPE decreased with every unit increase in creatinine clearance (OR = .98; 95% CI .96 – 1.00, *p* = .07). Although non-significant as confounding variables participants who drank alcohol regularly were twice as likely to develop PPE (OR = 2.18; 95% CI .77 – 6.12, *p* = .14) and participants with a performance status of 0 were nearly twice as likely to develop PPE compared to those with poorer performance status (OR = 1.64; 95% CI .30 – 8.83, *p* = .14).

Predictor variable	B	Wald χ^2	*p** value	OR (exp β)	95% CI
Alcohol No (64) (ref cat) Yes (49)	.78	2.16	.14	2.18	.77 - 6.12
Inflammatory conditions No (79) (ref cat) Yes (34)	.96	3.06	.08	2.60	.89 – 7.59
Metastatic spread Yes (58) (ref cat) No (55)	1.16	5.17	.02	3.18	1.17 – 8.61
Cool hands Yes (41) (ref cat) No (58)	.64	1.67	.06	1.90	.72 – 5.02
Performance status 2 & 3 (11) (ref cat) 0 (43) 1 (59)	.49 -.51	3.87 .39	.14 .53	1.64 .60	.30 – 8.83 .12 – 2.98
Age	-.07	6.03	.01	.93	.88 - .99
BMI	.13	4.03	.04	1.13	1.00 – 1.29
CrCl C1[a]	-.02	3.10	.07	.98	.96 – 1.00
Notes *significant at $p < .1$ (2-tailed) [a]Creatinine clearance cycle 1					

Table 4-75 Logistic regression output predictors of PPE purposeful entry model prospective data

Variables that were not included in the original model were added one at a time and logistic regression applied. Out of the 22 variables that had $p > .25$ in the bivariate tests, one (previous radiotherapy) became significant at $p < .1$ in this process. This variable was therefore added to the final model and reduced in the same way as before. Participants who had not had previous radiotherapy treatment were more likely to develop PPE than those that had previous radiotherapy (OR = 2.93; 95% CI 1.04 – 8.25, $p = .04$) (Table 4.76).

Predictor variable (n = 356)	B	Wald χ^2	*p** value	OR (exp β)	95% CI
Alcohol No (64) (ref cat) Yes (49)	 .95	 2.89	 .09	 2.59	 .86-7.79
Inflammatory conditions No (79) (ref cat) Yes (34)	 .98	 3.05	 .08	 2.67	 .89-7.06
Metastatic spread Yes (58) (ref cat) No (55)	 .91	 2.88	 .09	 2.48	 .87-7.10
Cool hands Yes (41) (ref cat) No (58)	 .67	 1.71	 .03	 1.95	 .72-5.3
Performance status 2 & 3 (11) (ref cat) 0 (43) 1 (59)	 .50 -.47	 .32 .32	.18 .57 .57	 1.65 .62	 .29-9.26 .12-3.21
Age	-.09	7.84	.005	.91	.86-.97
BMI	.16	5.46	.02	1.17	1.03-1.33
CrCl C1[a]	-.03	4.12	.04	.97	.95-.99
Previous radiotherapy Yes (61) (ref cat) No (52)	 1.07	 4.13	 .04	 2.93	 1.04-8.25
Notes * significant at $p < .1$ (2-tailed) [a]Creatinine clearance cycle 1					

Table 4-76 Logistic regression output predictors of PPE purposeful entry model with additional non-significant variables prospective data

Different entry methods were applied to the same variables as those in the purposeful strategy based on the rationale stated in section 4.2.2.3.

4.4.2.5 Forward and backward conditional entry model

The same 11 variables included in the purposeful reduction model were entered into the logistic regression analysis. 9 variables were removed in 2 steps in the forward entry method and 4 removed in 6 steps in the backward entry method.

The assessment of 'goodness of fit' is shown in table 4.77 demonstrating a good fit in both entry methods with 18% variance explained by the model in the forward entry method and 30% in the backward entry method. The ability of the model to correctly predict which category each case fits into was 65.1% in the forward entry and 66.0% in the backward entry method.

Test	Forward entry	Backward entry
Omnibus tests of Model Coefficients		
Chi-square	15.44	26.84
df	3	7
p	.001	< .001
Nagelkerke R^2	.18	.30
Hosmer & Lemeshow		
Chi-square	1.67	11.10
df	3	8
p	.64	.20

Table 4-77 Goodness of fit automated entry methods prospective data

As shown in table 4.78 the outcomes of the automated entry methods of the logistic regression analysis showed predictive models containing 2 variables in the forward entry strategy and 6 variables in the backward entry strategy which were significantly related to PPE development; alcohol consumption and cool hands were common in both models with metastatic spread, age, BMI, and CrCl level prior to commencing treatment in the backward entry model. Factors had variable ability to predict the development of PPE and were similar in the forward and backward entry methods for the 2 common variables.

Predictor variable	B	Wald χ^2	*p** value	OR (exp *β*)	95% CI
Forward entry method					
Alcohol No (60) (ref cat) Yes	.89	4.05	.04	2.45	1.02-5.85
Cool hands Yes (40) (ref cat) No (55)	.82	3.50	.06	2.30	.96-5.40
Backward entry method					
Alcohol No (60) (ref cat) Yes (46)	1.06	4.1	.04	2.88	1.03-8.04
Metastatic spread Yes (56) (ref cat) No (50)	1.04	4.37	.04	2.84	1.07-7.54
Coolhands Yes (40) (ref cat) No (55)	.62	1.71	.03	1.87	.73-4.76
Age	-.07	6.11	.01	.93	.88-.99
BMI	.14	4.69	.03	1.15	1.01-1.30
CrCl	-.02	4.10	.04	.98	.95-.99
Notes * significant at $p < .1$ (2-tailed)					

Table 4-78 Logistic regression output predictors of PPE automated entry methods prospective data

Participants who consumed alcohol regularly were more than twice as likely to develop PPE as those who did not drink alcohol or only occasionally drank; (OR = 2.45; 95% CI 1.02 – 5.85, p = .04) forward entry and (OR = 2.88; 95% CI 1.03 – 8.04, p = .04) backward entry. Those who had a tendency to have warm hands were just over twice as likely to develop PPE than those with cool hands (OR = 2.30; 95% CI .96 – 5.40, p = .06) forward entry model and (OR = 1.87; 95% CI .73 – 4.76, p = .03) in the backward entry model. In the backward entry model which contained an additional 4 variables, the absence of metastatic disease made it almost 3 times as likely that PPE would develop (OR = 2.84; 95% CI 1.07 – 7.54, p = .04). Increasing age showed a reduced risk of PPE (OR = .93; 95% CI .88 - .99, p = .01), and for each unit increase in CrCl level prior to commencing treatment, the risk of developing PPE decreased (OR= .98; 95% CI .95 - .99, p = .04). Finally, for each unit increase in BMI the risk of developing PPE increased (OR = 1.15; 95% CI 1.01 – 1.30, p = .03).

4.4.2.6 Receiver operating characteristic (ROC) curves

ROC curves were applied to the predicted probabilities created in each of the logistic regression entry methods to compare the accuracy of the models in terms of their sensitivity and specificity in predicting those that develop PPE within the first 3 cycles and those that do not.

The model with 8 variables remaining following the purposeful entry and retention strategy provides a slightly more accurate prediction of those who are likely to develop PPE and those who will not with AUC = .79 (95% CI .72-.88) compared to the models with 2 variables remaining in the forward entry method and 6 variables remaining using the backward entry method AUC = .71 (95% CI .61-.80) and AUC = .77 (95% CI .69-.86) respectively (figure 4.9). From the ROC curve applied to the purposeful reduction model, the most favourable sensitivity = 75% and specificity = 1 – 0.29 = 71% which is supported by the positive and negative predictive values calculated from the logistic regression output 74.3% and 69.7% respectively. However, since the confidence intervals are wide and overlap between the models, this would indicate that there is very little difference between the models predictive capabilities.

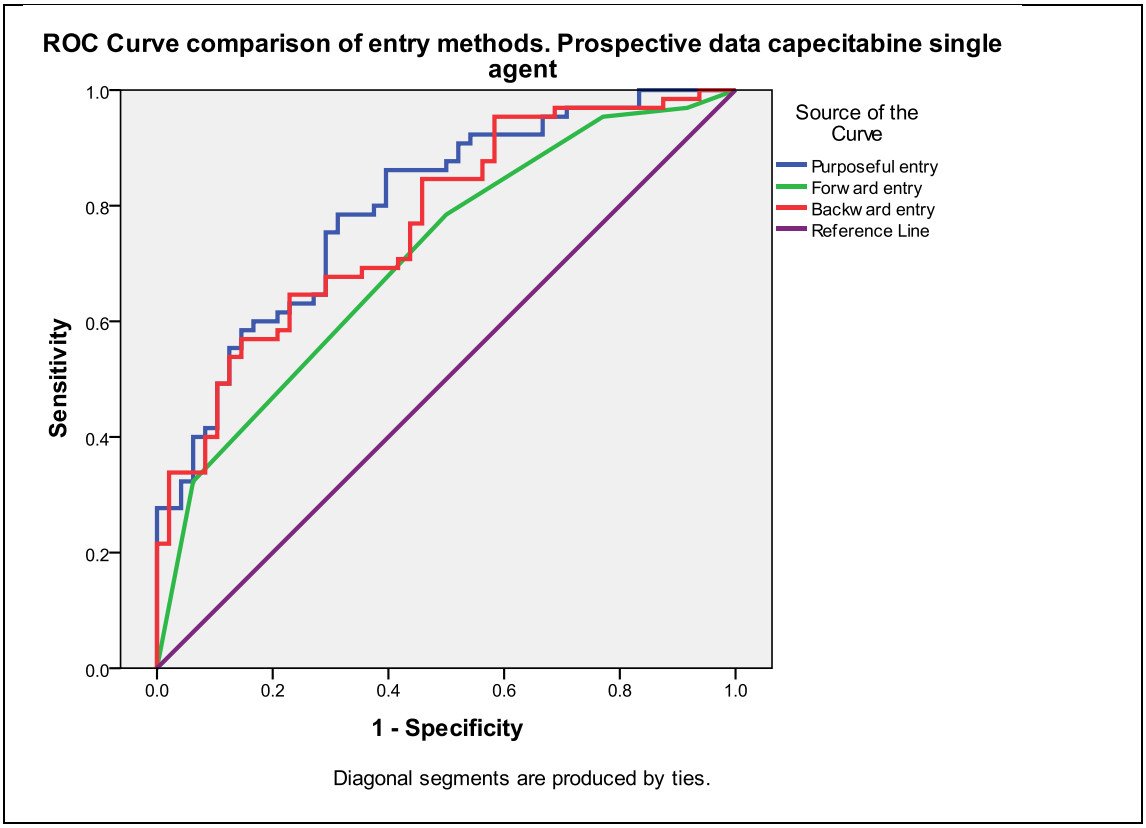


Figure 4-9 ROC curve comparison of entry methods. Prospective data

Test Result Variable(s) from figure 4.44		Area	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
	Purposeful entry	.798	.717	.879
	Forward entry	.710	.615	.805
	Backward entry	.771	.686	.857

A comparison between the final model and the same model including one variable that was non-significant in the bivariate analysis added (figure 4.10) showed that the latter model provided a more favourable ability to predict the development of PPE AUC = .81 (95% CI .73-.89) with a sensitivity = 77% and specificity = 1 – 0.23 = 76% The positive and negative predictive values calculated from the logistic regression output was 76.12% and 69.6% respectively. Since the confidence intervals are wide and there is overlap between the models, there is no statistical difference between them. Whilst it

could be suggested that the automated entry methods produce a model that adequately predicts the development of PPE within the first three cycles of treatment, the finding that the purposeful entry models showed a more favourable ability to predict the development of PPE in all three samples is of interest. This would indicate that the purposeful selection and retention strategy is a worthwhile method of model building and provides a potentially richer model.

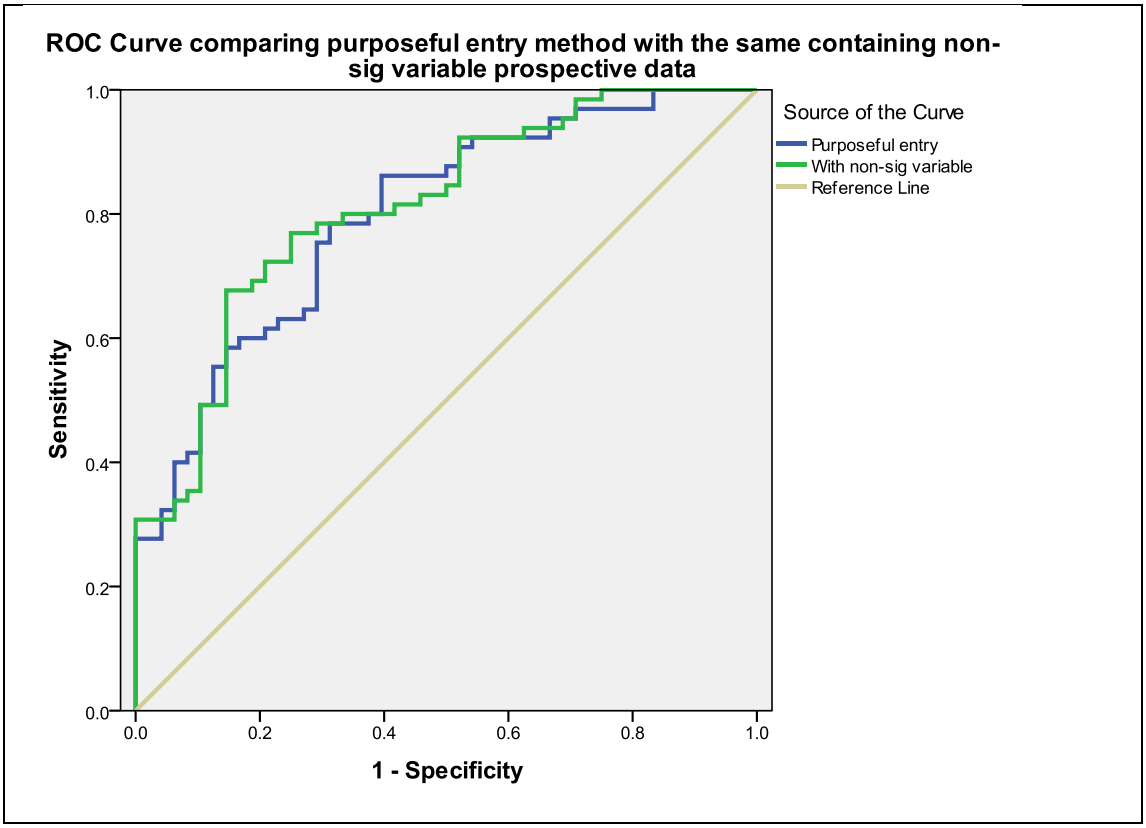


Figure 4-10 ROC curve comparing purposeful entry model with the same plus additional non-sig variables prospective data

Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
Purposeful entry	.798	.717	.879
With non-sig variable	.810	.731	.889

4.4.2.7 Summary of findings of logistic regression model

To summarise the findings from the purposeful selection and retention models, those most at risk of developing PPE were participants;

- Who were younger
- Who drank alcohol regularly
- Who were overweight or obese
- Who had a history of inflammatory conditions
- With a good performance status
- Who had not previously been treated with radiotherapy
- Whose tumour had not metastasised
- With a low pre treatment creatinine clearance level
- Who reported having warm hands most of the time

4.4.3 Comparison of retrospective data capecitabine monotherapy predictor variables in the purposeful entry and retention model with the prospective data

A comparison of the results of the purposeful entry and retention models between the retrospective capecitabine monotherapy sample and the prospective sample revealed the following (table 4.79). Of the 8 variables in the final model applied to the retrospective capecitabine monotherapy data, 3 also remained in the prospective data model containing 9 variables. The 3 variables were; metastatic spread; inflammatory conditions; and alcohol. Whilst the absence of metastatic spread was consistent in both samples, the other 2 variables were contradictory. In the retrospective sample the absence of a pre-existing inflammatory condition was associated with an increased risk of PPE. Conversely, in the prospective sample, participants with a pre-existing inflammatory condition had an increased risk of PPE. Participants who did not drink alcohol regularly had an increased risk of PPE in the retrospective sample, whereas, participants in the prospective sample who drank alcohol regularly had an increased risk of developing PPE. Possible explanations may

be the underreporting of past medical history and alcohol consumption in the retrospective sample or may have occurred by chance. The third variable related to weight of a participant, demonstrated conflicting results. In the retrospective sample, weight loss as a confounding variable carried an increased risk of PPE. However, in the prospective sample an increased BMI demonstrated an increased risk of developing PPE.

	Retrospective data Capecitabine monotherapy			Prospective data Capecitabine monotherapy		
Predictor variable	***p**** **value**	**OR (exp *β*)**	**95% CI**	***p**** **value**	**OR (exp *β*)**	**95% CI**
Gender	.12	1.91	.85-4.32	.50	1.37	.54-3.45
Inflammatory conditions	.07	2.83	.91-8.85	.05	2.40	.99-5.77
Seasonstart	.02	2.63	1.18-5.89	.33	1.48	.67-3.26
ALPC1	.02	.99	.98-.99	.99	1.00	.99-1.00
Metastatic spread	.04	2.47	1.06-5.75	.03	2.71	1.07-6.84
Note *significant at $p < .1$ (2-tailed)						

Table 4-79 Logistic regression output purposeful entry model variables applied to prospective data

Contradictory results also presented in two other variables; gender and the season in which the treatment started. Men were more likely to develop PPE in the retrospective sample, but women had an increased risk in the prospective sample, however, the differences were not significant. There was a more even distribution between males and females in the retrospective sample (M = 53%, F = 47%) than in the prospective sample (M = 39.2%, F = 60.8%) which may partially explain this discrepancy. The difference between the samples seen in the variable season in which the treatment started (retrospective = winter, prospective = summer) cannot be explained by any difference in distribution. Since the prospective sample is the smaller of the two samples, it may be that there is insufficient power to detect differences and this association would need to be further tested in larger samples. A summary of the variables retained in each model described in each of the three sections of this chapter is presented in table 4.80 to allow easy comparison for the reader.

Model	Retrospective data All	Retrospective data capecitabine monotherapy	Variables in final model of retrospective data capecitabine monotherapy applied to prospective data	Prospective data capecitabine monotherapy
Purposeful entry	Capecitabine monotherapy Low ALP Winter start No metastatic spread (confounder) Poor performance status (confounder)	Male Low ALP Winter start No metastatic spread Absence of inflammatory conditions	Metastatic spread Inflammatory conditions	Younger Low CrCl Alcohol No metastatic spread Inflammatory conditions Good performance status Increased BMI Warm hands
Forward entry	Capecitabine monotherapy Low ALP Winter start	No metastatic spread Low ALP Winter start	N/A	Alcohol Warm hands
Backward entry	Capecitabine monotherapy Low ALP Winter start	No metastatic spread Low ALP Winter start Absence of inflammatory conditions	N/A	No metastatic spread Younger Low CrCl Alcohol Increased BMI Warm hands
Purposeful entry with added non-significant variables	Capecitabine monotherapy Low ALP Winter start No metastatic spread (confounder) Poor performance status (confounder) No alcohol Male	Male Low ALP Winter start No metastatic spread Absence of inflammatory conditions Smoker No alcohol (confounder) Weight loss (confounder)	N/A	Younger Low CrCl Alcohol No metastatic spread Inflammatory conditions Good performance status Increased BMI Warm hands No previous radiotherapy
ROC AUC value Purposeful Forward Backward Purposeful + non-sig	 .852 (.806-.898) .845 (.798-.892) .845 (.798-.892) .872 (.827-.917)	 .800 (.724-.876) .765 (.686-.845) .777 (.699-.856) .843 (.777-.909)	N/A	 .798 (.717-.879) .710 (.615-.805) .771 (.686-.857) .810 (.731-.889)

Table 4-80 Summary of logistic regression variables all models

This chapter has presented the findings from data collected from the 3 samples (retrospective – whole sample and capecitabine monotherapy sample and prospective). Bivariate statistical tests were applied to each sample to examine any association between the dependent variable (PPE) and each independent variable. Variables that were significant at the defined alpha levels were then entered into a logistic regression model where different entry and retention strategies were employed. The probabilities from the models were entered into a ROC test to establish which model demonstrated the most favourable ability to predict the development of PPE during the first three cycles of treatment. Finally the regression model containing variables from the retrospective capecitabine monotherapy sample was applied to the same variables in the prospective sample. The purpose of this final step was to compare the effect each variable had in the two samples and to validate the findings from the retrospective sample.

Table 4.80 demonstrates that a comparison between the retrospective and prospective capecitabine monotherapy samples showed little consistency and was therefore unable to validate the findings. However, from the ROC results there is concurrence that using a purposeful algorithm including confounders to build a risk factor model is worthwhile.

The differences between the purposeful entry and retention models for the retrospective and prospective capecitabine monotherapy samples will be discussed in chapter 5.

CHAPTER 5 DISCUSSION OF FINDINGS

5.1 Introduction

The aim of this exploratory study was to identify factors that may increase the risk of developing PPE, focusing on PPE prior to cycle 4 of capecitabine monotherapy. The findings have the potential to be used by nurses, who, either inform and educate patients about their treatment or assess the patient's fitness for their next cycle of treatment.

In this chapter comparisons will be made between the findings from the retrospective (capecitabine monotherapy only) and prospective samples in this study with findings of studies reported in the literature. The incidence and severity of PPE will be discussed followed by the impact of PPE on tolerance of treatment. An analysis of any association between PPE and other toxicities from capecitabine is preceded by a discussion of potential risk factors for the development of PPE. Bar charts and tables are used to illustrate and enhance the text.

Where reference is made to "this current study"; "retrospective sample"; or "prospective sample" these allude to the study on which this thesis is based.
As a reminder to the reader statistical significance is inferred in the bivariate analysis using the conventional alpha level of $p < .05$. A relaxed alpha level was used in the logistic regression modelling algorithm, $p < .25$ for selection of variables into the model and $p < .1$ for retention of the variables. Therefore variables are deemed as achieving statistical significance in the regression model if they are $p < .1$. Page numbers are provided to enable the reader to cross reference with chapter 4 (findings).

The chapter concludes with comparison of the logistic regression models applied to the two samples from this study, a summary of the key findings and the unique contribution this study makes to the current body of knowledge.

5.2 Incidence and severity

5.2.1 Incidence

Initial clinical trials revealed an incidence of PPE, of any grade or at any cycle, of 60% (Roche 2010), 53.0% from pooled data of two trials (Saif 2009), 68.3% (Abushullaih et al 2002) and 55.0% from pooled data of three trials (Koukourakis et al 2008). In the current study, the incidence of PPE of any grade or at any cycle was greater in the prospective sample compared with the retrospective data (66.4% versus 50.3%) (pages 160 and 131). The overall incidence of PPE in this current study mirrors the studies summarised in appendix 5.1 (shaded red) where, although the range was 16% (Barrios et al 2010) to 87.7% (Brearley et al 2010) the majority had an incidence of between 50-69% (Blum et al 1999, 2001, Cassidy et al 2002, Reichardt et al 2003, Scheithauer et al 2003, Hong et al 2004, Pierga et al 2004, Van Cutsem et al 2004, Twelves et al 2005, Lee et al 2008, Kusama et al 2010). Sometimes the incidence was reported as grade 3, some as grade 2 and 3 and others gave no indication of their definition of severe PPE. The wide range of figures seen in these studies is possibly due to either the sample size or the difficulties in the way the incidence of PPE is reported. It is often unclear whether the figures refer to all grades of PPE or just to grades 2 and 3.

Blum et al's (1999) findings indicated a gradual increase in the incidence of first episodes of PPE over the period, although, contrary to this Abushullaih et al (2002) found that 92.9% of those who developed PPE did so within the first two cycles of treatment and suggests that Blum et al's findings are due more to a slower onset than a true cumulative effect. Other authors (Pierga et al 2004) support Blum et al's findings, stating that dose and treatment duration are linked to PPE, and while they state that there is a higher incidence of severe PPE in higher doses (20% versus 2%), no detail is provided of the presentation of PPE by cycle. Similar to Abushullaih et al (2002), the findings

in the current study showed that 82.9% of those who developed PPE did so within the first 3 cycles in the retrospective sample and 84.33% in the prospective sample. This finding is further supported by Heo et al (2004) who found that 86.2% of the patients in their study developed PPE within the first 3 cycles. The high incidence of PPE developing within the first 3 cycles would indicate that there are factors other than accumulation of the drug that causes PPE. This is supported by Lipworth et al (2009) in their review article where they presented contradictory findings. They found one retrospective study that demonstrated a statistically and clinically significant dose correlation with PPE incidence. However, a second prospective study found no correlation between dose accumulation and PPE incidence or severity. Lipworth et al (2009) referred to two further studies where PPE occurred mostly within the first 3 cycles of treatment, further suggesting that PPE rates are not affected solely by total cumulative dose of capecitabine.

5.2.2 Severity

The incidence of grade 3 PPE in initial trials was 11–24% (Roche 2010), 17.0% from pooled data of two trials (Saif 2009) and 11% (Abushullaih et al 2002). Despite a lower incidence overall in the retrospective sample of the current study, the incidence of grade 3 PPE at presentation was higher than in the prospective sample (21.0% versus 8.4% respectively) (pages 135 and 163). There was some difficulty in interpreting data from many studies, as it was unclear if the percentage given for each grade was that of the whole sample or purely the sample that developed PPE. It was also unclear at what point the development of grade 3 PPE was reported; whether it was the first presentation of PPE or the worst grade experienced. In studies of patients receiving capecitabine monotherapy 1250mg/m^2 BD where the incidence of grade 3 PPE was reported as a percentage of the whole sample, this ranged from 9.9% (Blum et al 1999) to 24.2% (Miller et al 2005). The samples in both studies were all female with metastatic breast cancer. A third study using a similar sample reported the incidence as 16.0% (Pierga et al 2004). In two other studies that included both men and women with colorectal cancer

receiving the same capecitabine dose as above, the incidence of grade 3 PPE were similar 17.0% (Twelves et al 2005) and 18.1% (Hoff et al 2001). When the percentage of grade 3 PPE is reported as a percentage of only those who developed PPE there appears to be more similarity between findings with comparable samples (female, metastatic breast cancer). Kaufmann et al (2005) reported an incidence of 20.0%; Fumoleau et al (2005) 21.0% and Venturini et al (2007) 21.9%. Similarly with samples containing both men and women with colorectal cancer, 29.0% (Scheithauer et al 2003) and 33.3% (Van Cutsem et al 2001). The variability shown in the studies is summarised in appendix 5.1 (shaded red and blue). A further difficulty arose in that different toxicity criteria were used in these studies; NCI-CTCAE (NCI 2006), NCIC-CTG (National Cancer Institute of Canada clinical trials group 1991), or World Health Organisation (WHO 1979). One example is that skin changes with pain interfering with function are equated with grade 3 in the NCI criteria but as grade 2 in the NCIC criteria. It is these difficulties that may explain some of the variability. The differences in incidence of particularly grade 3 PPE in the current study may be attributed to improved patient education, patient monitoring and early recognition of PPE by practitioners who have developed experience over time in using oral capecitabine.

Personal clinical experience has led to the questioning of whether patients who develop grade 1 PPE between cycles of chemotherapy are at risk of developing more severe grades with subsequent cycles. Unless questioned specifically about symptoms of PPE between cycles, the patient will not mention it as they either do not understand its significance or they are worried that their treatment will be delayed or stopped. An example of this was provided in chapter 4 pages 163-164 where one participant had not revealed to the doctor during the consultation that she had developed sore hands and feet with open cracks which had not yet healed completely. This was identified when supplying the capecitabine tablets to the participant. The opportunity was taken to educate the participant about the implications of not reporting toxicities. Action was taken to have the participant reviewed by the doctor who deferred the treatment by a week.

From the copious amount of literature retrieved which either made reference to PPE within the text or specifically contained PPE in the title, it was found that although there was the occasional mention that the onset of PPE between cycles was possibly under reported, only one study was identified that specifically collected and analysed this type of data (Tebbutt et al 2003). They demonstrated that more than half of the patients who developed grade 1 PPE did go on to develop grade 2 or worse in subsequent cycles.

The findings from the current study support this, although the proportions who developed grade 2 or worse PPE following the first presentation of grade 1 were slightly less than Tebbutt et al's study. Of the 43 participants (retrospective sample) who developed grade 1 PPE as their first presentation, 20 (46.5%) developed grade 2 or 3 PPE in subsequent cycles (page 134). Similarly in the prospective sample, 56 developed grade 1 PPE as their first presentation, with 23 (41%) subsequently developing grade 2 or 3 PPE (page 163).

As explained in chapter 3 section 3.2.2, the data obtained from the participant's diaries, which were maintained by approximately 50% of the sample, were transferred to the interview schedule. Those who did not maintain the diary were questioned about any signs or symptoms of PPE since the previous cycle. It was therefore difficult to present data to answer the question whether the development and resolution of PPE between cycles results in more severe PPE with subsequent cycles. The data from those who did not complete a diary could be unreliable as it relied on recall of the timing of the development of PPE.

5.2.3 Completion of treatment

Completion rates were analysed during this study to examine the effect of PPE on tolerance of treatment. The proportion of participants who complete the whole course of treatment were similar between the retrospective and

prospective samples (53.6% versus 57.6%) (pages 156 and 166). This compares well with a 45.7% completion rate in Brearley et al's study (2010), whereas, Son et al (2009) report a much higher rate of 90.5%, although, the reason for this is not apparent from scrutinising the sample characteristics.

There have been suggestions that the development of PPE may be a marker of the efficacy of treatment in patients receiving capecitabine, either as monotherapy or in combination with other agents. Five year data from the X-ACT (bolus 5FU versus oral capecitabine as adjuvant therapy for early-stage colon cancer) trial suggested increased efficacy in those who developed PPE compared with those who did not (Twelves et al, 2008). This finding has been replicated in a study of patients taking capecitabine for metastatic breast cancer (Kaufmann et al, 2010) and in a meta-analysis of 13 retrospective studies of patients receiving capecitabine monotherapy for colon, gastric and breast cancer (Roche, 2010). Others have developed this notion further and suggested that the severity of PPE, particularly grade 3, may be a predictor of efficacy (Chua et al 2003, Kurt et al 2006). Furthermore Han et al (2005) have reported a significant association between high levels of thymidine phosphorylase (TP) (the key enzyme involved in the conversion of capecitabine to 5-FU) in tumour cells and the development of PPE ($p=0.01$) and with tumour response ($p=0.004$). This poses the question of whether it is the TP level in tumour cells (which is not routinely measured) that influences the efficacy of the treatment and that PPE is merely a clinical sign of these raised levels.

This question warrants further research to compare TP levels and efficacy with the incidence of PPE. Yun et al (2010) compared the outcome of treatment after dose reduction or cessation of capecitabine in 173 Korean patients with colorectal cancer. Of the whole sample 114 (65.9%) developed PPE, with 45 of these assessed as grade 2 or above. The relapse rate between patients who completed all 8 cycles and patients who had an interruption in their treatment was 10.3% and 27.8% respectively. The 3-year survival rate for each group was 90.7% and 70.9% respectively. Patients who

completed 8 cycles of treatment had an improved recurrence rate (p = 0.05) and 3-year survival (p = 0.03) compared to those whose treatment was stopped before completion of the 8 cycles. This further supports the argument to maintain treatment as much as possible and also demonstrates that a reduced dose is effective in terms of outcome. Yun et al (2010), however, identify limitations of their study and question whether the difference in prognosis is solely due to dose reduction or interruption since the sample size is small (no details of power given), and that other factors such as performance status, age and gender may affect the outcome and are difficult to analyse. The group who received a dose reduction also contained an increased number of older patients.

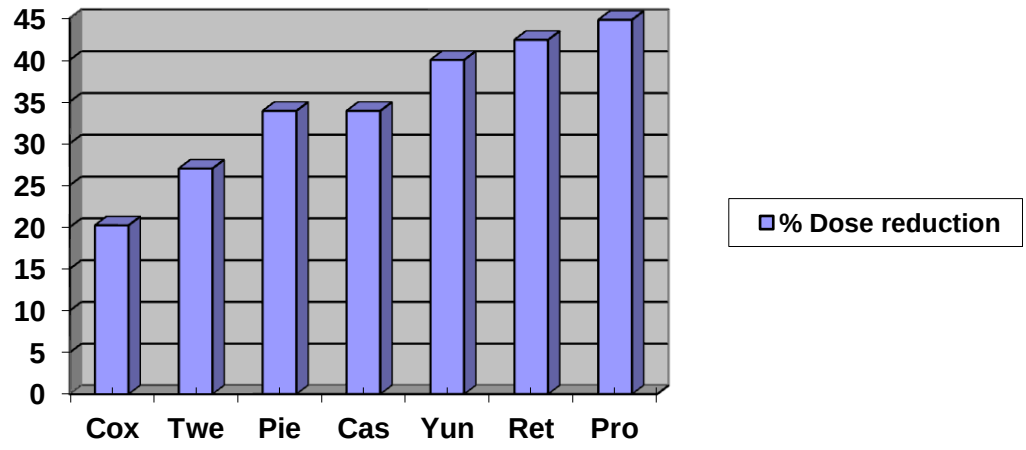
Dose reduction is recommended by the manufacturer in the management of severe toxicities, including PPE, from capecitabine and in cases where there is moderate renal impairment. Few studies have reported figures for the proportion who received a dose reduction, mainly reporting the median number of cycles received.

Abushullaih et al (2002) in their review of the literature suggested that the incidence of dose reduction at any cycle was between 12 and 50%, and in their own study stated that 16 of 41 (39%) patients received a dose reduction due to PPE. However, this study included patients receiving 5FU and the true incidence for those taking capecitabine is unclear. Dose reduction for any reason was 32% in Pierga et al's (2004) study with 19% due to PPE. Venturini et al (2007) reported 13.6% received a dose reduction due to PPE. In the current study dose reduction due to PPE was similar between the retrospective and prospective samples (34 (22.5%) (page 136) and 33 (26.4%) (page 166)) respectively, not too dissimilar to the studies above.

Reducing the dose of capecitabine for any reason in the current study produced similar rates between the two samples with 42.4% (64) in the retrospective sample and 44.8% (56) in the prospective sample. A similar picture was noted for dose reduction due to toxicities other than PPE, 19.9%

(30) in the retrospective sample (page 136) and 18.4% (23) in the prospective sample (page 166) were recorded. Pierga et al (2004) only reported dose reductions due to gastrointestinal toxicity in 10.0% of the sample.

Variable rates of dose reduction were reported in other studies, 20.2% (35) (Cox et al 1999), 27% (81) (Twelves et al 1999), 32% (63) (Pierga et al 2004), 33.9% (202) (Cassidy et al 2002) and 40% (121) (Yun et al 2010), although, details of specific reasons for these reductions were not provided. Figure 5.1 provides a graphical comparison of the percentage of dose reductions from studies in the literature to enable comparison between those and the rates in the current study. The data in these studies was collected prospectively in these studies with the exception of Pierga et al (2004) which evaluated data retrospectively from two phase III trials. Therefore the limitations of retrospective analysis apply. All of the studies mentioned above collected data from a large number of patients. The smallest sample size (n = 173) in Yun et al (2010) study and the largest (n = 596) (Cassidy et al 2002), although the latter was a combination of data from two phase III trials. The greatest proportion that had a dose reduction for any reason (Yun et al 2010) was seen in patients receiving capecitabine as adjuvant therapy for colorectal cancer. Twelves et al (1999) study based on the same criteria yielded a lower proportion having a dose reduction. Cox et al (1999) and Cassidy et al (2002) collected data from patients receiving capecitabine for metastatic colorectal cancer and had comparable proportions that had a dose reduction for any reason. Cultural or ethnic disparity between these studies may have influenced the differences in incidence, since Yun et al's (2010) study was restricted to a single country (Korea), and Pierga et al (2004) to France, whereas, the rest were international studies.



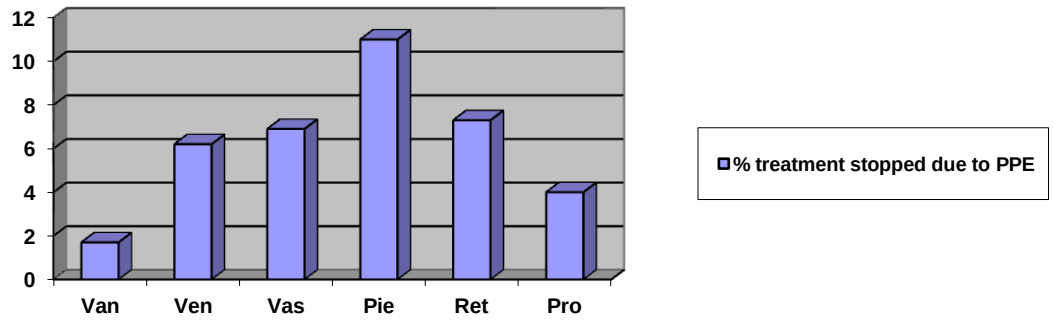
Notes; Cox = Cox et al 1999, Twe = Twelves et al 1999, Pie = Pierga et al 2004, Cas = Cassidy et al 2002, Yun = Yun et al 2010, Ret = Retrospective sample, Pro = Prospective sample

Figure 5-1 Percentage of dose reduction for any reason

Treatment was discontinued for any reason in 70 (46.3%) in the retrospective sample (page 136) and 53 (42.4%) in the prospective sample (page 166) in the current study. Of those who had their treatment discontinued, 11 (15.7%) (7.3% of whole sample) participants in the retrospective sample (page 136) and approximately half that number in the prospective sample 5 (9.4%) (4.0% of whole sample) (page 166) were due to PPE. Few studies reported numbers discontinued due to PPE and those that did varied from none (Abushullaih et al 2002), just 1 (Hyodo et al 2006, Son et al 2009), 5 (1.7%) (Van Cutsem et al 2001), 39 (6.2%) (Venturini et al 2007), with the largest proportion of 22 (11.0%) reported by Pierga et al (2004). The small numbers seen in the first three studies are based on data from small samples 41; 60 and 84 respectively although all were treated for metastatic colorectal cancer. Similarly a small number were reported in Van Cutsem et al (2001), although the sample size was larger, n = 301 and data were gathered from multiple centres compared with the previous three studies which were single institute studies. The two studies that found a larger proportion of patients having their treatment discontinued due to PPE were both based on a sample containing only females. Venturini et al (2007) and Pierga et al (2004) collected data from pre treated patients with advanced breast cancer. Vasey et al (2003) reported that 2 out of 29 withdrew after developing grade 3 PPE. Similarly, 3

(1 in each of three different dose groups) were reported to have discontinued due to grade 3 PPE in a study by Van Cutsem (2000).

In the current study, 3 participants from the retrospective sample (page 136) and 1 from the prospective sample (page 166) were changed to alternative treatment due to toxicity including grade 3 PPE. Figure 5.2 provides a graphical comparison of the percentage of patients who had their treatment stopped due to PPE from studies in the literature to enable comparison between those and the rates in the current study.



Notes; Van = Van Cutsem et al 2001. Ven = Venturini et al 2007, Vas = Vasey et al 2003, Pie = Pierga et al 2004, Ret = Retrospective sample, Pro = Prospective sample
NB the figures for the Ret & Pro samples are given as a % of the whole sample here contrary to those given in the text above which gives the % of those who stopped their treatment for any reason, to allow direct comparison with other studies.

Figure 5-2 Percentage of treatment stopped due to PPE

The rates of discontinuation of treatment due to other toxicities reported in the literature was relatively low, ranging from 4.9% to 13.5% (Van Cutsem et al 2000, Abushullaih et al 2002, Venturini et al 2007, Brearley et al 2010, Yun et al 2010), although it was not clear if the figures included all toxicities or just gastrointestinal toxicities.

In this current study there was a higher rate of discontinuation of treatment due to other toxicities in the prospective sample, 29 (54.7%) (page 166), compared with 23 (32.9%) in the retrospective sample (page 136). The reason for this may be due to a higher number of women with breast cancer in

the prospective sample receiving capecitabine for palliation. With this group of participants the aim is to ensure that the treatment does not cause more symptoms than the disease. In an attempt to confirm this notion, further analysis was carried out examining any association between treatment intent (aim of Rx2gps) and dose modification or cessation. In both the retrospective and prospective samples in the current study, more participants receiving treatment for palliation had a dose reduction at the start of their treatment. However, statistical significance was achieved only in the retrospective sample (p = .003) (pages 141 and 174). Dose reduction may have led to a reduced incidence of toxicities including PPE. Interestingly a higher proportion had a dose reduction due to PPE in the adjuvant group than the palliative group in both samples, whereas, the percentage receiving a dose reduction due to other toxicities was higher in the palliative group in the prospective sample but similar in the retrospective sample (pages 142 and 174). This difference may be due to under reporting in the latter sample. A higher number of participants completed all cycles in the adjuvant group, and there was no difference in the number who stopped treatment due to PPE between the adjuvant and palliative groups or between the two samples. As with dose modification, treatment was more likely to be stopped in the palliative group for other reasons, mostly disease progression (p = <.001 retrospective and p = .002 prospective) (pages 141 and 174). This confirms that participants receiving capecitabine for palliative intent are more likely to have their treatment modified to enable them to continue with treatment, either because the toxicities of capecitabine caused more symptoms than the disease or because of disease progression.

Evidence shows that since PPE is not life threatening, if it is managed with deferring a cycle and dose reduction, few patients require cessation of treatment as a result of PPE. It is the presence of other toxicities particularly diarrhoea or persistent bone marrow depression that result in cessation of treatment.

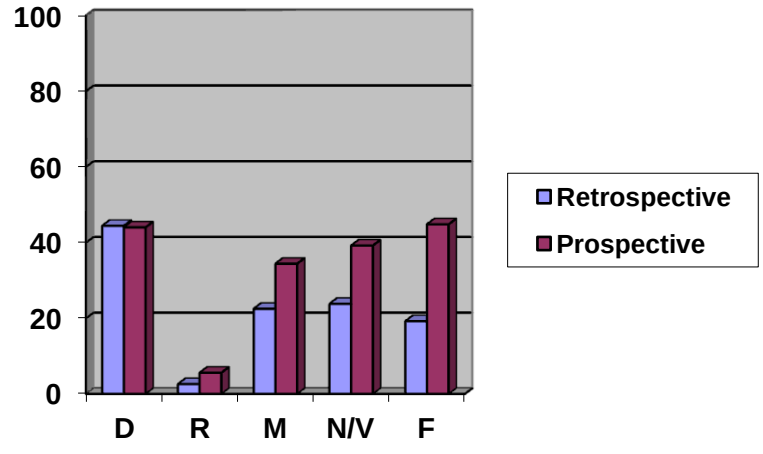
5.3 Other toxicities

The literature showed a great deal of variability in the incidence of capecitabine induced toxicities other than PPE (shaded pink in appendix 5.1). The incidence of diarrhoea range from 12% (Chua et al 2003) to 93.1% (Yun et al 2010) The incidence report by Chua et al (2003) was however based on a small sample of 17, whereas Yun et al (2010) had a larger sample of 173. Mucositis was reported as occurring in 8% (Barrios et al 2010) to 93.6% (Yun et al 2010). It is unclear why there is such a difference in the incidence of mucositis between these two studies. In both, sample size was similar 240 and 173 respectively and the same toxicity assessment tool was used. They both reported mucositis of any grade and in neither study were mucositis of grade 2 or above experienced by the participants. The only differences between the studies was that one was a single centre study on patients with colorectal cancer receiving capecitabine as adjuvant treatment (Yun et al 2010). The other was a multicenter study on females with previously treated HER2-negative advanced breast cancer (Barrios et al 2003). Data were collected retrospectively in the Yun et al study and prospectively in the Barrios et al one. Since the incidence of mucositis was lower in the latter study the limitations of retrospective data collected cannot explain the difference.

Nausea and/or vomiting ranged from 7.5% (Martinez-Trufero et al 2010) to 86.1% (Yun et al 2010) and fatigue 9% (Venturini et al 2010) to 99.4% (Yun et al 2010). It is interesting to note that of all the studies detailed in appendix 5.1 the incidence of these toxicities was markedly greater in Yun et al's (2010) study the reason for this remains unclear. This wide variability in the incidence made it difficult to make a comparison. As mentioned previously this wide variation is probably due to the methods of reporting the incidence. Interestingly the lowest incidence of diarrhoea was reported in 4 out of 5 studies carried out in China (Chua et al 2003, He et al 2011) or Japan (Hyodo et al 2006, Osako et al 2007, Kusama et al 2010), with wider variability in other Asian populations such as Taiwan and Korea. The reason for this is unknown but could be due to other factors, for example diet or under reporting

by patients. Possible confounding factors for diarrhoea in those with colorectal cancer are surgery or previous radiotherapy which may account for some reported diarrhoea.

The incidence in the current study of diarrhoea (44.4% vs 44.0%), and rash (2.6% vs 5.6%) were similar between the retrospective and prospective samples. However, there was an increased incidence of mucositis (22.5% vs 34.4%), nausea and/or vomiting (23.8% vs 39.2%) and fatigue (19.2% vs 44.8%) in the prospective sample (pages 132 and 161). This difference can probably be attributed to the under reporting of mild mucositis or nausea in the retrospective sample. Since fatigue is not viewed as a side effect that can be treated with medication it is often not explored by the healthcare practitioners despite its impact on the patient's quality of life. Extreme fatigue can be the side effect that influences the patient's motivation to continue with their treatment. This view is supported by Saif et al (2008) who state that many patients receiving capecitabine report fatigue as the side effect that causes the most disruption to their everyday lives, often continuing long after treatment has ended. Further research to explore the impact of fatigue on quality of life is warranted and could lead to strategies to help patients manage this effect. Figure 5.3 presents the comparison of toxicities other than PPE between the retrospective and prospective samples in the current study.



Notes: D = diarrhoea, R = rash, M = mucositis, N/V = nausea and/or vomiting, F = fatigue

Figure 5-3 Comparison of incidence of toxicities other than PPE from the retrospective and prospective samples (pages 132 and 161)

A favourable comparison can be made between the current study and the data provided in the manufacturers prescribing information (Roche 2011). A phase III trial of capecitabine versus 5FU/leucovorin for colorectal cancer and a second pooled data of two phase III trials of capecitabine versus 5FU/leucovorin as first line therapy in metastatic colorectal cancer showed an incidence of diarrhoea (47.0 and 55.0%), mucositis (22.0 and 25.0%), Nausea and/or vomiting (34.0 and 43.0%) and fatigue (16.0 and 42.0%) respectively (Roche 2011).

Application of a chi-square test to these toxicities in the current study revealed a statistically significant association between diarrhoea and fatigue and PPE development (p = .004) at any cycle in the retrospective sample (page 133). An increased incidence of PPE was seen in those who did not develop diarrhoea or were fatigued. While this trend was replicated in the prospective sample for fatigue despite the higher incidence it did not achieve statistical significance. The opposite trend was seen for diarrhoea. Those who developed diarrhoea also developed PPE more frequently. However, there was no statistically significant association. A statistically significant association between mucositis (p = .05) and nausea and/or vomiting (p = .02) and PPE at any cycle was seen in the prospective sample (pages 161-162), both of which showed no association in the retrospective sample. Differences may be due to the small numbers in some cells in the chi-square test, although all were greater than 5. Other reasons for this difference may be the under reporting of mild toxicities or may simply be due to chance.

Studies examining any association between PPE and other toxicities were limited with 3 studies identified. A retrospective study (n = 330) found that mucositis (42.0%) was three times more likely in those who developed PPE (p = .0001), whereas the incidence of vomiting was lower in those who developed PPE (p = .045) (Tanyi et al 2009). While these results both support (mucositis) and refute (vomiting) those found in the current prospective sample, the sample in Tanyi's study received pegylated liposomal doxorubicin

for gynaecological cancers and would therefore have a gender bias and a different toxicity profile to capecitabine. Thereafter the usual deficiencies of retrospective analysis have to be taken into account. Heo et al (2004), in their study of patients receiving capecitabine-containing regimes, found that prior occurrence of oral mucositis was associated with the development of PPE p = 0.029. However, a similar association was not seen with other toxicities. Again this association between mucositis and the development of PPE supports the findings from the current study; although whether the mucositis appeared prior to PPE or vice versa was not tested. The third study by Tebbutt et al (2003) found that early grade 1 diarrhoea was predictive of grade 2 or worse PPE in subsequent cycles in patients receiving infusional 5FU with or without mitomycin.

The only toxicity that shows consistent association with the development of PPE appears to be oral mucositis and further examination of this association may confirm this toxicity to be a predictor of PPE.

5.4 Age and gender

5.4.1 Age

Over 60% of cancers occur in the over 65 age group and this group present unique challenges due to age-related changes that may affect their tolerance to treatments for cancer particularly chemotherapy (Hurria & Lichtman 2008).

Age related changes include;

- Changes to gastrointestinal tract
- Reduction in total body water
- Declining glomerular filtration rate
- Delays in DNA repair
- Reduced Dihydropyrimidine Dehydrogenase (DPD) enzyme production.

Many changes occur as a result of the ageing process. Changes to gastrointestinal tract may affect drug absorption (Hurria & Lichtman 2008). A reduction in total body water changes the volume distribution of water soluble drugs. With the decrease in serum albumin and haemoglobin seen in the elderly, this further affects the volume distribution of these drugs and increasing the risk of toxicities in drugs bound to albumin and haemoglobin (Balducci & Extermann 2000, Hurria & Lichtman 2008). Declining glomerular filtration rate leads to increased toxicity due to reduced excretion of the drug or its metabolites via the kidneys (Balducci & Extermann 2000). Since age forms part of creatinine clearance calculations and age appears to be a risk factor for toxicities, older patients taking capecitabine may require a reduced starting dose and careful monitoring (Balducci & Extermann 2000, Cassidy et al 2002). Although, serum creatinine which also forms part of creatinine clearance calculations is a poor indicator of renal function in the elderly due to their reduced muscle mass (Hurria & Lichtman 2008). Although reduced renal excretion of drugs is seen in the elderly the same effect is not seen with plasma clearance indicating that there is an alternative method of drug disposition when glomerular filtration reduces; therefore reducing drug dosage based on renal function in the elderly cannot be recommended (Balducci & Extermann 2000). These authors go on to suggest that other mechanisms that may increase the risk of toxicity in elderly patients receiving chemotherapy comprise delays in DNA repair, and more relevant to capecitabine is delayed drug catabolism due to reduced DPD enzyme production.

Two key age milestones have been suggested to be linked with toxicities from chemotherapy agents; 70 and 85 years. Age-related changes follow a flat line trend but increase markedly between 70 and 75 with an even sharper increase after 85 years (Balducci & Extermann 2000).

In this current study, the median age and range were similar in both the retrospective and prospective samples 69 (39-85) and 65 (36-83) respectively (pages 131 and 160), and is comparable with other studies (appendix 5.1

shaded purple). Independent samples *t*-test revealed no statistical association between age and the development of PPE at any grade in both the retrospective and prospective samples (p = .27 and p = .06 respectively) (page 149 and 182). This result did not achieve significant in the bivariate analysis taking an alpha level of $p < .05$. As previously explained a more liberal alpha level of $p < .25$ was used as the inclusion criterion for candidate variables into the multivariate analysis. Only data from the prospective sample achieved this level of significance. In this multivariate logistic regression model younger participants were more at risk of developing PPE than older participants (p = .01) (page 184).

A statistically significant association between older patients and development of PPE has been see with the use of 5FU (Meta-analysis Group 1998), but has not been clearly seen with capecitabine, although, when given in combination with other agents, age ≥ 52 years was shown to be associated with PPE (Heo et al 2004). A single institute study in America of 41 patients with colorectal cancer receiving capecitabine monotherapy found no association between age and PPE (Abushullaih et al 2002). Scheithauer et al (2003) examined the difference in PPE between ages ≥ 65 years and < 65 years and found similar incidence of any grade between the two groups (63% versus 61% respectively), and of grade 3 PPE (20% versus 16%), although no statistical test was applied to determine any significance.

This current study supports these findings in the retrospective sample. However, the opposite trend was seen in the prospective sample, with younger participants having an increased risk of PPE at any cycle, with a similar incidence of grade 3 PPE. In the retrospective sample comparing the two groups ≥ 65 years and < 65 years, a similar incidence was found of PPE between the groups (50.6% and 50.0% respectively), and grade 3 PPE (40.9% and 34.4% respectively). In the prospective sample an incidence of 55.6% and 77.0% respectively p = .02 with a higher proportion of those < 65 developing PPE of any grade but similar incidence of grade 3 PPE between the two age groups 12.7% and 11.5% respectively (pages 143 and 175).

Figure 5.4 shows a graphical representation of the findings from the retrospective and prospective samples from the current study.

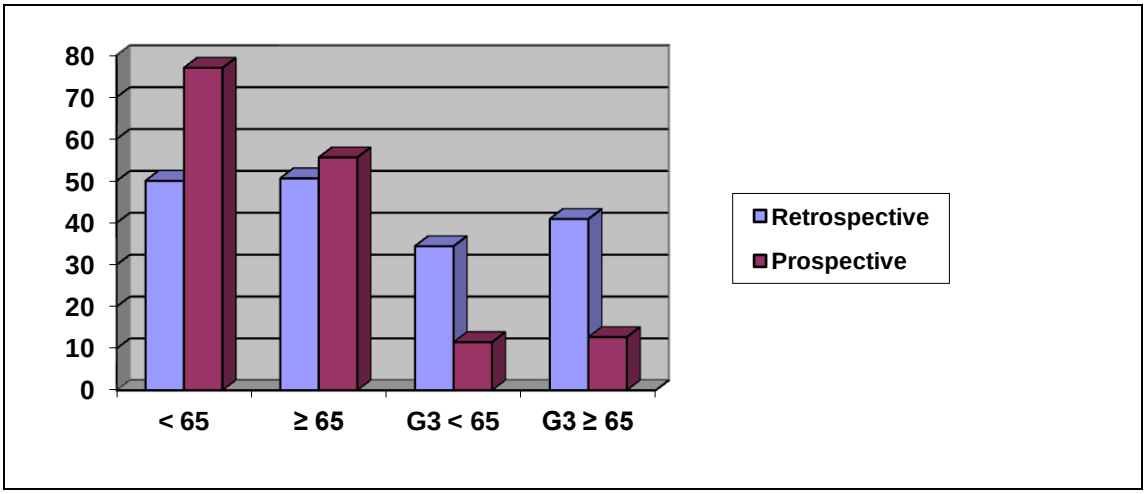


Figure 5-4 Comparison of the incidence of PPE between 2 age groups from the retrospective and prospective samples

In the past there has been an under use of adjuvant treatment for elderly patients with cancer. Studies of anti-neoplastic agents which demonstrated a survival advantage were often restricted to the under 70s (Reddy et al 2007). In the past there were concerns about the ability of elderly patients to tolerate capecitabine treatment, but more recently treatment in the elderly has become the focus of several research studies. Two small studies by Zamora et al (2004) and He et al (2011) concluded that capecitabine is tolerable in older patients and toxicity is reduced if treated with a reduced dose of 1000mg/m^2 without loss of efficacy.

Similar toxicities were found in patients older than 70 years compared to younger patients in two studies (Feliu et al 2005, Diaz-Rubio et al 2007). Feliu et al (2005) found that there was no relationship between grade 3 toxicity and age comparing the age groups 70-79 versus ≥ 80 years. However, with only a small number who developed grade 3 toxicity and the small sample size of 51 there was insufficient power to definitely rule out any potential relationship. Conversely, Cassidy et al (2002) analysed pooled data from two multi-centre phase III studies in patients over 75 years old, and found that the incidence of

grade 3 PPE was 64 (17.1%) for the whole sample of 596, being especially high in those aged 80 or above 13 (15%). Furthermore, they stated that this might be explained by age-related renal function. When age was entered into a multivariate regression analysis, adjusting for creatinine clearance, showed that age in isolation was not an independent predictor of toxicity of capecitabine (p = 0.72).

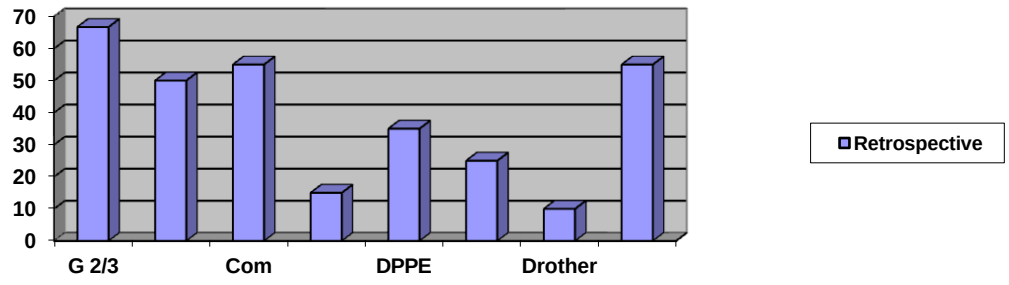
In women with breast cancer receiving capecitabine, patients aged 80 and above had an increased incidence of grade 3 or 4 toxicities (Blum 1999), although the proportion of the sample who fell into this age group and which toxicities this applied to were not identified. A more recent trial (Focus 2) evaluating treatment of elderly patients receiving capecitabine 1250mg/m^2 and bevacizumab revealed 54% developing grade 3 or 4 toxicities with an increased rate of these in patients with reduced renal function (Feliu et al 2010).

A retrospective single institution study evaluating toxicity and overall survival in octogenarians (80-89) and nonagenarians (90-99), found that all 25 patients who received chemotherapy (all but one regime contained 5FU or capecitabine) where given a reduced starting dose. Despite this initial reduction 82% developed grade 3 or 4 toxicities requiring further dose reduction and treatment delay. PPE incidence was 18%, however, no patient received capecitabine alone. This study suggests that patients greater than 80 years old behave differently to septuagenarians who appear to tolerate full doses, and that the older population require substantially reduced doses of chemotherapy (Reddy et al 2007). They did however, acknowledge the limitations of this study particularly due to its retrospective nature; in that co-morbidities or other confounding variables may have been missed and toxicities wrongly attributed to chemotherapy.

An analysis of data from the retrospective sample of the current study revealed 20 (13.2%) participants aged more than 79yrs with 12 (60%) developing PPE prior to cycle 4, 8 (66.7%) developed grade 2 or 3 for their

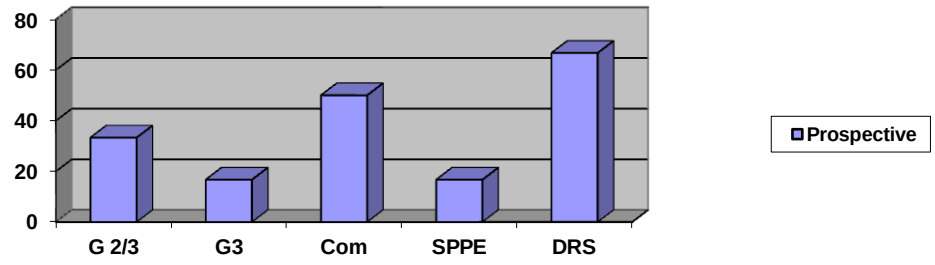
first presentation and 6 (50%) grade 3 as their worst episode. 11 (55%) of the 20 completed all planned cycles with only 3 (15%) stopping due to PPE. 7 (35%) were deferred due to any toxicity and all 7 (35%) had a dose reduction, 5 (25%) due to PPE and 2 (10%) for other toxicities, although they also had grade 1 PPE. 11 (55%) of the 20 started on a reduced dose of capecitabine, 9 (45%) of these had moderate renal failure (CrCl of 30-50mls/min). 6 (30%) of these participants still went on to develop PPE, 5 (25%) at grades 2 or 3 (page 143). In the prospective sample, only 6 (4.8%) were aged over 79 years with 2 (33.3%) developing PPE and 1 (16.7%) participant developing grade 3 as their worst episode. 3 (50%) of the 6 completed all planned cycles with only 1 (16.7%) stopping due to PPE. 4 (66.7%) out of 6 participants aged > 79 years, 4 (66.7%) started on a reduced dose with 1 (16.7%) developing grade 1 PPE for which a delay in treatment occurred with a further reduction in the dose of Capecitabine (page 176).

Figures 5.5 and 5.6 present this data in graphical form, with separate graphs for the retrospective and prospective samples.



Notes: G = grade of PPE, Com = completed all planned cycles, SPPE = stopped due to PPE, DPPE = deferred due to PPE, DRPPE = dose reduction due to PPE, Drother = dose reduction due to other toxicities, DRS = dose reduction at start of treatment

Figure 5-5 Retrospective sample age > 79 years n = 12 incidence of PPE and impact (page 143)



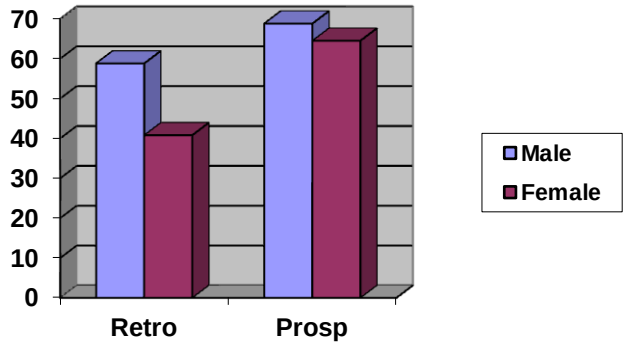
Notes: G = grade of PPE, Com = completed all planned cycles, SPPE = stopped due to PPE, DRS = dose reduction at start of treatment

Figure 5-6 Prospective samples age > 79 years n = 6 incidence of PPE and impact (page 176)

In both the retrospective and prospective samples statistical significance could not be tested, since with only such small numbers, no firm conclusions can be drawn, and there were no nonagenarians in either sample to allow comparison with other studies.

5.4.2 Gender

There was a difference in the gender distribution with the prospective sample (page 160) weighted towards females (60.8%) compared with 47% in the retrospective sample (page 131). Although summary figures may be slightly altered by a ratio other than 50:50, the statistical tests used to analyse this data allows for different ratios in the categories. Having said that, both samples showed that men were more likely to develop PPE than women (figure 5.7). However, the association achieved statistical significance (p = .03) only in the retrospective sample (page 137). When gender was combined with other variables from the retrospective sample in the multivariate regression model, men were almost twice as likely as women to develop PPE (OR = 1.91), although it was not confirmed statistically (p = .12), but remained in the model as a confounder (page 152).



Note;
Retro = Retrospective sample
Prosp = Prospective sample

Figure 5-7 Percentage of males and females with PPE from both samples

Studies (Abushullaih, et al 2002, Sun, et al 2009) have shown no difference in frequency or relationship between gender and PPE, with a similar finding in the over 70s (Feliu et al 2005). Conversely Park et al (2009) found a statistically significant difference (p = .04) with men more likely to develop PPE than women. This may be explained by the small sample size (n = 17) and the imbalance of gender in the sample, with only 3 women included. Since this small number would have resulted in less than 5 cases in the expected count in half the cells of the cross tabulation, no firm conclusion can be drawn from this study.

5.4.3 Age and Gender combined

As previously alluded to, age alone does not appear to be a predictor of toxicity. It is acknowledged that large prospective studies are needed to confirm this since in the past there has been a reluctance to administer chemotherapy to older patients. Age and gender were combined into four groups; men < 65yrs; men > 64yrs; women < 65yrs; and women > 64yrs to examine the influence of gender on age and the incidence of PPE. A chi square test applied to this variable showed no statistically significant association in either the retrospective sample (page 143) or the prospective sample (page 176). When the same variable was entered into a regression

analysis, younger men were more likely to develop PPE than older men in the prospective sample (OR = 3.55, p = .04) (page 176). However, although this trend was replicated in the retrospective sample it did not achieve statistical significance (OR = 1.05, p = .92) (page 144), therefore this finding cannot be confirmed.

This raised the question of whether younger men were receiving capecitabine as adjuvant treatment and therefore less likely to have delays or dose reductions to maintain dose intensity, leading to a higher incidence of toxicity. A chi square test applied to the variables age and gender combined and treatment intent achieved statistical significance association (p < .001) in both samples (pages 144 and 177). The question posed above was refuted since both age groups of men had a higher proportion receiving adjuvant treatment. In both samples there were higher proportions of younger women receiving capecitabine with palliative intent for breast cancer.

Trials of older patients receiving capecitabine show that this can be administered to people over 70 years as long as they wish to receive aggressive therapy and accept the higher rate of toxicities (Feliu et al 2005, Diaz-Rubio et al 2007). There is some controversy over the role of renal function and drug dosage in the elderly with some (Cassidy et al 2002) suggesting that this should be taken into account for dose adjustments and others (Balducci & Extermann 2000) disagreeing. However, there appears to be consensus that drugs with overlapping toxicities should be avoided in these patients. Emerging evidence also suggests that the very elderly, i.e. aged over 80 yrs, appear to respond differently and should receive a dose reduction from the start of capecitabine therapy (Blum 1999, Reddy et al 2007, Feliu et al 2010). The effect of age on the incidence of PPE is contradictory in the literature and replicated between the two samples in this current study. This may be due in part to the different proportions of each age group within study samples, the tumour type, ethnicity and other co-morbidities or performance status that may not have been accounted for.

5.5 Ethnicity

5.5.1 Incidence

The incidence of PPE of any grade in non-white ethnic groups was appreciably higher (greater than 85%) than in the white skinned population in both samples in the current study. The incidence of PPE in white skinned participants differed between the samples, with 41 of 95 (43.1%) in the retrospective sample and 73 of 113 (27.4%) in the prospective sample. This difference can possibly be attributed to the fact that ethnicity was unknown in 31.8% of the retrospective sample, with 58.33% of these participants developing PPE at any cycle. In a chi-square analysis, ethnicity confirmed the trend of non-whites having an increased risk of developing PPE at any cycle but did not achieve statistical significance in either sample (p = .07 and p = .72 respectively) (pages 140 and 168). While the increased incidence of PPE in the non-white population is interesting to note, firm conclusions cannot be drawn. This is due to the small numbers of non-white participants in the samples, and the reason that ethnicity was not included as a variable in the logistic regression model. Further research is warranted in order to examine more closely the role of ethnicity in the development of PPE.

The majority of studies in the literature do not provide details on the ethnicity of the sample, and of those that do, few test any association between ethnic origin and toxicity. From the studies presented in appendix 5.1 on first reading, it would appear that there is similar variability in the incidence of PPE between countries in the western world and those in the far east. However, on closer inspection the incidence of PPE of any grade appears to be higher in studies carried out in Korea than in other countries. Firm conclusions cannot be drawn from this observation, since, it is based on the assumption that the samples in the Korean studies consisted of participants indigenous to that country, whereas, populations in many western countries may be more ethnically diverse. Two studies (Hyodo et al 2006, Yun et al 2010) reported a higher incidence of PPE in Japanese and Korean patients (73% and 65.9% respectively), but a lower incidence of grade 3 PPE (13% and 10.4%

respectively) and found the tolerability of treatment to be similar to the western patient population. Lee et al (2008) also suggested that there is a lower incidence of grade 3 PPE in Asian patients (6-13%) compared with a multinational phase III trial (17%). Komamura et al (1995) suggest that the increased incidence of PPE in Japanese patients may be explained by the usage of G-CSF more frequently than other countries. In chapter 2 section 2.7.4 (page 33) evidence was presented that pegylated G-CSF is associated with an increased incidence of PPE (Burnstein et al 2005, Bardia et al 2006, Lee & Lynch 2007). It is unclear in Komamura et al's (1995) paper whether they are referring to pegylated G-CSF or nonpegylated G-CSF.

A meta-analysis of 18 trials (1 UK, 1 multi-national and 16 china) comparing toxicities of capecitabine with infusional 5FU found an increased incidence of grade 3 PPE in both Caucasian [sic] and Asian patients taking capecitabine compared with 5FU, although this difference achieved a statistically significant association only in the Caucasian [sic] group (p = 0.005 and p = 0.06 respectively) (Ma et al 2011). A word of caution in the interpretation of these findings was given, since the comparison was based on data from different trials for the two ethnic groups and would benefit from a larger international trial. In another retrospective study of three phase III trials by Haller et al (2008) a comparison was made of the incidence of toxicities between USA populations and non-USA populations, split into east Asia and the rest of the world. However, specific details of ethnicity were not provided. The study found that the incidence of any grade 3/4 toxicity was higher in the USA than the non-USA samples, with the lowest incidence in the east Asian group. This supports previous studies demonstrating a lower incidence of grade 3 PPE in non-Caucasian [sic] populations. However, the overall incidence was not provided making it unclear whether the east Asian group had a higher or lower incidence of PPE of any grade to allow comparison with the other studies. Haller et al (2008) suggested that regional variations may be due to ethnic factors such as, genetics, physiological or pathological conditions, cultural factors such as diet, or different trial methodology.

5.5.2 Presentation

A phenomenon linked to ethnicity, that appears to be gaining interest, is the different presentation that is seen in dark skin. Although the country where studies were carried out can be identified, the lack of data on the ethnicity of the samples developing PPE is a weakness of the literature. Most examples have been single or series case studies and describe hyperpigmentation of the skin on the hands and feet. Sometimes this hyperpigmentation presented with an odd distribution appearing on the dorsum of the hands particularly over the knuckles and in the creases of the palms. Many also developed keratoderma-like thickening of the skin (Narasimhan et al 2004, Lee et al 2007, Saif & Elfiky 2007a, Vasudevan 2010 & Akash & Bhounsule 2011). It has been suggested that hyperpigmentation may be a different entity to PPE (Vasudevan 2010) and that the grading of PPE be adapted to include hyperpigmentation in grade 1 and keratoderma-like thickening in grade 2 (Lee et al 2007, Saif 2011) (Table 5.1).

Grade	Manifestations of PPE in white patients	Manifestations of PPE in non-white patients
1	Minimal skin changes or dermatitis (e.g., erythema) without pain	Hyperpigmentation of palms and soles without pain
2	Skin changes (e.g., peeling, blisters, bleeding, oedema) or pain, not interfering with function	Thickening of skin of palms and soles with pain and no loss of function
3	Ulcerative dermatitis or skin changes with pain interfering with function	Ulceration, dermatitis or desquamation (with pain interfering with function)

Table 5-1 New staging proposed by Saif (2011 p164) in non-white patients

In the current study darkening of the palms was seen in those of Indian or Philippino origin (8 participants) who developed PPE with one female also revealing a similar hyperpigmentation of the tongue, comparable to the one reported by Vasudevan (2010). Chapter 4 section 4.4.1.3 (page 64) described one case to support the different presenting features of PPE in participants with dark skin. This hyperpigmentation was clearly evident in the creases of the palms and fingers with blistering on some of the finger tips.

It would appear that ethnic variation may influence the overall incidence of PPE. On the other hand, severe PPE does not appear to be as much of a problem in the non-white population compared with white skinned people. There is some uncertainty concerning the grading of PPE in people with dark skin or if indeed the hyperpigmentation is a separate entity unique to these populations. Larger scale studies would be required to confirm any link between ethnicity and PPE and to exclude other factors.

5.6 Past Medical History

The risk of developing PPE in the presence of other co-morbidities, past illness or previous treatment has not been analysed in any large scale studies and only a few single case reports suggest any association.

5.6.1 Peripheral vascular disease

The single case from the current study reported in chapter 4 page 171-172 appears to be the first case reported anywhere in the literature of PPE possibly due to peripheral vascular impairment as a result of Reynaud's Disease. PPE developed early (grade 1 after cycle 1 and grade 3 during cycle 2) despite a dose reduction on commencement of capecitabine. It demonstrates the need for careful assessment and monitoring of patients taking capecitabine since this participant did not contact the hospital when he started to show worsening signs of PPE. Whilst his Reynauds disease appears to be a plausible risk factor for PPE, other factors may also have contributed, such as a synergistic effect of methotrexate, alcohol consumption, and regular activities that exposed his hands to heat and friction. Statistical analysis of data in the current study showed no significant association between PPE and peripheral vascular disease. However, in the

retrospective sample there were insufficient numbers to produce reliable results.

5.6.2 Previous chemotherapy treatment

There is some evidence to suggest that people who had developed PPE with previous chemotherapy treatment have a recurrence with subsequent treatment with PPE inducing chemotherapy (Chiara et al 1997). This is supported by the findings in the current study of capecitabine monotherapy However, the association only achieved significance in the retrospective sample $p = .04$ (page 138). With such small numbers (only 6 had developed PPE with previous chemotherapy regimes, with 5 developing PPE with capecitabine), and with the limitations of retrospective sampling this result may not be reliable. Conversely Fabian et al (1990) found that 10 (71%) of previously untreated patient developed moderate to severe PPE compared with 3 (27%) of previously treated patients. They suggested that this may be due to longer total infusion time (continuous infusion of 5FU) in the former group 7.3 months versus 4.5 months. Their findings were however based on small numbers and would need confirming in a large study.

Heo et al (2004) reported a significant association between docetaxel induced nail toxicity and PPE. One case from the prospective sample reported in chapter 4, who although did not develop PPE, demonstrated how nail loss following previous chemotherapy with docetaxel may not resolve when commenced on capecitabine.

5.6.3 Diabetes

Two case reports in the literature have mentioned diabetes and PPE. One (Narasimhan et al 2004) reported a black [sic] patient with diabetes who developed grade 3 PPE, which resulted in amputation and concluded that this group of patients may be more at risk of severe PPE. However, this

suggestion is based on a single case of a patient who had already had a previous amputation due to his diabetes. No assumptions can be made and begs the questions whether the diabetes or ethnicity were predictive factors or indeed the combination of the two. The second report was of a 71 year old white male with type II diabetes who, following his fourth cycle of capecitabine, was referred to a burns unit with severe blistering of lesions on the palms of his hands and soles of his feet, which healed within 7 days with treatment and discontinuing capecitabine (Goutos et al 2009). No suggestion was made in this article that diabetes was linked to the development of PPE and is therefore an area where further evidence is required to confirm or refute any significant link between diabetes and the risk of developing PPE. It is probable that it is not diabetes per se that is a risk factor, rather the consequences of this co-morbidity such as cardiovascular disease and neuropathy, which may prevent the patient from recognising the early signs of PPE.

In this current study only 18 out of a sample of 150 were reported to have a history of diabetes in the retrospective sample. Similarly 17 out of a sample of 125 in the prospective sample had diabetes. No association between diabetes and PPE was observed in either sample (p = .93 and p = .11 respectively) (pages 140 and 168). The variable diabetes in the prospective sample met the relaxed alpha level (p < .25) for inclusion in the logistic regression model. This was removed according to the algorithm described in chapter 3 and therefore was not included in the final model.

5.6.4 Inflammatory diseases

A significant association between PPE and other inflammatory diseases such as rheumatoid arthritis or asthma (p = .05) was found in the prospective sample of the current study (page 169). This variable was subsequently included in the multivariate logistic regression model. Participants with a pre-existing inflammatory condition were almost three times more likely to develop PPE than those who did not suffer from any inflammatory conditions (pages

184-185). The hypothesis that people with a predisposition towards inflammatory diseases would also be more prone to developing PPE is supported by the suggestion that PPE is thought to be caused by an inflammatory response. However this finding would need to be tested in a larger sample that the one in the current study.

As previously alluded to in chapter 2, Palmar Plantar Keratoderma (PPK) is associated with pre-existing inflammatory conditions. PPK becomes progressively worse when signs of PPE are seen (Do & Kim 2001). Keratoderma has also been suggested as a presenting feature of PPE in non-white patients (Narasimhan et al 2004, Schellens et al 2005, Hood and Reeck 2006, Saif & Elfiky 2007). This appears to lend support to the findings in the current study that there is an association between the presence of inflammatory conditions and the development of PPE.

The link between peripheral vascular or sensory insufficiency and the increased risk of PPE points to the need for careful history taking to identify patients with compromised peripheral and autonomous nervous system. Regular monitoring and patient education is needed to avoid an underestimation of severe PPE in these patients.

5.7 Performance status

Performance status provides an indication of the patients' functional ability in relation to everyday activities, and can be used to assess a patient's response to treatment and the impact of disease. There are two scales that are commonly used the Eastern Co-operative Oncology Group (ECOG) (Oken et al 1982) (sometimes also known as WHO or Zubrod) & Karnofsky (Karnofsky and Burchenal 1949) (Appendix 2.1).

Unlike other toxicities, PPE has been reported to have a higher incidence in patients with good performance status receiving 5FU (Chiara et al 1997, Meta-analysis group 1998, Abushullaih et al 2002). Conversely Comandone

et al (1993) and Heo et al (2004) found no association between performance status and PPE. The current study supports a statistically significant association between the development of PPE at any cycle or prior to cycle 4 and performance status 0 or 1 (ECOG) but only in the prospective sample (p = .04) (page 170). In the retrospective sample there were 58 missing cases and less than 5 cases in more than one cell in the chi-square test, questioning the reliability of the finding. Performance status was included in the multivariate regression (page 184) as a variable from the prospective data and while non-significant when combined with other variables, it remained in the model as a confounder, since it affected a change in another variable, alcohol, when removed (see chapter 3 pages 69-70 for details on selection of variables for the logistic regression model). Neither of the two studies (Chiara et al 1997, Abushullaih et al 2002) performed a multivariate analysis although Abushullaih et al (2002) did provide a rationale for not carrying this out, which was the small numbers in each category.

One might consider that this association between performance status and PPE could be attributed to dose, in that those with poor performance status may receive a reduced dose or have more delays in treatment. However, this detail was not provided in either study to enable these conclusions to be drawn. A chi square test applied to the two samples in the current study to test for any association between performance status and dose reduction at the start of treatment showed no association p = .75 in the retrospective sample (page 144) and p = .06 in the prospective sample (page 177), thereby refuting the notion above. If it is true that PPE can be a result of trauma and friction then it would seem logical that people with a good performance status are more likely to develop it, since, they are more likely to be engaged in activities that cause the trauma or friction. This is a personal opinion and is unsubstantiated in the literature.

Since the removal of performance status from the logistic regression model affected a change in the variable alcohol, chi-square was applied to test any association between these two variables. This showed that those with a good

performance status were more likely to drink alcohol regularly than those with poor performance status, although this association did not achieve significance $p = .23$.

Although there are contradictory findings in the literature concerning any association between performance status and the development of PPE, there were no studies identified that tested this association in patients receiving capecitabine monotherapy. The findings in the current study may be the first report of such an association, and while firm conclusions cannot be drawn from the retrospective sample due to the number of missing cases, the fact that the association was confirmed in the prospective sample adds support to this relationship. Further work may explore how PPE affects quality of life in those with good performance status compared with those with poor performance status to ascertain if performance status is an important factor to consider in the management of PPE.

5.8 Hormones and breast cancer

An analysis of hormone status in both samples in this current study revealed insufficient numbers to draw any conclusions in the retrospective sample. In the prospective sample there was a significant association between oestrogen receptor positive tumours and the development of PPE ($p = .007$) (page 178) but no difference in progesterone receptor status (page 176). These findings are contradictory to those in Kurt et al (2006) study, who found a significant association between progesterone positive tumours and PPE. These opposing findings may be due to the different characteristics of the sample, particularly ethnicity, with Kurt et al's (2006) study based on a sample of 94 women in Turkey. The prospective sample in this current study was based on a sample of 44 women in England. Details of the ethnicity of Kurt et al's (2006) sample were not provided therefore it would be a assumption to deduce that the majority were Turkish. Of the 44 women from England in this current study 40 (91%) were white.

5.9 Nutritional deficits and weight

A risk factor identified in the literature which could include both drug and patient factors is the role that malnutrition plays in the development of PPE. Particular factors that have been implicated are albumin or folate levels, weight loss and body mass index.

5.9.1 Albumin bilirubin and folate

Many drugs are bound to albumin as a carriage mechanism and any reduction in the serum albumin level, or raised level of other molecules which are protein bound e.g. bilirubin, may result in an increased level of circulating drug and therefore greater risk of toxicity (Jansman et al 2000). It was for this reason that albumin and bilirubin levels were analysed as part of the current study. Independent *t*-test applied to the data demonstrated a statistically significant association between pre-treatment serum albumin levels and the development of PPE in the retrospective sample (p = .009) (page 149), though this association was not replicated in the prospective sample (p = .09) (page 182). This variable was then entered into a regression analysis and in both samples, it failed to achieve statistical significance. Similarly pre-treatment bilirubin levels demonstrated a statistically significant association with the development of PPE only in the retrospective sample (p = .009) (page 149), although interestingly, participants with a raised bilirubin level were less likely to develop PPE. These findings indicate that in this study the hypothesis that pre-treatment serum albumin or bilirubin levels have an influence on the development of PPE cannot be supported.

One dietary constituent, folate, has been linked to the incidence of toxicities. Raised folate levels prior to commencing treatment showed an increased incidence of capecitabine-induced toxicity during the first cycle and over the whole treatment period (Hurria & Lichtman 2008).

Careful questioning of the patient prior to commencing treatment on the use of supplements bought over the counter or concurrent folic acid administration is required to identify this potential synergistic effect. Folate levels were not collected during either the retrospective or prospective parts of the current study, and may be an interesting factor to analyse in future work.

5.9.2 Weight loss

An increased incidence of PPE has been seen in patients who had lost weight prior to a diagnosis of cancer, similarly these patients were more likely to develop severe PPE (Andreyev et al 1998). Weight loss cross-tabulated with PPE in the two samples in the current study revealed no statistically significant association between these two variables (p = .41 retrospective sample, p = .59 prospective sample) (pages 140 and 168). In the retrospective sample weight loss was not recorded in the majority of cases (108 out of 151) and similar to other studies, weight loss was subjectively reported by patients. Future studies would benefit from analysing the influence of the percentage of weight lost prior to treatment on the development of toxicities which may help clinicians in deciding the appropriate dose of chemotherapy for people who have lost weight, rather than an arbitrary reduction in starting dose.

5.9.3 Body Mass Index (BMI) and Body Surface Area (BSA)

Sparreboom et al (2007) evaluated data from studies of eight different chemotherapy drugs comparing BMI > 30 with BMI < 25 (WHO definition of obesity 2008) and found no evidence to support the practice of reducing or capping the dose (at 2.0m^2) in obese patients There are several physiological changes that occur in overweight individuals that may affect the way drugs are processed by the body. These include, alterations in lean body mass, adipose tissue mass, organ size, blood volume and cardiac output. However, prospective pharmacokinetic studies are required to demonstrate whether

increased body weight is a risk factor for toxicities from chemotherapy agents (Baker et al 1995, Jansman et al 2000).

Individual patient chemotherapy doses are based on calculated body surface area (BSA). An independent samples *t*-test was applied to BSA in the current study and revealed no association between BSA and the development of PPE (p = .56 retrospective sample and p = .09 prospective sample). Logistic regression showed that for every unit increase in BSA the risk of developing PPE increased, but once again failed to achieve significance. Although these findings indicate a trend towards a higher BSA increasing the risk of developing PPE, since they did not achieve statistical significance, no firm conclusions can be drawn.

Alternative suggestions to BSA include a fixed dose for all sizes, however, this showed wide variations in drug exposure and toxicity and those with a low BSA were particularly vulnerable to an increase in toxicity. This suggestion was refined to recommending fixed dose for BSA clusters ≤ 1.65m^2; 1.66 – 2.04m^2 and ≥ 2.05m^2, which needs testing in clinical trials (Loos et al 2006). There is also a growing body of evidence that lack of chemotherapy-induced toxicity is associated with a worse outcome in terms of time to disease progression and overall survival. Toxicity-adjusted dosing is suggested as a way to provide individualised treatment schedules (Gurney 2005 & 2006). Indeed Hénin et al (2009) agree with this suggestion and are currently developing a dose-toxicity model specifically to attempt to reduce the duration of grade 2/3 PPE and maintain patients on capecitabine.

There have been few studies investigating the effects of obesity on anticancer drugs (Baker et al 1995). Gordinier et al (2006) tested any difference between BMI and PPE in a retrospective analysis of patients records over 7 years (n = 103) and found that there was no significant difference between those that had PPE and those that did not. This finding was replicated by Tanyi et al (2009) in a study of 330 patients, thus suggesting that Body Mass Index (BMI) is not a risk factor for PPE in patients receiving pegylated liposomal

doxorubicin. No similar analysis was found in studies of capecitabine. In the current study no significant association was found in either sample in a bivariate independent samples *t*-test (retrospective sample $p = .73$ and prospective sample $p = .07$) (pages 149 and 182). Regression analysis was applied to BMI and PPE and showed a trend that for every unit increase in BMI the risk of PPE increased, though only confirmed statistically in the prospective sample (OR = 1.09, $p = .05$). In the prospective sample BMI was included in the purposeful entry and retention multivariate regression model. BMI achieved significance $p < .1$ in combination with other variables entered and reduced in the model as detailed in chapter 3 and remained significant at $p = .04$ (pages 185). Since BMI demonstrated no significant association in the bivariate analysis this would show support for the findings in the studies by Gordinier et al (2006) and Tanyi et al (2009). However, when in combination with other variables it did affect the chances of developing PPE. It is unclear whether age or pre-treatment creatinine clearance (CrCl) levels, also included in the final model, in combination with BMI caused this effect. The rationale for this notion is that BMI generally decreases with age and age and weight are factors used to calculate creatinine clearance. A multicollinearity diagnostics test applied to BMI and age and BMI and CrCl showed no high correlation between them. A linear regression applied to BMI and CrCl showed a statistically significant association $p < .0001$ suggesting that it is probable that CrCl in combination with BMI are predictors for the development of PPE.

5.10 Renal function

It is well established that renal impairment is a risk factor associated with severe toxicities of capecitabine.

However, creatinine clearance calculated using the Cockroft-Gault formula has been criticized for its lack of precision and accuracy in that the dose reductions recommended by the manufacturers of capecitabine based on CrCl discriminates against individuals with lower weight, older age and raised serum creatinine, the variables used to calculate CrCl with this formula. The

other factor used in this formula is gender, for which it reduces the CrCl by 15% in females, which may result in smaller women being under-dosed compared to larger men (Ratain 2002). Baracskay et al (1997) also supports the opinion that this mathematical formula to calculate CrCl in the elderly does not give accurate results since serum creatinine may remain normal as renal function declines with age.

During the data collection phase of the current study, observations suggested that among the participants receiving capecitabine monotherapy, those with a CrCl between 50-80mls/min appeared to develop PPE more frequently.
Tests were applied to CrCl at baseline to ascertain any influence on the development of PPE at any cycle and any grade, and PPE development within the first 3 cycles of capecitabine monotherapy. Logistic regression applied to the retrospective data, PPE at any cycle or grade and CrCl, identified that for every point increase in CrCl the risk of developing PPE decreases (OR = .99, 95% CI .99-1.01). The same result was found when applied to PPE developing within the first three cycles of treatment.

CrCl was categorized using the same parameters described by Poole et al (2002);

Normal renal function = > 80.01 mls/min
Mild renal impairment = 50.01-80 mls/min
Moderate renal impairment = 30-50 mls/min

Logistic regression was repeated using these categories (page 146), with the findings from the retrospective sample showing that participants with mild renal impairment were twice as likely to develop PPE at both any cycle (OR = 2.10) and within the first 3 cycles (OR = 1.77) than those with moderate renal impairment. This finding is perhaps not surprising since a 25% dose reduction is recommended for a CrCl of 30-50mls/min, which may reduce the risk of developing PPE and other toxicities. The logistic regression also showed that participants with mild renal failure were almost twice as likely to develop PPE at any cycle (OR = 1.78) and within the first 3 cycles (OR 1.93) than those

with normal renal function confirming the personal observation mentioned above.

Poole et al (2002) found that people with mild renal impairment and those with normal renal function had a similar probability of developing grade 3 or 4 adverse events from capecitabine. Of the 29 participants in the retrospective sample of the current study who developed grade 3 PPE, 15 had a base line CrCl between 50.01 and 80.00 and 14 had a CrCl greater than 80.00, thus agreeing with Poole et al's (2002) findings of similar patterns of grade 3 toxicity between the groups. A Chi-square test applied to the retrospective data confirmed the lack of statistical significance between baseline CrCl and grade 3 PPE (p = .64) (page 145). When the prospective data from the current study were examined, 15 participants had grade 3 PPE. Of these 15, 10 had a baseline CrCl between 50.01 and 80.00 and 4 had a CrCl greater than 80.00 A Chi-square test showed a statistical difference between baseline CrCl and grade 3 PPE χ^2 (6, n = 125) = 14.40 p = .03 with a medium to large effect phi = .34 (page 179). A logistic regression test was not subsequently applied to baseline CrCl (collapsed into the 3 groups) and PPE from the prospective sample, since there were very small numbers in one category. Pre-treatment CrCl, in the prospective sample, showed no statistically significant association with the development of PPE (p = .22) in a bivariate independent samples t-test (page 182). However, this alpha value met the criteria for inclusion into the logistic regression model and in conjunction with the other variables achieved significance (p = .07) and remained in the final model (page 185). It is possible that the presence of age and BMI as other variables in the same model may have affected the behaviour of CrCl in the model, since both are used to calculate CrCl as already stated above. However, multi-collinearity diagnostics did not reveal a high correlation between these variables.

From the findings of the current study and from studies reviewed in the literature, the role of CrCl as a predictor of PPE seems well established. Although the manufacturers recommend a dose reduction for patients with moderate renal failure, there are no recommendations for those with mild

renal failure. Although there are similarities between the incidence of grade 3 PPE in those with normal renal function and mild impairment, the overall incidence of PPE was higher in those with mild renal failure. This would need confirming in large scale studies, it is a factor worth considering when monitoring patients receiving capecitabine.

5.11 Patient activities

As identified in chapter 2, many authors (Baer et al 1985, Vukelja et al 1989, Arias et al 1997, Mrozek-Orlowski & Sanborn 1999, Lassere & Hoff 2004) make reference to the increased risk of PPE when there is increased vascularisation of the hands and feet caused by increased temperature, pressure, friction and long-term alcohol intake. These studies suggest that educating patients to avoid activities that cause these, to reduce their risk of developing PPE is needed. There appears to be consensus based on anecdotal evidence, and case reports, since studies providing any statistical analysis of these risk factors could not be found during the search of the literature. This is supported by Gualandi et al (2009) who carried out a search of the literature up to May 2008 to examine scientific evidence for non-pharmacological management of side effects of chemotherapy. They found no scientific evidence (using the levels of evidence from the Oxford Centre for evidence-based medicine) for any non-pharmacological management of PPE.

The findings in the current study are discussed below in the context of those presented in the literature. Since it was impossible to obtain data from the retrospective sample on these activities, with the exception of the season in which the treatment started and alcohol intake, the findings are from the prospective sample only.

5.11.1 Temperature

The body has a temperature gradient from trunk to extremities. Drug eruptions over distal surfaces may be attributed to the effect of temperature on antigen-antibody reactions since the metabolites of a drug are recognised by the immune system as potential harmful antigens (Bhasin et al 2005).

Participants were questioned on whether they had a tendency to have cool or warm hands and feet; if they wore socks and gloves to keep warm, and activities where they exposed their hands and feet to hot water such as hand washing crockery and cutlery or clothes and taking baths or showers that were as hot as they could stand.

Participants who reported a tendency to have warm hands was significantly associated with PPE (p = .05) (page 170) whereas, warm feet did not achieve significance p = .09 (page 168). The alpha value for cool feet fell below the threshold (p < .25) for inclusion in the purposeful selection logistic regression model. It was not included, since a multi-collinearity diagnostic test revealed a high correlation between cool hands and feet. The association in the bivariate test of cool hands was confirmed in the logistic regression model showing a 2-fold risk of PPE in those with warm hands compared to those with cool hands (OR = 1.95 p = .03) (page 186).

Whilst the association between warm hands and the development of PPE appears initially to support the suggestion that temperature does influence the incidence of PPE, the results should be viewed with caution. There was no significant association between regular exposure to hot water and development of PPE p = .30 (page 168); the limitations of self reported measures; and a simple yes or no answer may make this finding difficult to replicate. It is a difficult factor to measure since it would change depending on the time of day and activities being undertaken. No scale measure was used to assess the immersion in hot water and future studies would need to include a more detailed measure of the frequency of immersion and possibly the

temperature of the water. Despite these limitations, this is an important finding since it is the first study to confirm that increased temperature is a risk factor for PPE.

Some authors have suggested active cooling to reduce the risk of PPE. Baer et al (1985) suggests cooling measures during the period when peak drug levels are reached. Molpus et al (2004) evaluated the effect of regional cooling on the incidence of PPE caused by PLD, which consisted of ice packs applied to the wrists and ankles, and drinking iced liquids during the infusion of PLD and for 24 hours after completion of the infusion. They found a higher incidence of severe PPE in those who did not use regional cooling methods compared to those that did (67% versus 6%) $p = .047$, indicating that cooling may reduce the incidence of PPE induced by PLD. Conversely, Tanyi et al (2009) in a study of 330 patients receiving PLD for gynaecological cancers reported an incidence of PPE in 30.9% and tested for any association between active cooling and the development of PPE. The cooling regime consisted of the application of ice packs to the wrists and ankles during the infusion of PLD. They found an increased incidence of PPE in those who used cooling (48/123; 39%) compared to those that did not (54/207; 26%) $p = .014$ which is a surprising finding since cooling is intended to prevent PPE. Both of these were retrospective studies and they stated that if cooling was not mentioned in the medical notes it was assumed that it was not used, which may have affected the results. Also in Molpus et al's (2004) study the sample size was very small with 17 women using regional cooling measures and only 3 who did not use these measures, thus bringing into question the reliability of the results. To date there have been no published studies on the affect of cooling on the incidence of PPE in patient receiving capecitabine monotherapy. Capecitabine is taken every day either for 14 days or continuously making active cooling difficult and could be unbearable for the individual. Education to avoid excessive exposure to heat may be more appropriate for patients receiving capecitabine.

Another area connected to temperature is the role of sweat in the development of PPE that has been studied in patients receiving PLD. A 62 year old female with angiosarcoma had measurements of PLD or its metabolites taken using laser scanning microscopy, prior to treatment, then half hourly intervals up to 4.5 hours post infusion and at 24 hours. Measurements were taken from the forearms, palms, soles, axilla and forehead. There was no detection of PLD prior to treatment, but PLD was detected after 1 hour on the forehead and axilla confined to the furrows and sebum around hair. After 2 hours and lasting for 2-3.5 hours reducing in intensity PLD was detected on the palms and soles over the whole skin area, demonstrating that sweat and sebaceous glands may be a pathway for the release of PLD or its metabolites onto the skin (Jacobi et al 2004). A later study by the same lead author confirmed these findings, although again measurements were only taken on one patient (Jacobi et al 2005).

In the current study, participants were questioned whether they had a tendency to sweat on their hands and/or feet. No statistically significant association was found between those who reported sweaty hands and/or feet and developed PPE and those that did not $p = .89$ (for both hands and feet) (page 168). The accuracy is difficult to determine as this was a self reported factor with no measurement of the frequency or amount of sweat produced. This is the first documented analysis of any association between sweating and the incidence of PPE in patients receiving capecitabine monotherapy. This finding indicates that capecitabine is not carried to the surface of the skin by sweat in the same way as PLD, therefore refuting the theory suggested in the literature by Gressett et al (2006).

The time of year and the external temperature could also affect the temperature exposure to the hands and feet and subsequent sweating. To examine the influence of the time of year on the development of PPE, initially the month during which the treatment was started was cross-tabulated with PPE. However, with only small numbers in some months the results would be questionable. This variable was then collapsed into the four quarters of the

year (January – March; April – June; July – September and October – December), but again there were still too few in some cells to be able to trust the results. Finally, this was collapsed into two categories; Summer and Winter, with April – September classed as summer and the rest as winter. The rationale for examining the influence of the time of year was that since the temperature is generally higher in the summer, one would assume that the incidence would be higher during this season.

The effects of the season in which treatment started may differ from year to year depending on whether we have a hot summer or very cold winter. This may partly explain the contradictory findings between the retrospective data and the prospective data. An association (p = 0.2) was found in the retrospective sample, with those commencing their treatment in the winter more likely to develop PPE (page 139). Conversely, in the prospective sample those who commenced their treatment in the summer were more likely to develop PPE but did not achieve significance (p = .48) (page 168). The season in which treatment commenced was included in the multivariate regression model applied to the retrospective data. This revealed that those who started their treatment in the winter were just over 2.5 times more likely to develop PPE than those who started in the summer (OR = 2.75; p = .02) (page 152). The latter finding disproves the assumption made above and following consideration would appear rational. In normal circumstances during the summer months active measures are taken to cool down, while in the winter months active measures are taken to keep warm, for example, by wearing socks and gloves, taking hotter baths or showers, having the heating higher in the house and warming hands on hot drinks by encircling the cup or mug.

Suggestions have been made that PPE is more common in the summer because of the theory that PPE is caused by the elimination of capecitabine via the eccrine glands of which large numbers are found on the hands and feet (Mrozek-Orlowski et al 1999). However, changes to the skin, making it more sensitive to damage are more likely in the winter (Son et al 2009). There

is often less humidity in the winter coupled with the low humidity of indoor heating resulting in drying of the skin (winter xerosis) which becomes more vulnerable to flaking or cracking at the finger tips (Harvard Health Publications 2012). It would therefore seem logical to have an increased risk of PPE in the winter.

There are few studies that have tested any association between PPE and the time of year in which treatment is administered. In a retrospective review of 330 patients notes Tanyi et al (2009) found no association between the season in which the first dose of PLD was administered and the development of PPE, with 22% in the summer versus 28% at other times of the year p = .21. The authors did not state their definition of summer months. In a Japanese study of 47 patients receiving capecitabine for colorectal cancer grade 2 or 3 PPE was seen in 10 patients (21.7%). However this incidence increased to 15 (32.6%); 5 of these were cherry farmers with the increase in incidence attributed to friction of the hands and legs thus supporting the investigation of patient activities as important factors to predict the development of PPE (Suto et al 2010). Although the assumption made in that study was that the increased incidence was due to friction, it may not be friction per se but may be associated with the combination of other factors such as higher temperatures of the summer.

Another chemotherapy-induced phenomenon thought to be a consequence of PPE caused by capecitabine is onycholysis (detachment of the nail from the nail bed). One study reported onycholysis in 5 out of 21 patients who received more than 6 cycles of weekly paclitaxel. In all 5 patients it developed during the summer months (not defined) but was not seen in those who received less than 6 cycles of 3-weekly paclitaxel or doxorubicin. The authors stated that onycholysis is exclusive to anthracycline and taxanes and recommend protecting nails from sunlight (Hussain et al 2000). In opposition, in a second report of 36 patient receiving irinotecan/capecitabine, 2 patients developed onycholysis, however it developed during the winter (not defined) in covered toenails (Muñoz et al 2003). Personal experience has not been that

onycholysis in patients receiving capecitabine monotherapy is a common occurrence, with a more frequent appearance of paronychia in the great toe. Paronychia refers to an infection around the nail (US National Library of Medicine 2012a), and often results in a delay in treatment to allow healing to take place. Records have not been made of the true incidence and whether it is more prevalent at different times of the year. Figure 5.8 shows an example of a toe nail with a fungal infection seen in one participant after 5 cycles of capecitabine and who had developed grade 3 PPE prior to this which was resolving.

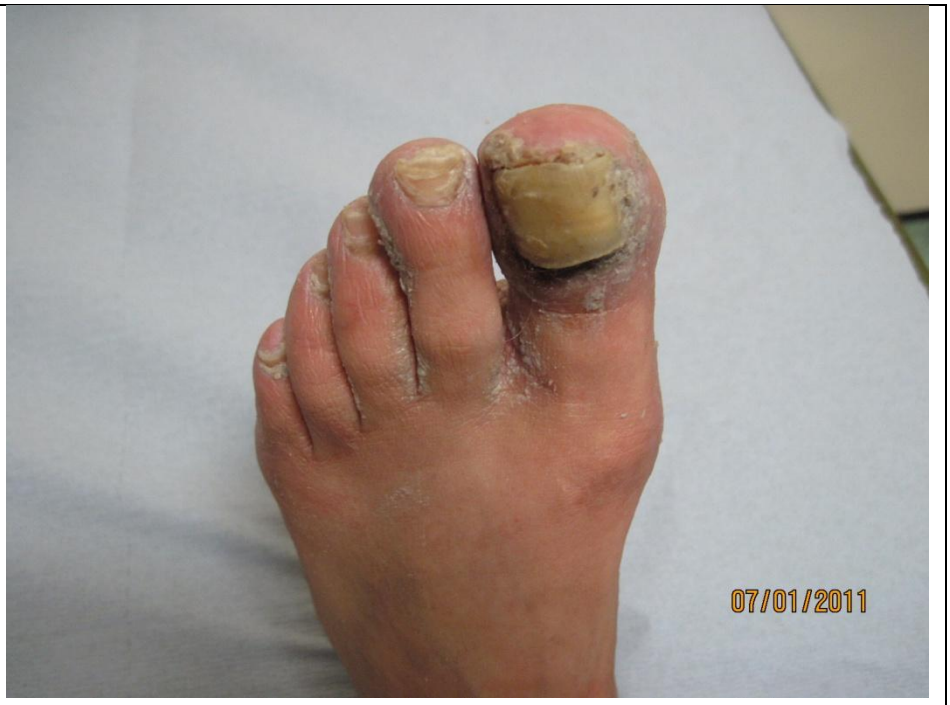


Figure 5-8 Fungal infection of the great toe

There have been a few reports of nail toxicity with capecitabine monotherapy including paronychia as well as onycholysis and onychomadesis, although seen in a minority of cases (Chen et al 2001 and 2003, Maino et al 2003, Vaccaro et al 2008).

Contradictory findings have been found when examining any association between the time of year that treatment is received and the development of PPE. Findings have been based on small numbers or retrospectively collected

data. Large prospective studies are required to examine this association further.

5.11.2 Sunburn and radiation recall

In this current study no significant association was found in either sample between PPE and previous radiotherapy treatment (*p* = .48 retrospective sample, *p* = .33 prospective sample) (pages 140 and 168). This variable was not included in the initial logistic regression models. In the prospective sample when this variable was added to the final model (as described in chapter 3) it became significant *p* = .04 and remained in the model as a confounder (page 186). When in combination with other variables, participants who had not received radiotherapy previously were nearly three times more likely to develop PPE than those who had received previous radiotherapy (OR = 2.93; 95% C.I 1.04 – 8.25) (page 186).

Initial thoughts were that participants who had previously received radiotherapy were more likely to be prescribed capecitabine with palliative intent. They were therefore more likely to have a dose reduction due to mild to moderate toxicities than those receiving capecitabine with curative intent. Descriptive analysis demonstrated that 58.6% of the participants who had previously been treated with radiotherapy had breast cancer and 92.9% of these participants had received previous radiotherapy. Less than 25% had a dose reduction either at the start of their treatment or at any subsequent cycles, indicating there must be some other reason for this finding.

Many cytotoxic agents sensitize the skin to sunlight making the patient more vulnerable to sunburn. Participants in the prospective sample of the current study were questioned on any history of sunburn in the past and their skin type, and were tested by cross tabulation to examine any association with the development of PPE. Of the 18 participants who had reported sunburn in the past, more developed PPE (13) than did not (5) but with no statistically significant association seen *p* = .49 (page 168). With such a small sample, the

dependence on recall from the past, and no degree of sunburn given, firm conclusions cannot be drawn about the relationship between sunburn or radiation exposure and the development of PPE. However, this is the first report of a study to examine any association between a history of sunburn and the development of PPE. Since there were small numbers in this study, a multi-centre study would recruit a larger sample to be able to establish whether an association exists.

Due to small numbers of participants with some skin types, data were collapsed into two group (Type I & II and III-VI table 5.2) based on the definitions that types I and II have an increased risk of sunburn and therefore may have increased risk of PPE. This hypothesis was rejected since more type III-VI developed PPE (34) than types I and II (29) p = 1.0 although both groups of skin type had a higher incidence of participants who developed PPE than those who did not.

SKIN TYPE	
Type I	Often burns, rarely tans. Tends to have freckles, red or fair hair, blue or green eyes
Type II	Usually burns, sometimes tans. Tends to have light hair, blue or brown eyes
Type III	Sometimes burns, usually tans. Tends to have brown hair and eyes
Type IV	Rarely burns, often tans. Tends to have dark brown eyes and hair.
Type V	Naturally black-brown skin. Often has dark brown eyes and hair.
Type VI	Naturally black-brown skin. Usually has black-brown eyes and hair.
Ref: Cancer Research UK. Sunsmart. www.cancerresearchuk [Accessed 14.10.08]	

Table 5-2 Skin type

Of the 18 participants who stated they had been sunburnt in the recent past or when they were younger, some participants at the same time as developing PPE, developed non painful erythema over sites where they had been sunburnt in the past (3 participants), or over old scars and blemishes making them more prominent (3 participants). One participant developed erythema over a previous irradiated site and another developed erythema where a dressing was applied to a central venous catheter site, this effect also being reported by Zimmerman et al (1995). One of the 3 who developed erythema over previous sunburnt sites was an 83 year old man who had been diagnosed with Actinic Keratosis, also known as solar keratosis which

presents as small rough areas on skin exposed sun, usually the hands, face, scalp, back of hands and chest (US National Library of Medicine 2012b). These are precisely the areas where the erythema developed in this participant. He has also been diagnosed with Lentigo Maligna, a non-invasive melanoma which presents initially as blue/black in colour (US National Library of Medicine 2012c), although these lesions did not change during treatment.

This occurrence appears akin to radiation recall dermatitis, the development which is similar to acute radiation reaction, of a previously irradiated area. This recall can be as a result of receiving certain drugs and has been reported with 5FU, although the cause and incidence are unknown (Camidge & Price 2001). Zimmerman et al (1995) report two cases in patients receiving docetaxel. One patient developed erythema at a site of recently applied electrocardiograph (ECG) pads, and the other, erythema on the back of the neck and a V-shaped area on the chest, where previously exposed to the sun. Another case reported a 65 year old man taking capecitabine 1000mg twice a day who developed a rash over his upper trunk and arms after the second cycle which became worse after the third. He also developed PPE at the same time which also worsened at each cycle. On questioning he reported working in his garden bare-chested, although he wore a hat and applied sunscreen to his face (Peramiquel et al 2006). A final report by Markman et al (2004) described a female patient who received PLD for ovarian cancer and who became badly sunburnt (severe erythema without blistering) a few days before she was due to start cycle 2. Treatment was delayed for a week to allow the sunburn to resolve with the dose reduced by 25%. One week after the start of cycle 2, she developed severe redness, swelling and blistering of both hands and similar but less severe on both soles of the feet. With steroid creams and pyridoxine the PPE gradually resolved over a period of 5 weeks. These cases lend support to the notion of photo-recall phenomenon, and also highlight that skin almost recovered from injury, such as sunburn, is sensitive to further damage if exposed to another toxin.

5.11.3 Alcohol

A case study (Vukelja et al 1989) reports a 63 year old man with metastatic pancreatic cancer who received bolus 5FU 900mg per week increased to 1150mg per week. He developed severe PPE after 11 weeks of treatment but which was not felt to be due to drug accumulation. The patient had a history of alcohol abuse, however had recently stopped drinking. The PPE in this case was suggested to be similar to neuritis caused by isoniazid in chronic alcoholism as described by Goldman and Braman (1972) and Pellock et al (1985). Vukelja et al (1989) go on to suggest that patients with long term alcohol abuse should be commenced on pyridoxine at the outset of treatment to prevent or reduce the severity of PPE.

In the current study, no association with the development of PPE was found in the bivariate analysis applied to each sample, between those that drank alcohol regularly and those that did not. In the retrospective sample 64 (42.4%) had no mention of alcohol consumption in the notes and therefore were recorded as missing, leaving just 87 cases to analyse. It was unclear from the information available whether the intake of alcohol was regular or not in the 51 participants where this was recorded and therefore the limitations of a retrospective review can be applied. The remaining 36 participants were reported as not consuming alcohol or only occasionally.

Participants in the prospective sample were questioned about their alcohol intake. However, it was difficult to record the actual number of units consumed in a week, since many merely responded “regularly” or “occasionally”. The findings revealed that of the 50 participants who drank alcohol regularly 36 developed PPE compared with 14 who did not develop PPE, but did not achieve significance in the bivariate analysis $p = .21$ (page 168). Alcohol was included in the multivariate regression model which demonstrated that those who drank alcohol regularly were more likely to develop PPE than those who did not (OR = 2.18; $p = .14$) (page 185). Alcohol remained as a confounder, as it altered the beta value of other variables by more than 20% as described

in chapter 3. To test any association between gender, alcohol and PPE, cross tabulation of these variables was applied using only the participants who stated they drank alcohol regularly. This demonstrated that men who drank alcohol regularly were more likely to develop PPE than women who drank regularly, although the association did not achieve statistical significance p = .21. Another cross tabulation was applied to the development of PPE and alcohol consumption taking each gender individually. This showed that twice as many men who drank alcohol regularly developed PPE than those who did not drink regularly, whereas, the opposite was found for women. Twice as many women who did not drink regularly, developed PPE compared to those who drank regularly, but neither achieved statistical significance (p = .42 and p = .89 respectively) (page 180).

Although these results were not significant it is interesting to note since an association between men and the development of PPE was shown in the retrospective sample. Thus it may be that male gender in combination with regular alcohol consumption increase the risk of developing PPE.

5.11.4 Hobbies and activities causing friction

Studies providing results from statistical analysis of patient factors, other than biographical and laboratory data, have not be found in the literature searched so far. Confirmation of the value of exploring this subject is supported by Von Moos et al (2008) in a review of PLD-associated PPE who also identified that there is currently no validated predictive model identifying the risk of developing PPE.

Participants were questioned about activities such as regular walking, dancing, gardening, DIY, playing musical instruments, sewing, knitting, rubbing hands with moisturising cream regularly or any other activities that may cause friction to the hands or feet. No statistically significant association was found between those who developed PPE and those who did not and those who regularly performed activities that caused friction and those who

did not. The incidence of PPE was higher in both groups with 38/58 in the activity group and 25/43 in the non-activity group but no statistical association was found $p = .58$ (page 168).

Moisturising the hands and feet regularly is recommended by the manufacturer to reduce the severity of PPE however, which emollient to use has not been established by scientific evidence. The very action of rubbing the cream into the hands and feet may cause the very friction that has been suggested to increase the risk of PPE. There were similar numbers of those who developed PPE and used hand cream regularly (33) and those who developed PPE but did not use hand cream (30) with no difference between the groups found $p = 1.00$ (page 168). While these findings would indicate that friction causing activities alone have no association with the development of PPE, no scale measurements were used. Yes/no was assigned based on personal judgement, which, although providing consistency in this study as the researcher was the sole data collector and analyser, would prove difficult for others to replicate.

Participants were also asked whether they worked or not and the type of work they did. Initially the variable was coded with four categories, with insufficient numbers in each category to apply any statistical tests. When collapsed into three categories a cross tabulation revealed an association between the variables job3gps and the development of PPE $p = .05$. However, there were less than 5 cases in one of the cells and this variable could therefore not be included in a multivariate regression. Finally the data were collapsed into two categories (working and not working) and cross tabulation applied. When analysed using PPE development at any cycle an association was seen $p = .04$ with an increased incidence in those who were in employment. When analysed using PPE development prior to cycle 4 no association was seen $p = .36$ but still with a higher incidence of PPE in those who were working (page 168). Table 5.3 shows the categories that this variable contained as it was collapsed from its original state. While firm conclusions cannot be drawn, in this exploratory study there is a trend to suggest that those who continue to

work while receiving capecitabine, regardless of whether it is manual or non-manual labour, have an increased risk of developing PPE and is worth considering when advising patients on how to reduce the risk of developing PPE.

Job	Job3gps	Job2gps
Manual work 18 (14.7%)	Manual work 18 (14.7%)	Working 45 (36.9%)
Non-manual work 27 (22.2%)	Non-manual work 27 (22.2%)	Not working 77 (63.1%)
Retired 70 (57.4%)	Not working 77 (63.1%)	
Unemployed 7 (5.7%)		

Table 5-3 Categories within the variable job and when collapsed

This again is the first reported study examining any association between friction causing activities and the development of PPE. Since this indicates no association between activities and PPE, advising patients to avoid these has not evidence base. People who continue to work during treatment do however appear to have an increased risk of PPE. This would indicate that it may be the exposure of hands and feet to regular general activities that increase the risk. Advising patients receiving capecitabine to avoid activities or hobbies that they enjoy has no evidence base and may affect their psychological well-being. A more sensible approach would be to advise those who develop early PPE to avoid these activities to prevent progression to more severe PPE.

One variable that could possibly influence the participant's ability to carry out friction causing activities would be their performance status, since it could be argued that those with a poorer performance status by its definition would be unable to carry out these activities on a regular basis, and would be less likely to be currently working. An investigation of any association between these activities and performance status did indeed reveal a statistically significant association p = .04 showing more participants assessed as performance status 0 engaged in friction causing activities (page 178).

There have been no large scale studies to evaluate patient factors that cause increased temperature, trauma or friction to the hands and feet to test the

suggestions in the literature that these may increase the risk of developing PPE. Hence the lack of discussion in this section regarding these variables. The current study is the first of its kind to do so and although confirmed the link between temperature indicated by warm hands, the season in which the treatment started and PPE, it refuted others, i.e. temperature indicated by exposure to hot water, hyperhydrosis, regular alcohol intake and friction causing activities. This study also tested and demonstrated no association between previous sunburn, skin type or the regular use of hand cream and the development of PPE. Limitations of the data collection tools have been identified and would need to be addressed in future research. However, this does not detract from the usefulness of the findings from this first large scale study of patient factors and PPE and would indicate that these factors alone may not be predictive of PPE. It may be that in combination with other variables they are predictive, hence the rationale for performing multivariate regression analysis.

5.12 Comparison of logistic regression models

The rationale for the use of a purposeful entry model was provided in chapter 3, and the ROC curve results demonstrated that there was little difference between the purposeful entry method and the automated entry methods. Despite this result the purposeful model may provide a richer one in terms of range of risk factors and it is for that reason that it will be discussed here.

This is the first study to use this method to develop a model that predicts the development of capecitabine induced PPE particularly prior to cycle 4. Although, several studies have applied logistic regression to the data it has often been bivariate with only the occasional mention of multivariate analysis. Even then, the models did not include patient factors such as friction causing activities and exposure to high temperatures.

Table 5.4 provides a reminder of the variables that remained in the final purposeful entry and retention logistic regression models applied to the two samples in this study.

Retrospective sample	Prospective sample
Absence of pre-existing inflammatory condition	Presence of pre-existing inflammatory condition
Commenced treatment during the winter	Absence of metastases
Absence of metastases	Warm hands
Pre treatment ALP value within normal limits	Younger age
Smoker	Higher BMI
Male gender (confounder)	Pre treatment CrCl below normal limits particularly 50.01-80mls/min
No regular alcohol (confounder)	Drinking alcohol regularly (confounder)
No weight loss prior to treatment (confounder)	Good performance status (confounder)
	No previous radiotherapy treatment (confounder)

Table 5-4 Final models of purposeful entry and retention logistic regression

Comparisons between the final purposeful entry models from both samples revealed only one similarity. Participants whose tumour had not metastasised had an increased risk of developing PPE. There was also two contradictory findings between the two samples. In the retrospective sample, participants who did not have a history of inflammatory conditions had an increased risk of developing PPE. Conversely, in the prospective sample, those with a pre-existing inflammatory condition had an increased risk. In the retrospective sample those who did not drink alcohol regularly had an increased risk of developing PPE. However, in the prospective sample, those who drank alcohol regularly had an increased risk. The remaining variables in the retrospective sample that were risk factors for PPE were not present in the prospective sample and vice versa. Therefore these findings could not be validated as risk factors for the development of PPE. Out of the additional variables in the prospective model that were not present in the retrospective model, 1 (warm hands) was not tested in the latter sample.

The inclusion of age and BMI in the prospective model but not in the retrospective model may be due to type I error (where the null hypothesis is

rejected when it is in fact true) and may be as a result of the difference in numbers in each group. For example there was a difference in the age range between the two samples with a more equal number between those less than 65 years and those 65 years or older in the prospective sample than in the retrospective sample (49.2% and 50.8% and 40.6% and 59.4% respectively). The addition of alcohol and performance status in the prospective sample may be due to the number of missing data in the retrospective sample for these two variables. It is not clear why the pre treatment ALP value was a risk factor for the development of PPE in the retrospective sample but not in the prospective one. Participants with breast cancer were more likely to have a raised ALP level due to the presence of bone metastases. There is a larger variation between numbers of participants with breast cancer and colorectal cancer in the two samples (30 and 110 in the retrospective sample vs 45 and 70 in the prospective sample), this may partly explain the reason.

Contradictions between the retrospective and prospective data were most likely not due to sample size. The prospective data are likely to be richer and more accurate, since they were directly collected from participants and there may have been under-reporting in the retrospective sample. Another explanation that these differences occurred by chance is a possibility.

In the prospective model comparing the automated entry methods, there are differences in the odds ratios for alcohol and cool hands. This is probably because of the additional variables retained in the backward entry model. Thereby reflecting the influence exerted on these variables when in combination with the other variables.

Two of the variables in the model from the prospective sample, metastatic spread and performance status were suspected as being clinically associated. A cross-tabulation of metastatic spread and performance status did indeed reveal an association (p = .04) showing as expected that those with poor performance status were more likely to have metastatic spread than those with good performance status. Based on this finding it was assumed that

there would be an increased likelihood of those with metastatic spread having a dose reduction of capecitabine, at the start of treatment or as a result of toxicities. Any association between performance status and a dose reduction prior to commencing treatment was discussed earlier, finding no association. Similarly when a chi-square test was applied to performance status and dose reduction due to toxicities of capecitabine no statistically significant association was found. The same tests applied to metastatic spread and dose reduction found a statistically significant association between participants with metastatic spread and a dose reduction at the start of treatment in the retrospective sample but not the prospective sample. Conversely, participants whose tumour had not metastasised were more likely to have a dose reduction due to PPE. There was no association between metastatic spread and a dose reduction due to other toxicities. As there was no association found between performance status and dose reduction, the former cannot be considered a confounder as was first thought. It is more difficult to state the same with metastatic spread and dose reduction since there are contradictory findings between the samples. If we believe the prospective data to be more reliable as previously stated, then the notion of metastatic spread being a confounding variable can also be refuted with both performance status and metastatic spread considered as risk factors of the development of PPE in patients receiving capecitabine.

Conclusions that may be drawn from the multivariate logistic regression model applied to the prospective sample are that patients receiving capecitabine monotherapy are more likely to develop PPE, if they are less than 65 years old; have a good performance status and absence of metastatic spread; presence of a pre-existing inflammatory condition; have a tendency to have warm hands, drink alcohol regularly; are overweight or obese and have a pre treatment creatinine clearance level of 50.01-80.00 millilitres/minute. Having said this, further study would be required to categorise some of these variables more accurately, particularly, warm hands, units of alcohol consumed per week, and degree of excess weight.

5.13 Summary

The aim of this exploratory study was to identify factors that may increase the risk of developing PPE, focusing on PPE prior to cycle 4 of capecitabine monotherapy therapy. Risk factors have been discussed. Comparing the findings from the retrospective (capecitabine monotherapy only) and prospective samples in this study with others in the literature has demonstrated that findings are comparable for some risk factors, while for others there is contradiction.

In this study more than 50% of participants developed PPE of any grade, with more than three quarters of these developing PPE during the first three cycles of treatment. 59% of participants who developed PPE had grade 2 or 3 as their worst episode. As stated above PPE is more likely to occur in people who are less than 65 years old; with good performance status and absence of metastatic spread; presence of a pre existing inflammatory condition; have a tendency to have warm hands (and feet); drink alcohol regularly; are overweight or obese and have a pre treatment creatinine clearance level of 50.01-80.00 millilitres/minute. These factors would seem reasonable given the evidence presented in the discussion in this chapter. Raising awareness through the dissemination of these findings will provide nurses with a basis on which to identify patients more at risk of developing PPE. Other factors to consider are hormone receptor status of women with breast cancer; ethnicity; time of year when treatment is given; employment; history of sunburn and presence of other capecitabine induced toxicities. In this study, women with oestrogen receptor positive tumours were more likely to develop PPE. Participants whose ethnicity was described as non-white were more likely to develop PPE and given the evidence that presentation of PPE differs in this population it is worthy of further study. Comparisons between the time of year that treatment is commenced and the development of PPE have not been studied in large samples. There were contradictory results between the two samples in this study, but this may have been due to under reporting of mild PPE in the retrospective sample.

Participants who continue to work during treatment with capecitabine were more likely to develop PPE. This variable could be linked with performance status, since those with poor performance status were unlikely to be in employment. There were only a small number of participants who admitted to being sunburnt in the past. The link between previous sunburn and the recurrence of erythema at these sites would seem logical, since radiation recall is a known phenomenon with some chemotherapy agents. The association between previous sunburn and PPE is interesting and would warrant further exploration. Patients who developed capecitabine induced diarrhoea, mucositis or nausea and vomiting appear to develop PPE more frequently. Whether the development of these other toxicities increases the risk of PPE or whether the development of PPE increases the risk of developing the other toxicities is unclear. Further examination of this would be required to accurately record the onset of symptoms of these toxicities. Having said that, awareness of this association is useful to identify patients who may require increased monitoring to recognise early development of these toxicities and prompt management. This may avoid the development of severe toxicities which would result in delays in treatment.

The individual case reports add to the body of knowledge on unusual features of PPE. The modelling algorithm used for selection and retention of variables in multivariate logistic regression and application of statistical tests to establish association between patient activities and the development of PPE are the distinct features that demonstrate the uniqueness of this study. The findings from this study demonstrate the impact of PPE on participants and the importance of thorough questioning and examination to identify PPE particularly its early occurrence, which may develop into a more severe form later.

The following chapter will draw together the conclusions from the findings of this study, reflect on study design, identify the contribution to current

knowledge on capecitabine-induced PPE and recommend areas for future work.

CHAPTER 6 CONCLUSIONS AND RECOMMENDATIONS

6.1 Introduction

Although PPE is said to be rarely serious and never life-threatening, it can cause severe pain and interfere with everyday activities. There have, however, been reports of serious consequences of PPE, such as, increasing the risk of infection via breaks in the skin, which in some cases has led to amputation of a digit or limb. Interest in this toxicity of chemotherapy has increased, particularly since the introduction of more PPE-inducing agents into clinical practice.

While there is sufficient evidence to show that the dose and schedule of capecitabine plays a large role in the development of PPE, the fact that many patients still go on to develop severe PPE following a dose reduction would indicate that there are other factors which influence the risk of developing PPE.

Many studies have analysed biographical characteristics, such as age, gender and ethnicity to assess any association with the incidence of PPE. Other factors that have been explored as predictors of PPE are performance status, co-morbidities and renal function. The findings from these studies have been contradictory with the exception of renal function where there is agreement that a reduction in creatinine clearance increases the risk of developing PPE.

No study has previously collected data to specifically assess the potential of patient activities as risk factors of PPE. The aim of this study was to identify factors, other than the drug itself that may influence the development of PPE. The statistical analysis focused on those who developed PPE within the first 3 treatment cycles of capecitabine monotherapy. This was based on the assumption that PPE developing in later cycles is more likely to be due to accumulation of the drug.

This chapter starts with a summary of the research and the key findings which answer the research questions. It presents the implications of these findings to nursing practice as well as the methodological implications, and the contribution it makes to the current body of knowledge. The chapter concludes by describing the limitations of the study and recommendations for future research.

Risk factors that have previously been studied were analysed. In the majority of cases these were from clinical trials of the drug, to assess its effectiveness in terms of survival, in particular phase III trials. Only a few studies were specifically designed to explore the relationship between factors and the incidence of PPE. Factors that had been analysed in the literature included age, gender, ethnicity, performance status, nutritional deficits and weight loss, organ function, co-morbidities and genetics. These findings were often contradictory, with many based on small samples or case reports. All but genetics were included in the current study to enable comparison of the findings from this study with those in the literature. An examination of strategies employed to minimise the severity or to manage PPE demonstrated some interesting and promising potential agents requiring larger prospective randomised trials to confirm their effect on PPE. A review of the literature concluded that there is a lack of empirical evidence to support the advice given to patients to avoid certain activities that have been suggested as potential risks for developing PPE.

The review of the literature influenced the focus of this study, in terms of the sample group and the data collection tools with two purposes in mind. Firstly to compare the findings from this study with those in other studies, adding to the growing knowledge of PPE and to support or refute those findings. Secondly to analyse risk factors previously based on consensus but unsubstantiated by empirical evidence.

Chapter 3 provides detail of the methods utilised to collect and analyse the data and the rationale for the selection of the algorithm used in the modelling process. Chapters 4 and 5 presented the analysis and discussions of the findings in response to the research questions. The next section answers the research questions summarising the findings.

6.2 Answering the research questions

This section discusses the responses to the two questions this study set out to answer. The responses will be taken from the prospective analysis of participants receiving capecitabine monotherapy to reflect the refined study aim. The prospective data are likely to be richer and more accurate since they were directly collected from participants and there may have been under-reporting in the retrospective sample in addition to the large number of missing data in some variables in the latter sample. A brief summary to compare findings from the retrospective sample and the prospective sample will be included to show where similarities exist.

1. Can risk factors be identified to predict the development of PPE?

In order to answer this question the study formulated a number of hypotheses to be tested. There were 31 hypotheses tested in both samples (one for each variable) details of which can be found in chapter 3.

The bivariate analysis examined any association between other capecitabine-induced toxicities which revealed that participants who developed mucositis or nausea and/or vomiting were more likely to develop PPE than those who did not develop these other toxicities. No association was seen between diarrhoea, fatigue or a rash and PPE.

Biographical data which included age, gender and ethnicity found that age alone showed no association, but when age was broken down into two groups (≤ 64 and ≥ 65) an increased risk of PPE of any grade was seen in the < 65

age group, but no difference between the age groups for severe PPE. While men were more likely to develop PPE than women in this sample it was not confirmed statistically. When age and gender were combined, younger men had an increased risk of PPE possibly explained by the fact that older men were more likely to commence treatment on a reduced dose than younger men. Ethnicity revealed an increased risk of PPE in the non-white population. This was an interesting finding and although the small numbers of non-white participants meant that no firm conclusions could be drawn, it is worthy of further attention.

No association was found between the variables related to social history and the development of PPE. These included marital and employment status, smoking and alcohol consumption. These factors were examined based on the notion that those who lived alone or worked would be undertaking more activities that expose the hands and feet to high temperature and friction. The incidence of PPE as expected was higher in those who did work than in those who did not work. Smoking and alcohol both have an effect on vascularisation and although neither achieved significance in the bivariate analysis, alcohol was included in the regression model since it met the criteria for inclusion and remained in the final model as a confounder.

Co-morbidities have been reported in the literature as linked to the development of PPE. Data were collected on those co-morbidities that had been linked to PPE, namely, diabetes and peripheral vascular disease (PVD). Others were included because of possible clinical relevance. The presence of peripheral neuropathy (PN) would reduce sensation which would prevent the patient from recognising early signs of PPE. Since PPE is a cutaneous toxicity, a history of skin complaints such as eczema may make the skin more sensitive to chemical insult. PPE has been purported to be due to an inflammatory response, therefore it would seem logical that if an individual has a pre-existing inflammatory condition such as arthritis, they may be more likely to develop PPE. No association was seen between PPE and diabetes, PVD, PN or skin conditions, although with only small numbers with PVD or PN

these findings are unreliable. An association was seen between the presence of an inflammatory condition and the development of PPE.

The performance status of each participant was assessed and illustrated an association with the development of PPE. Those with a good performance status (0 or 1) were more likely to develop PPE than those with poor performance status (2 or 3). At first it was thought that this may be related to those with poor performance status having a dose reduction at the start of treatment. When this potential link was explored by statistical testing, no association was found thereby refuting this initial thought. No studies were found in the literature which tested the association between performance status and PPE and this may be the first report of such an association. Although firm conclusions could not be drawn from the retrospective sample due to the number of missing cases, the fact that the association was confirmed in the prospective sample adds support to this relationship.

Tumour related factors were examined and included; the tumour site, presence of metastases, treatment intent and previous radiotherapy treatment. An association was seen between PPE and participants who did not have metastatic spread and were receiving capecitabine as adjuvant treatment. Although a multicollinearity test showed no correlation between performance status, metastatic spread or treatment intent, clinically one could assume an association. Cross tabulation confirmed this clinical assumption showing that participants with a good performance status were less likely for their tumour to have metastasized and more likely to receive capecitabine as adjuvant therapy.

No association between albumin levels or weight loss prior to commencing treatment and PPE were found. However, being overweight or obese appeared to increase the risk of developing PPE. The logistic regression indicated that for every unit increase in BMI the risk of developing PPE increased. This finding, that BMI in combination with other variables increases

the risk of PPE, adds to the debate on the value of using BSA to calculate chemotherapy dosage.

Organ function can affect the clearance of drugs and increase the risk of toxicities. Pre-treatment laboratory data collected included; creatinine, creatinine clearance (CrCl), ALT, ALP, bilirubin and albumin. None of these variables reached significance in the bivariate analysis. Creatinine clearance and albumin met the criteria for inclusion in the regression model. Albumin was removed, but CrCl was retained as a significant variable and demonstrated that for every unit decrease in CrCl the risk of PPE increased. During the data collection phase observations suggested that participants with a CrCl of between 50 and 80mls/min (mild renal impairment) had an increased incidence of PPE. This observation was confirmed in a logistic regression containing just CrCl and PPE.

The effects of the season in which treatment started may differ from year to year depending on whether we have a hot summer or very cold winter. This may partly explain the contradictory findings between the retrospective data and the prospective data. An association was found in the retrospective sample, that participants commencing their treatment in the winter were more likely to develop PPE than those commencing their treatment in the summer. Conversely, in the prospective sample participants who commenced their treatment in the summer were more likely to develop PPE, however, this was not confirmed statistically.

One of the study aims was to utilise the prospective data to validate the findings from the retrospective sample. When applying the conventional alpha level of $p < .05$, there were only two variables that were significantly associated with the development of PPE in the retrospective sample that also achieved significance in the prospective sample. The two variables were participants whose cancer had not metastasized and were receiving capecitabine monotherapy as adjuvant treatment. When the relaxed alpha level of $p < .1$ was applied to both samples an additional two variables

achieved significance. There was consensus between the two samples of the creatinine clearance level (50.01-80.00) associated with an increased risk of developing PPE. However, a co-morbidity of an inflammatory condition indicated contradiction between the samples. Participants in the prospective sample whose medical history included the presence of an inflammatory condition were more likely to develop PPE. Conversely in the retrospective sample those with no history of inflammatory conditions were more likely to develop PPE. This difference may be due to under reporting of this medical history in the latter sample.

2. Do individual activities that cause friction or exposure to heat increase the risk of developing PPE?

The same 31 hypotheses tested in the retrospective sample were re-tested in the prospective sample with an additional 10 hypotheses related to individual activities.

The 10 additional variables included; history of previous sunburn, regular engagement in friction-inducing activities or exposure to hot water, a tendency to have dry skin, cool or sweaty hands and feet, regular application of hand cream and skin type.

Participants who reported a tendency to have warm hands had an increased risk of PPE than those who reported having a tendency to having cool or cold hands. No association was found between participants who reported sweating on their hands and feet regularly and PPE. Similarly no association was found in those who regularly exposed their hands and feet to hot water. Self reported measures (simple yes or no answer) and lack of any scale measurement make this difficult to replicate. Future studies would need to address this and include measures of, for example, the frequency of immersion and temperature of the hot water.

No association was seen between friction-inducing activities or regular application of hand cream, despite consensus advice to moisturise regularly and avoid activities that cause friction. In this exploratory study self reported measures were taken. To make the findings generalisable, scale measures would need to employed to include the type, frequency, and amount of activity and moisturisers.

The skin type of the participants showed no association with PPE, and interestingly those who had skin types more sensitive to sunburn had a reduced risk of developing PPE. Despite a few reported cases of radiation recall in areas that had previously been sunburnt, a history of sunburn showed no association with PPE.

There have been no large scale studies in the literature to evaluate patient factors that cause increased temperature, trauma or friction to the hands and feet to test the suggestions that these may increase the risk of developing PPE. The current study is the first of its kind to do so and in bivariate analysis confirm a link between temperature indicated by warm hands and PPE. The study however, refuted others such as temperature indicated by exposure to hot water, hyperhydrosis, and friction causing activities. This study also tested and demonstrated no association between previous sunburn, skin type or the regular use of hand cream and the development of PPE. Limitations of the data collection tools have been identified and would need to be addressed in future research. This does not detract from the usefulness of the findings from this first large scale study of patient factors and PPE and would indicate that these factors alone may not be predictive of PPE and it may be that in combination with other variables they are predictive, hence the rationale for performing multivariate regression analysis.

Variables, from the prospective data, to answer both research questions were entered into the regression model based on the purposeful algorithm described in chapter 3. A number of entry methods were employed in regression modelling and applied to the data to compare the conclusions or to

validate the model results. Following this analysis the probabilities generated in each model were tested using ROC curve to assess which model provided the most accurate prediction of PPE. The purposeful selection model containing one additional variable that was not significant in the bivariate analysis achieved the highest score. This model contained 6 significant variables ($p < .01$) and 3 confounders (caused a > 20% change in the beta coefficient of another variable when removed from the model).

Table 6.1 lists the categories that were included in the final model and established those that were predictive of PPE. The greater the odds ratio the more important that variable may be as a risk factor of PPE. It seems accepted that renal impairment is a risk factor for toxicity of capecitabine. One might question whether some of the variables might be associated with a dose reduction and therefore influence their effect on the development of PPE. These variables are participants with metastatic spread, older age, have received previous radiotherapy treatment (particularly breast cancer) and assessed as poor performance status. These all showed a reduced risk of developing PPE. To test this notion bivariate tests were applied and no association was found between each variable and dose reduction at the start of treatment, or at any time due to PPE or other toxicities. This would indicate other reasons why these variables may act as risk factors.

Significant category	Odds ratio
Absence of metastatic spread	3.18
Pre-existing inflammatory condition	2.60
Warm hands	1.90
Overweight or obese	1.13
Renal impairment	.98
Younger age	.93
Confounders	**Odds ratio**
No previous radiotherapy treatment	2.93
Regular alcohol intake	2.18
Good performance status	1.64

Table 6-1 Variable categories in final regression model predictive of PPE

One might also question the link between BMI, age and renal function, since weight and age form part of the equation to calculate CrCL. A multicollinearity diagnostic test revealed no correlation between these variables.

Conclusions that may be drawn from the multivariate logistic regression model applied to the prospective sample are that participants receiving capecitabine monotherapy are more likely to develop PPE, if they have a good performance status and absence of metastatic spread. Others include a tendency to have warm hands, drink alcohol regularly, and be overweight or obese. Finally a pre treatment creatinine clearance level of 50.01-80.00 millilitres/minute. Having said this, further study would be required to categorise some of these variables more accurately, particularly, warm hands, units of alcohol consumed per week, and degree of excess weight.

In an attempt to validate the findings from the retrospective sample, the variables from this sample that were entered into the regression model were applied to the prospective data. This model was reduced according to the same purposeful algorithm as before. Only two out of the variables entered remained significant, namely the absence of metastatic spread and the presence of pre existing inflammatory conditions, with no confounders. This between samples comparison could not validate all variables as risk factors of PPE. This may be due to the limitations of retrospectively collected data and validation of the findings from the prospective sample would need to be confirmed by further prospective studies.

6.3 Contributions to research and practice

The unique contributions of this study to research include the modelling algorithm applied to the data, the uniqueness of certain data collected and analysed and the valuable information that has been provided to support future research and development.

Stepwise regression models depend on statistical criteria to reduce and fit the final model. The advantage of purposeful selection of variables is that the analyst makes the decision at each step based on statistical and clinical relevance. This results in a model containing confounders in addition to the significant variables. The use of this modelling technique as a unique contribution of this study adds to the current literature. It is the first study to use this type of purposeful selection algorithm to fit a regression model to analyse risk factors of capecitabine-induced PPE. The results from the ROC tests show that it is worthwhile and gives a potentially richer model with the inclusion of confounders, although statistically there was little difference between the various entry methods.

This research explored numerous potential risk factors of PPE. The findings will add to the current evidence of biographical data, performance status, co-morbidities and renal function as risk factors of PPE. Since this is the first time that individual activity related factors have been studied, this is the unique contribution made by this research. The findings raise questions about the current advice given to patients receiving capecitabine to avoid activities that cause friction or exposure to high temperatures. Whilst it is acknowledged that the findings need validating by further research they have implications for nursing practice.

Current practice with patients commencing capecitabine involves advising them to avoid activities that cause friction, pressure or high temperature. The evidence base for this is based on consensus and case reports. There are no previous large studies to validate this advice. This study is the first that has tested any association between activities that cause friction, pressure or high temperature and PPE.

The advice to avoid exposure to heat and keeping the hands cool has been confirmed in this study. All other activities were not confirmed statistically as having any association with the development of PPE. Whilst these findings

will need validating in further large prospective studies, they do suggest that avoidance of some activities is unnecessary unless PPE develops.

The prospective purposeful entry model indicates that participants who drink alcohol regularly, are overweight and have an inflammatory condition as co-morbidity have an increased risk of developing PPE. With the possible exception of having a pre existing inflammatory condition, the other two variables were not supported by the retrospective model and therefore have to be treated with caution until these are confirmed or refuted in other studies.

Other findings in the literature and supported in this study that increase the risk of PPE is that patients with mild renal impairment (CrCl 50 – 80 mls/min) should be monitored closely for early signs of PPE and may require a dose reduction. Nurses should also be aware that older patients and those with poor performance status are not necessarily at risk of PPE, although they may be for other toxicities. Careful assessment should be made of patients over the age of 80 receiving capecitabine since they appear to respond differently to the drug and may be at more risk of toxicity. Implementation of a risk assessment tool such as the CRASH tool presented by Extermann et al (2010) may increase confidence in treating older patients with chemotherapy. Awareness amongst nurses who educate or monitor patients receiving capecitabine should be raised to ensure they can advise patients and recognise the different presentation of PPE in people with dark skin.

Until such a time that the evidence base for avoiding friction or pressure causing activities is established, the focus should be on careful monitoring, questioning and assessment. There is evidence that early onset of grade 1 PPE results in an increased risk of developing more severe PPE in subsequent cycles. Careful questioning of patients to identify PPE developing between cycles which has resolved, may identify those who would benefit from early dose reduction to avoid delays in treatment due to severe PPE. This is particularly important in light of the emerging evidence that PPE may

be a marker of efficacy of treatment. This would indicate that those who develop PPE and the ones most likely to benefit from continuing treatment.

Another recommendation would be to ensure men receiving agents that are known to cause PPE are educated about the possibility of penile and scrotal involvement, giving them permission to report this, which, if identified early, may reduce its severity.

The evidence for strategies to prevent or manage PPE once it develops is weak. The only agent that has been subjected to randomised controlled trials is pyridoxine demonstrating that the findings cannot support its use to avoid or manage PPE. The use of emollients has not been subjected to rigorous testing. However, since one of the early symptoms of PPE is dryness and flaking, the use of emollients would seem logical. Since it a safe and uncontroversial substance its use can be recommended without ill effects.

6.4 Limitations

Every effort is made to use the best available data to answer the research questions. Despite this it is inevitable that there will be factors that affect the findings of the study. These factors include limitations of the study design or other factors within the study that may affect the findings. The following limitations apply to this study;

Collection of data retrospectively is easy and inexpensive but can be limited in its accuracy. There can be operational difficulties in collecting retrospective data. In this study, this included; difficulties in obtaining several sets of notes and large amounts of missing data from some variables. This can affect the external validity of the findings and could not be recommended for use in clinical practice without further validation in prospective studies. The prospective data collection phase of this study set out to validate these findings and also to collect data about individual participant activities which were not available from retrospective notes.

Randomisation was not appropriate in this study since comparison was not being made between those who received an intervention and those who did not. Stratification, the process of dividing members of the population into homogeneous subgroups before sampling (Marston 2010) may have produced different results. However, this would have required a much larger sample from which to randomly select subjects from each group.

Data collection restricted to one geographical site lacks generalisability. Similarly data collection restricted to a single chemotherapy agent cannot be generalised to other agents. Although, if we accept the notion that there may be different pathophysiological mechanisms and risk factors for PPE between different agents, this may in fact be the study's strength. Large scale studies focusing on each different drug would enable comparison of data to test commonality or variability.

The analysis was not definitive, since it was not possible to consider all covariates due to a limited number of participants per category within a variable.

The analysis described has certain disadvantages. It has been performed in a series of participants and the results applied to this particular series only. Even if the validity were tested and confirmed in another similar series, it would not necessarily be applicable to a different group of patients because of the probable presence or absence of other known risk factors.

Although the logistic regression analysis discussed had some limitations, it was undertaken in the spirit of a preliminary investigative study and was a worthwhile exercise.

Some variables lack scale measurement such as friction-inducing activities, exposure to high temperature and alcohol consumption. Responses were coded based on the judgement of the researcher. Since there was a single

investigator collecting and analysing the data there was consistency in the definition for this sample but would prove difficult to replicate by other investigators.

The study was restricted by time which resulted in occasions where information had to be gathered from other staff or patient records.

Despite these limitations, this study was worthwhile in that it has contributed to the existing body of knowledge and demonstrated the usefulness of an algorithm that produces a richer risk factor model. It has succeeded in providing the first steps in providing an evidence-base for education delivered by nurses to patients receiving capecitabine by nurses. Based on these preliminary findings planning a prospective and a much larger study for testing the discrimination of the independent variables would be a meaningful venture.

6.5 Future research

From the study outcomes in response to the research questions, and emerging literature during this study a number of supplementary areas worthy of prospective research are identified. The following are suggestions for future research;

There is a dearth of literature examining any association between other toxicities of capecitabine and PPE. Further exploration of these may identify if the advent of toxicities such as diarrhoea or stomatitis predict the subsequent emergence of PPE. Alternatively whether the advent of PPE predicts for other toxicities of capecitabine. This would enable nurses to identify patients that may require more vigilant monitoring, education and support.

Fatigue was identified in this study to occur in almost 50% of participants in the prospective sample. Participants often described this as the one side effect that they found most difficult to cope with. It does not appear to be a

transient effect, that is, it does not resolve completely with treatment delay or dose reduction. Personal clinical experience has shown that fatigue can persist for up to a year after treatment and sometimes never resolves completely. A study to examine the onset and severity of capecitabine-induced fatigue and its impact on quality of life would demonstrate the scale of the problem. This may then lead on to identifying and testing strategies to manage fatigue.

One of the limitations of this study was that the variables related to friction-inducing activities and those that exposed the hands and feet to high temperatures lacked reproducibility. Development of measurement scales and further testing of these variables would provide a basis for other researchers to replicate and make comparisons

Since PPE is not life-threatening, it has rarely been examined in terms of its impact on quality of life. This and other studies have demonstrated an association between good performance status and PPE. Personal clinical experience is that some patients decide to stop their capecitabine treatment, even when it is given as adjuvant therapy, because of the impact of fatigue on their everyday lives. A study to further examine the association between PPE and performance status would confirm the findings from this study. Inclusion of well recognised tools such as the Hospital Anxiety and Depression Scale (HADS) and other quality of life assessment tools would clearly show the impact of PPE on patients.

This study found an association between BMI and PPE, with participants that were overweight or obese having an increased risk of PPE. Arguments were presented suggesting that LBM may be a more appropriate measurement on which to calculate chemotherapy doses. A study to compare LBM, BMI and capecitabine-induced toxicities may add to this ongoing debate.

Small scale studies have examined a link between serum folate levels and severe PPE. A large scale prospective study to explore any influence of pre-

treatment folate levels and dietary folate intake on toxicities of capecitabine would refute or confirm these findings. This in turn would provide evidence for nurses and dieticians to educate patients on how to reduce their folate intake during treatment with capecitabine.

Studies have suggested that PPE may be a predictor of efficacy of capecitabine (TTP and OS) with one study suggesting that Thymidine Phosphorylate (TP) levels in tumour cells are associated with efficacy of capecitabine (TTP and OS) and PPE. This raises questions of whether it is the TP level in tumour cells that influences the efficacy of the treatment and whether PPE is a clinical sign of these raised levels and would warrant further research to compare TP levels and efficacy with the incidence of PPE.

Evidence in the literature suggests that the older adult may be at increased risk of toxicities from chemotherapy. Studies of patients over 70 years old, incorporating a geriatric assessment with clinical and treatment variables, produced a validated risk assessment tool. This Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH) was validated in patients receiving many different chemotherapy regimes and tumour types in the samples studied (Extermann et al 2010). The next step would be to develop this further by studying its use in specific regimes such as capecitabine (Feurst 2010).

This study showed that there is an association between having warm hands and PPE. There is contradictory evidence that regional cooling reduces the risk of PPE in patients receiving PLD. An investigation into the usefulness of regional cooling to reduce the incidence and/or severity of capecitabine-induced PPE would add to the evidence-base to support advice given to patients. This could be developed as either a randomised controlled trial or applying regional cooling to just one hand, thereby using the other as a control. This may present some difficulties, given that capecitabine is taken twice a day for 14 days. The timing and length of cooling would need to be carefully planned based on the pharmacological knowledge of capecitabine.

Chapter 2 presented the evidence for several agents that have been suggested to either prevent or manage PPE. Further randomised double-blinded trials are required on several of these to establish their efficacy. These agents include cod liver oil; hempseed oil; Vitamin E and henna.

Since this was an exploratory study examining many factors future research may concentrate on individual factors to ensure detailed measurements which could then be replicated.

The future studies suggested above provide a real opportunity for nurses to be engaged in multi-professional research. Collaboration could be between nurses and physiotherapists, occupational therapists, dieticians, scientists, as well as doctors.

6.6 Conclusion

A summary of the study and the findings to answer the research questions has been presented. The unique contributions to research and to nursing practice were identified. These include the unique application of the purposeful selection algorithm, where the analyst not the computer makes the decisions at each step. This produces a richer and more controlled model containing significant variables in addition to confounders. The contribution to nursing practice adds cumulative evidence to current knowledge and new evidence which may support patient education and monitoring strategies.

PPE appears to be a problem of multi-factorial nature where it is difficult to report and collect reliable data. This is evidenced by the conflicting reports in the literature and perhaps explains some of the differences between the two samples in this study. There were difficulties in interpretation of the findings in the literature due to the different toxicity measurement tools and ways of presenting the data. Many of the differences in this study, however, could be explained by the limitations of the retrospective nature of the first sample.

The limitations of this study were described and despite these the study was worthwhile because of its unique contribution. Finally suggestions were made for further studies to answer different questions about risk factors for PPE and to confirm or refute agents to prevent or manage PPE.

This thesis commenced by stating that PPE is not life-threatening, although serious consequences have been reported. It was also suggested that the impact of PPE on a patient's quality of life sometimes results in refusal to continue with treatment because of the pain and discomfort it causes. Being able to identify those at most risk in order to initiate preventative measures including appropriate education would reduce the severity and thereby prevent delays in treatment or cessation of treatment. This would seem a fitting place to finish and to take forward the implementation of the following recommendations for nursing practice.

6.7 Summary of recommendations

The following recommendations provide guidance to nurses who manage patients receiving capecitabine

- Patients should be educated prior to commencing capecitabine;
    - Emphasise the importance of reporting all signs and symptoms of PPE as soon as they appear. This will ensure that PPE is managed appropriately, in a timely manner and reduce delays in subsequent treatment.
    - To keep hands cool as much as possible
    - That PPE can occur in areas other than the hands and feet such as areas previously irradiated or sunburnt and inter-triginous areas such as the scrotum in men and under the breast in women.
- Careful monitoring of patients who may have an increased risk of PPE;
    - Those who develop early grade 1 PPE, since they are at risk of developing more severe PPE at subsequent cycles.

- Aged under 65 years, have a good performance status, no metastatic spread from their primary cancer and who continue to work during their treatment.
- Aged 80 years or above and consider implementing an older persons risk assessment tool.
- Are over weight or obese.
- Those with a history of diabetes, peripheral vascular disease or peripheral neuropathy, as they may have a reduced ability to feel the early onset of pain associated with PPE.
- Patients with other inflammatory conditions such as rheumatoid arthritis.
- Have mild renal impairment (CrCl 50-80 mls/min)
- Ethnic minority groups with dark skin. Include the toxicity grading suggested by Saif (2011) and described on page 221 into local toxicity assessment tools
- Patients who develop mucositis and/or diarrhoea should be assessed for signs of PPE.

➢ At each visit prior to receiving the next cycle of treatment the nurse should;

- Question the patient carefully about any signs and symptoms of PPE that occurred between cycles which have resolved. This should include questioning any redness or soreness in areas other than the hands and feet.
- Examine the hands and feet at each visit to identify and signs of PPE which the patient may not have revealed.
- Patients who develop PPE should be questioned about any symptoms of mucositis and diarrhoea.

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CHAPTER 8 APPENDICES

APPENDIX 2.1 PERFORMANCE STATUS

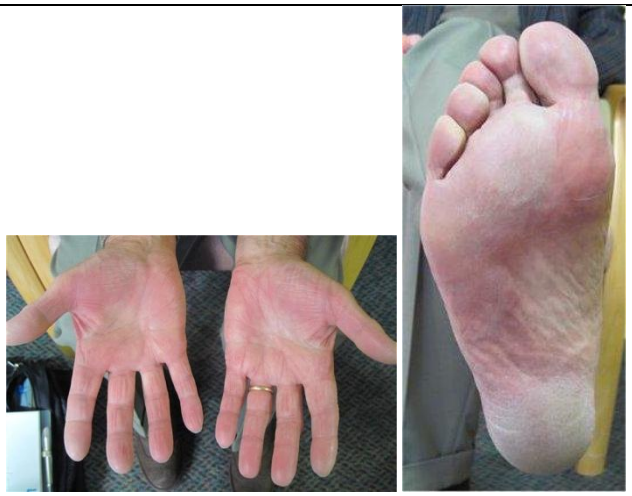
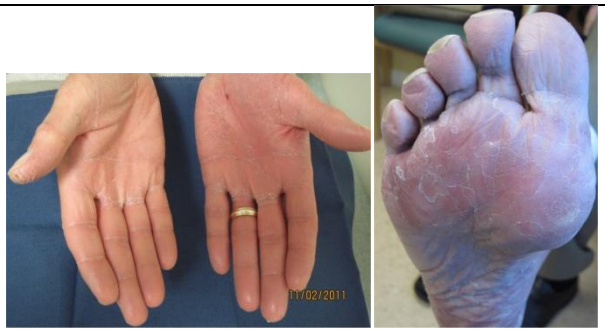
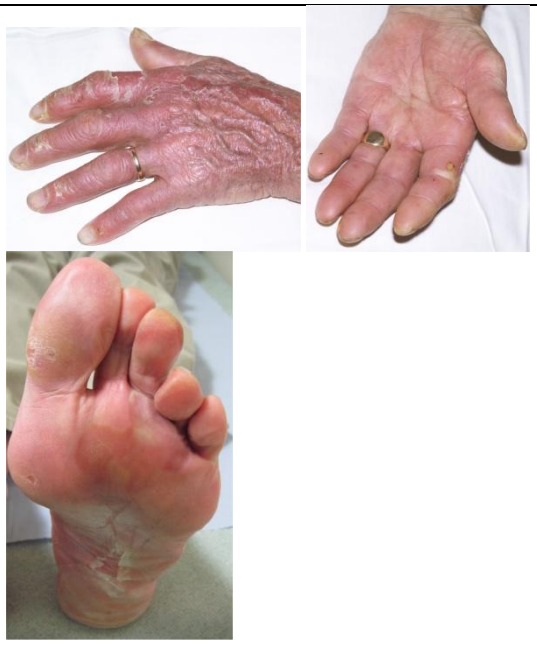
ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken et al (1982)

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX 2.2 PPE GRADING SYSTEMS

NCI criteria for PPE (NCI CTCAE v 3.0 2006)		
Grade	**Definition**	
1	Minimal skin changes or dermatitis without pain (e.g. erythema, peeling)	
2	Skin changes (e.g. peeling, blisters, bleeding, oedema) or pain, not interfering with function	
3	Ulcerative dermatitis or skin changes with pain, interfering with function	
National Cancer Institute Common Toxicity Criteria of Adverse Events version 3.0 (NCI 2006)		

Grade	
1	Dysesthesia/ paraesthesia, tingling in the hands and feet
2	Discomfort in holding objects and upon walking, painless swelling or erythema
3	Painful erythema and swelling of palms and soles, Periungual erythema and swelling
4	Desquamation, ulceration, blistering, severe pain
WHO Toxicity criteria (WHO 1979)	

Grade	Clinical domain	Functional domain
1	Numbness, dysesthesia/ paraesthesia, tingling, painless swelling or erythema	Discomfort that does not disrupt normal activities
2	Painful erythema, with swelling	Discomfort that affects activities of daily living
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform activities of daily living
Capecitabine Clinical Trials toxicity criteria (Blum et al 1999)		

APPENDIX 3.1 MEDICAL NOTES DATA EXTRACTION FORM

Trial Id no:

Unit no: **RTD no:**

Male ☐ **Female** ☐

Age ☐

Marital status	
Single	
Married/ cohabiting	
Divorced/separated	
Widow(er)	

Ethnic group (Optional)					
British		Irish		White & Asian	
White & Black Caribbean		White & Black African		Pakistani	
Any other mixed background		Indian		Caribbean	
Bangladeshi		Any other Asian background		Chinese	
African		Any other Black background		Not stated	
Any other ethnic group		Any other White background			

Past medical history;

(Note specifically dermatological or inflammatory conditions)

Medication;

ECOG Performance status (please circle score)	
Score	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light nature, e.g., light housework, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.

TUMOUR DETAILS	
Site and cell type of tumour (e.g. adenocarcinoma of the rectum)	
Stage & Grade	
Metastatic spread (where)	
Hormone receptor status (if applicable)	

Previous chemotherapy **YES/NO**

If Yes state regime(s)

PPE with previous chemo **YES/NO** **Worse grade of PPE**

Other toxicities with previous chemo (Please state)

Previous radiotherapy **YES/NO** **Site:**

MOST RECENT CHEMOTHERAPY REGIME				
Aim (please tick)		**Drug (s)**	**Dose**	**Frequency**
Adjuvant **Neoadjuvant** **Palliative**				
Planned number of cycles				

HEIGHT (cms)	**WEIGHT (Kg)**	**BSA (M^2)**	**BMI**

Employment

Smoker **YES/NO** **No per day**

Recent smoking history (if stopped)

Alcohol **YES/NO** **Type** **Units/week**

Recent weight loss? (amount)

Menstrual status pre-menopausal/ post menopausal

PRE CYCLE 1

Date:

PRE TREATMENT BLOOD RESULTS			
Urea		**ALP**	
Creatinine		**Bilirubin**	
Cr clearance		**Albumin**	
Neutrophils		**ALT**	

GCSF support **YES/NO**

Name of GCSF prescribed

Any changes to proposed chemotherapy regime?

Any comments;

PRE CYCLE 2 (There will be sheets for cycles 3 – 6)

Date:

Is PPE present? **YES/NO**

Grade (see below) **1** **2** **3**

Grade	Clinical domain	Functional domain
1	Numbness, dysesthesia/paraesthesia, tingling, painless swelling or erythema	Discomfort that does not disrupt normal activities
2	Painful erythema with swelling	Discomfort that affects normal daily activities
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform normal daily activities

Any other toxicity present? (please state type & grade)

PRE TREATMENT BLOOD RESULTS			
Urea		**ALP**	
Creatinine		**Bilirubin**	
Cr clearance		**Albumin**	
Neutrophils		**ALT**	

GCSF support **YES/NO**

Name of GCSF prescribed

TREATMENT DECISION				
FULL DOSE	**DEFERRED** (how long)	**DOSE REDUCTION** (by how much)	**STOPPED**	**CHANGED TO OTHER REGIME**

Comments:

APPENDIX 3.2 CODING OF INDEPENDENT VARIABLES

(before collapsing categories with small numbers)

VARIABLE	CATEGORIES
Gender	Male = 0; Female = 1
Age	Actual age
Marital status	Single = 1; Married/cohabiting = 2; Divorced/separated = 3; Widow(er) = 4
Ethnic origin	White British = 1; White & Black Caribbean = 2; Any other mixed background = 3; Bangladeshi = 4; African = 5; Irish = 6; White & Black African = 7; Indian = 8; Any other Asian background = 9; Any other black background = 10; White & Asian = 11; Pakistani = 12; Caribbean = 13; Chinese = 14
Diabetes	No = 0; Yes = 1
Peripheral Vascular disease	No = 0; Yes = 1
Peripheral neuropathy	No = 0; Yes = 1
Skin complaint	No = 0; Yes = 1
Inflammatory condition	No = 0; Yes = 1
Previous cancer diagnosis	No = 0; Yes = 1
NSAID	No = 0; Yes = 1
Steroids	No = 0; Yes = 1
Cox-2 inhibitors	No = 0; Yes = 1
Other anti-inflammatory drugs	No = 0; Yes = 1
Performance status	Actual figure 0 – 4
Tumour site	Colon = 1; Rectal = 2; Oesophageal = 3;Breast = 4; Gastric = 5; Unknown primary = 6; Cholangiocarcinoma = 7; Pancreas = 8; Pseudomyxoma peritonei = 9; Neuroendocrine = 10; Ovary = 11
Metastatic spread	No = 0; Yes = 1
Previous chemo	No = 0; Yes = 1
PPE with previous chemo	No = 0; Yes = 1
Previous radiotherapy	No = 0; Yes = 1
Aim of current treatment	Adjuvant = 1; Neoadjuvant = 2; Palliative = 3
Regime	Capecitabine SA = 1; Capecitabine/Radiotherapy = 2; ECX = 3; Folfox = 4; Capox = 5; Cisp/Cap/RTD = 6; Cap/Docetaxel = 7; Bev/Cap = 8; Folfiri = 9; Gem/Cap

	= 10; Cap sa trial = 11; EOX = 12
BSA	Actual figure
BMI	Actual figure
Employment	No = 0; Yes = 1
Smoker	No = 0; Yes = 1
Alcohol	No = 0; Yes = 1
Recent weight loss	No = 0; Yes = 1
Cycle of 1st presentation of PPE	Actual figure 1 – 6
Grade at 1st presentation of PPE	Actual figure 1 – 3
Worst grade	Actual figure 1 – 3
Other toxicities	No = 0; Yes = 1
Outcome	Completed all planned cycles = 1; Stopped due to PPE = 2; Stopped due to other toxicities = 3; Stopped for other reason = 4; Changed to other treatment due to PPE = 5
Deferred due to PPE	No = 0; Yes = 1
Deferred due to other toxicities	No = 0; Yes = 1
Dose reduction at 1st cycle	No = 0; Yes = 1
Dose reduction due to PPE	No = 0; Yes = 1
Dose reduction due to other toxicities	No = 0; Yes = 1
Creatinine cycle 1	Actual figure
CrCl cycle 1	Actual figure
ALP cycle 1	Actual figure
ALT cycle 1	Actual figure
Bilirubin cycle 1	Actual figure
Albumin cycle 1	Actual figure
No. of cycles received	Actual figure
Month at start of treatment	Actual figure
Additional variables in prospective sample	
Recent sunburn	No = 0; Yes = 1
Hobbies with friction	No = 0; Yes = 1
Hot water	No = 0; Yes = 1
Skin type	Actual figure 1 – 6
Dry skin	No = 0; Yes = 1
Cool hands	No = 0; Yes = 1
Cool feet	No = 0; Yes = 1
Sweaty hands	No = 0; Yes = 1
Sweaty feet	No = 0; Yes = 1
Regular hand cream	No = 0; Yes = 1

APPENDIX 3.3 INTERVIEW SCHEDULE

IDENTIFICATION OF RISK FACTORS THAT PREDICT THE DEVELOPMENT OF PALMAR-PLANTAR ERYTHEMA (PPE)

PHASE 1

Patient identification label Please stick label here

This sheet is used to enable the research team to identify which patient this document refers to during the data collection stage to prevent data from patients being mixed up.

This sheet will be shredded immediately after the 6th cycle of chemotherapy which is the end of the data collection period.

PATIENT INTERVIEW SCHEDULE

Check consent form has been signed. ☐

Date: **Trial Id no:**

Unit no: **RTD no:**

Male ☐ **Female** ☐

Age ☐

Marital status	
Single	
Married/ cohabiting	
Divorced/separated	
Widow(er)	

Ethnic group (Optional)					
British		Irish		White & Asian	
White & Black Caribbean		White & Black African		Pakistani	
Any other mixed background		Indian		Caribbean	
Bangladeshi		Any other Asian background		Chinese	
African		Any other Black background		Not stated	
Any other ethnic group		Any other White background			

Past medical history;

(Ask specifically about dermatological or inflammatory conditions)

Medication;

ECOG Performance status (please circle score)	
Score	**Description**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light nature, e.g., light housework, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.

TUMOUR DETAILS	
Site and cell type of tumour (e.g. adenocarcinoma of the rectum)	
Stage & Grade	
Metastatic spread (where)	
Hormone receptor status (if applicable)	

Previous chemotherapy **YES/NO**

If Yes state regime(s)

PPE with previous chemo **YES/NO** **Worse grade of PPE**

Other toxicities with previous chemo (Please state)

Previous radiotherapy **YES/NO** **Site:**

CURRENT PROPOSED CHEMOTHERAPY REGIME				
Aim (please tick)		**Drug (s)**	**Dose**	**Frequency**
Adjuvant **Neoadjuvant** **Palliative**				
Planned number of cycles				

HEIGHT (cms)	**WEIGHT (Kg)**	**BSA (M^2)**	**BMI**

Employment:

Smoker **YES/NO** **No per day**

Recent smoking history (if stopped)

Alcohol **YES/NO** **Type** **Units/week**

Recent weight loss? (amount)

History of recent sunburn (please describe degree & area affected)

HOBBIES	
Gardening	
DIY/using tools	
Walking	
Dancing	
Sewing/knitting	
Other (especially using hands & feet)	

DAILY ACTIVITIES	
Washing up **With/without rubber gloves** (please circle)	
Hand washing clothes	
Bath/Shower (please circle)	**Temperature** (please circle) **Cool Warm Hot**
Number of hot drinks per day	
Kneeling or leaning on elbows (e.g. cleaning floors etc)	
Normally wear socks / gloves (please circle)	**Socks Gloves**

SKIN TYPE						
Skin type (see description below)	**I**	**II**	**III**	**IV**	**V**	**VI**
Patient's own description (please circle)	**Dry**		**Moist**		**Sensitive**	
Patient's hands normally	**Cool**		**Warm**		**Hot**	
Patient's feet normally	**Cool**		**Warm**		**Hot**	
Is the patient prone to sweaty palms in warm weather or when stressed/anxious?	**YES**			**NO**		
Is the patient prone to sweaty feet in warm weather or when stressed/anxious?	**YES**			**NO**		
Does the patient use hand cream regularly?	**YES**		**NO**	**How often?**		

SKIN TYPE	
Type I	**Often burns, rarely tans. Tends to have freckles, red or fair hair, blue or green eyes**
Type II	Usually burns, sometimes tans. Tends to have light hair, blue or brown eyes
Type III	Sometimes burns, usually tans. Tends to have brown hair and eyes
Type IV	Rarely burns, often tans. Tends to have dark brown eyes and hair.
Type V	Naturally black-brown skin. Often has dark brown eyes and hair.
Type VI	Naturally black-brown skin. Usually has black-brown eyes and hair.
Ref: Cancer Research UK. Sunsmart. www.cancerresearchuk [Accessed 14.10.08]	

CYCLE 1

Date:

PRE TREATMENT BLOOD RESULTS			
Urea		**ALT**	
Creatinine		**ALP**	
Cr clearance		**Bilirubin**	
Neutrophils		**Albumin**	

GCSF support **YES/NO**

Name of GCSF prescribed

Any changes to proposed chemotherapy regime?

Any comments;

CYCLE 2 (There will be sheets for cycles 3 – 6)

Date:

Any symptoms of PPE between cycles? **YES/NO** (if YES complete table)				
When did it occur?	**Which symptoms?**		**Which part of the body was affected?**	
	Tingling		**Palms of hands**	
	Itching		**Soles of feet**	
	Burning sensation		**Armpits**	
	Redness		**Groin area**	
	Flaking skin		**Mouth**	
	Swelling		**Other parts of the body** (please state)	
	Small blisters			
	Small sores			
	Other (please state)			

Is PPE current present? **YES/NO**

Grade (see below) **1** **2** **3**

Time after treatment to onset:

How does PPE affect daily activities; (please circle)

Not at all **A little** **Moderately** **a lot**

Which activities are affected? (please state)

Grade	Clinical domain	Functional domain
1	Numbness, dysesthesia/paraesthesia, tingling, painless swelling or erythema	Discomfort that does not disrupt normal activities
2	Painful erythema with swelling	Discomfort that affects normal daily activities
3	Moist desquamation, ulceration, blistering, severe pain	Severe discomfort, unable to work or perform normal daily activities

Any other toxicity between cycles or present? (please state type & grade)

PRE TREATMENT BLOOD RESULTS			
Urea		**ALP**	
Creatinine		**Bilirubin**	
Cr clearance		**Albumin**	
Neutrophils		**ALT**	

GCSF support **YES/NO**

Name of GCSF prescribed

TREATMENT DECISION				
FULL DOSE	**DEFERRED** (how long)	**DOSE REDUCTION** (by how much)	**STOPPED**	**CHANGED TO OTHER REGIME**

Comments: (e.g. any change in activities, performance status etc)

APPENDIX 3.4 SYMPTOM RECORD

SYMPTOM RECORD

Trial Id no:

Unit no:

RTD no:

Please bring this record with you to each chemotherapy visit.

Chemotherapy regime;

Frequency of treatment;

Date started treatment;

Please **remember** to contact the chemotherapy suite or oncology wards if you have any of the side effects listed on your yellow chemotherapy card or if you feel unwell in any way.

If you are taking chemotherapy tablets and suffer from any of the side effects, do not take any more tablets until you have contacted the hospital. Contact the hospital straight away, do not delay to see if your symptoms go away.

Contact details of researcher;

Please record any symptoms you have of Hand Foot Syndrome (HFS) or other side effects in this record booklet between each treatment cycle.

BETWEEN TREATMENT NUMBER 1 and 2 (There will be pages for subsequent cycles)

Have you had any symptoms of HFS between treatment cycles? YES/NO

If you answered YES which of these symptoms did you have

	Tick
Numbness	
Tingling	
Painless Swelling	
Redness with no pain	
Redness with pain	
Burning sensation	
Flaking skin	
Small blisters	
Small sores	
Severe pain of hands or feet	
Other (please state)	

Which part of your body was affected?

	Tick
Palms of your hands	
Soles of your feet	
Armpits	
Groin area	
Mouth	
Other parts of the body (please state)	

When did it start?

When did it disappear?

If you had symptoms of Hand Foot Syndrome, how did it affect you day-to-day?

No problems with hands or feet	
Discomfort that does not disrupt normal activities	
Discomfort that affects normal daily activities	
Severe discomfort, unable to work or perform normal daily activities	

Did you have any other side effects between treatment cycles?

SIDE EFFECT	NONE	MILD	MODERATE	SEVERE
Diarrhoea				
Mouth ulcers				
Fever				
Feeling sick				
Being sick				
Other (Please state)				

Did you have to contact the hospital about any side effects? YES/NO

If YES which side effect?

Have you suffered with sun burn?

Any other notes or comments: (e.g. any change in activities that you do using your hands and feet)

APPENDIX 3.5 PATIENT INFORMATION SHEET (Version 3.0)

IDENTIFICATION OF RISK FACTORS FOR PALMAR-PLANTAR ERYTHEMA (PPE)

This research is being carried out by:~

Introduction

You will have attended a consultation with your specialist chemotherapy nurse to discuss the chemotherapy treatment that has been recommended for your type of cancer.

The type of chemotherapy you will receive can, in some patients, cause a condition known as Palmar-Plantar erythema (PPE), also known as 'Hand-foot syndrome'. This is a known side effect of the type of chemotherapy you will receive and usually disappears once the chemotherapy treatment is discontinued. You are invited to take part in a research study.

Before you decide whether to participate in the study it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with your family and friends if you wish. Please ask Annie, or your chemotherapy specialist sister if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part, you will be asked for your decision when you attend for your first chemotherapy treatment.

Some questions you may have about this study:~

1. **What is PPE?**

   PPE is a side effect of some (not all) chemotherapy drugs, and mostly affects your hands and feet but can occur in other areas of the body.

The first sign is usually redness of the affected area, which can then develop into cracks and small blisters followed by peeling of the skin if not picked up at the first signs. It can cause pain and discomfort making it difficult to carry out day to day activities.

The treatment for PPE is to delay the next dose of chemotherapy by a week or two until the PPE has resolved or to reduce the dose of chemotherapy. In severe cases the chemotherapy treatment may need to be stopped.

2. What is the purpose of this study?

You are invited to participate in this study to help find out if there are any particular factors that may make it more likely for people to develop PPE.

3. What is the purpose of this study?

PPE is a side effect of some chemotherapy drugs and can cause pain and discomfort and affect your ability to carry out day to day activities. The treatment for this is to delay the next dose of chemotherapy by a week or two until the PPE has resolved or to reduce the dose of chemotherapy. In severe cases the chemotherapy treatment may need to be stopped.

In order to learn more about this side effect and to identify if there are any particular factors that may make it more likely for people to develop PPE you are invited to participate in this study.

4. Why have I been approached?

All patients commencing chemotherapy that contains 5-Fluorouracil, Capecitabine, Caelyx or Docetaxel will be invited to take part in the study as these are the drugs that commonly cause PPE. During the period of the study 200 patients will be asked to take part in the study.

5. Do I have to take part?

No, the study is entirely voluntary. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

6. What is involved in the study?

When you attend the chemotherapy suite for your first treatment you will be asked a series of questions about yourself and activities involving your hands and feet such as work and hobbies.
Many of these questions would be asked routinely of all people commencing chemotherapy treatment, therefore the additional questions should not extend your visit by more than a few minutes.

You will be asked to keep a record of any symptoms of PPE that you may experience between treatments. If you are unable or prefer not to keep a record to keep a record, you will be telephoned once a week between treatments and be asked about any symptoms of PPE.

Each time you attend the hospital for chemotherapy treatment you will be assessed for any side effects of the treatment (this is carried out with all patients whether participating in the study or not). You will be asked questions specific to PPE by a member of the research team or your chemotherapy specialist sister either during the visit or by telephone following your visit, but this should not extend the length of your visit. Your participation in the study will end once you have had 6 courses of chemotherapy.
If you develop any signs of PPE a photograph will be taken (with your permission) of the affected area (e.g. your hands or feet) to enable the research team to build up a catalogue of pictures to show how PPE

appears and if it varies in different individuals. Some photos may be included in the final report, in articles in medical or nursing journals and presentations at conferences. It will not be possible to identify you from the photo.

7. Will the information obtained in the study be confidential?

The fact that you are helping us with this study will be recorded in your medical notes and all information will be treated with the usual degree of confidentiality under the Data Protection Act. You GP will be notified that you are taking part in this study.

At the time of entering the study you will be allocated a specific study number and it is only this study number which will be recorded on the documents used to collect information. No one will be able to identify you from the study.

Only the researcher, the researcher's supervisor and a statistician will have access to the data

Sensitive data under the terms of the Data Protection Act 1998 on Ethnicity is being collected. You have a choice whether you want to reveal this information. If you choose not to answer this question the other information gathered will still result in a valid set of data.

However, if you disclose any information that indicates someone may be at risk of harm, is against the law, unprofessional behaviour or unsafe practice, this will have to reported to the appropriate authorities.

8. What happens to the information?

The information obtained will be put into a computer to be analysed. The computer will be kept in a secure location and accessible by a

password. All written information obtained will be stored in a locked office at the university or hospital and only the researcher will have access to it. At the end of the study any features that could be used to identify an individual will be removed.

9. Who has reviewed the study?

This study has been reviewed by the De Montfort University and the Leicestershire, Northamptonshire and Rutland Research Ethics Committees.

All research that involves NHS patients or staff, information from NHS medical records or uses NHS premises or facilities must be approved by an NHS Research Ethics Committee before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

10. What if something goes wrong?

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspects of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms would be available to you.

11. What will happen to the results of the study?

The results from this study will be analysed to identify factors that appear to be linked with the development of PPE. These factors will be used to develop an assessment tool with a score given to each factor. This tool will then be tested on a further sample of patients receiving the chemotherapy drugs listed in point 2 to check that it can predict those patients that are most likely to develop PPE.

While data collected, once analysed, may be used in a report of the research being undertaken and published, no information will be made available in the report or publication that identifies individuals directly or indirectly.

The results will be made available following the completion of the study. A summary will be provided and you will be able to receive a copy of this if you wish.

12. Who is organising and funding the study?

The study is organised by the researcher at the hospital and university. The study is funded by the Smith & Nephew Foundation. The Smith & Nephew Foundation funds nurses to carry out research into areas of tissue damage. http://www.snfoundation.org.uk/

13. Where can I get further information?

If you would like any further information about the study please contact

APPENDIX 3.6 CONSENT FORM

Title of project: Identification of risk factors for Palmar-Plantar Erythema (PPE)

Name of researcher: Mrs Annie Law

	Initials
1. I confirm that I have read and understand the information sheet (Version 3.0) for the above study. I have had the opportunity to ask questions and have had these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
3. I give permission for the researcher to look at my medical records to get information relevant to this study. I understand that the information will be kept confidential.	
4. I give permission for my General Practitioner to be informed I am taking part in this study.	
5. I agree to be interviewed by the researcher or specialist chemotherapy sister prior to commencing my chemotherapy treatment and at each treatment visit for 6 cycles, or to be telephoned following the visit, and to keep a record of symptoms for this period. If I am unable or prefer not to maintain a record I agree to a weekly phone call between treatments.	
6. I understand that I will not benefit financially if this research leads to the development of a new treatment or medical test.	
7. I agree to a photograph being taken of any area of skin affected by the chemotherapy which will be used to illustrate the findings of the research. I understand that I have the right to decline to have a photograph taken.	
8. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from regulatory authorities or from the NHS trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	
9. I know how to contact the researcher if I need to and how to get information about the results of the research	
10. I agree to take part in the above study	

Name of Participant		Date
Name of person taking consent (if different from researcher)		Date
Researcher		Date

APPENDIX 3.7 DMU ETHICAL APPROVAL

dmu.ac.uk
DE MONTFORT UNIVERSITY
LEICESTER

13th November 2008

Annie Law
PhD Candidate
School of Nursing & Midwifery
Faculty of Health & Life Sciences

Dear Annie,

Re: Ethics application – Identification of risk factors for Palmar-Plantar Erythema (PPE) (ref: 418)

I am writing regarding your application for ethical approval for a research project titled to the above project. This project has been reviewed in accordance with the Operational Procedures for De Montfort University Faculty of Health and Life Sciences Research Ethics Committee. These procedures are available from the Faculty Research and Commercial Office upon your request.

I am pleased to inform you that ethical approval has been granted by Chair's Action for your application. This will be reported at the next Faculty Research Committee, which is being held on 29th January 2009.

Should there be any amendments to the research methods or persons involved with this project you must notify the Chair of the Faculty Research Ethics Committee immediately in writing. Serious or adverse events related to the conduct of the study need to be reported immediately to your Supervisor and the Chair of this Committee. Also, The Faculty Research Ethics Committee should be notified by e-mail to HLSFRO@dmu.ac.uk when your research project has been completed.

Yours sincerely,

Professor Paul Whiting
Chair
Faculty of Health and Life Sciences
Research Ethics Committee

Faculty of Health and Life Sciences, The Gateway, Leicester LE1 9BH.
Tel: (0116) 255 1551 / **Fax:** (0116) 257 7135

APPENDIX 3.8 NHS ETHICS APPROVAL

Leicestershire, Northamptonshire & Rutland Research Ethics Committee 2
1 Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 0115 8839428
Facsimile: 0115 9123300

16 March 2009

Mrs Annie Law
Practitioner/Lecturer
University Hospitals of Leicester NHS Trust
Cancer Services
Leicester Royal Infirmary
Leics
LE1 5WW

Dear Mrs Law,

Full title of study: **Identification of risk factors for Palmar-Plantar erythema. This research is in 2 phases;1. Identification of risk factors for Palmar-Plantar erythema.2. Develop and validate a PPE risk assessment tool. This application is for phase 1 and further ethical approval will be made for phase 2.**

REC reference number: **09/H0402/12**

Thank you for your letter of 09 March 2009, responding to the Committee's request for further information on the above research, and enclosing the following revised documents:

Document	*Version*	*Date*	
Confirmation of access to medical records		04 March 2009	
Student Annual Review		09 October 2008	
Statement regarding identifiable data		09 March 2009	
Response to Request for Further Information		09 March 2009	
Participant Consent Form	2.0	04 March 2009	
Participant Information Sheet	3.0	04 March 2009	

The further information and revised documentation has been considered on behalf of the Committee by the Chair.

The Committee was satisfied with the responses to:

Points clarified at the meeting:

- The Committee asked whether the participants would understand the abbreviation 'PPE' and asked if a lay explanation could be included in the information sheet. You explained that patients would have been informed about PPE as a possible side effect of the chemotherapy agent at their meeting with the nurse but she would be happy to explain it in the information sheet.
- The Committee noted that the information sheet refers to emotional distress, and asked for further clarification as to the potential risk. You explained that there is very little potential risk from the study but patients are often distressed, especially when they first attend for treatment and it is this distress not specifically because of PPE that they may need further support with.
- The Committee asked why the application states that the participant's GP will be informed but there is no mention of informing their consultant. You explained that the consultants and clinical director have given permission for patients to be contact and so are already aware of the study.
- The Committee asked for further details as to what information will be collected from the medical notes and how eligible patients will be identified. You explained that you will use the note review form submitted. A pharmacist will provide a list of patients who have had the chemotherapy agents in the last year. You will review 100 -200 patients' notes looking for threads. This will be done concurrently with the interviews and the patients interviewed will not be the same people as those whose notes are reviewed. There will be a master list of patient's whose notes have been accessed to prevent duplication.

Requests for changes / further clarification:

1. The Committee require confirmation that you have gained Trust permission to access patient medical notes for the research without taking consent to do so.
2. The master list with identifiable patient data must be securely stored separately to the study data. Confirmation that this will be done in accordance with Trust policy is required.
3. The Committee require a copy of the written feedback from the annual review carried out in October 2008.
4. The Committee request the following changes / amendments to the patient information sheet:
    a. A lay explanation of the abbreviation PPE must be included.
    b. Under 'What is involved in the study?' the use of photographs must be explained.
    c. As discussed under 'What is involved in the study?' the sentence 'If you are unable or unwilling to keep a record, you will be telephone once a week between treatments…' should be reworded. The Committee advise that anyone unwilling to carry out the study requirements should be excluded. It would be more appropriate to offer the option of telephone calls if the patient <u>prefers</u> it to keeping a diary.

5. The Committee request the following changes / amendments to the consent form:
   a. The standard statement allowing audit of the research should be included (amended as appropriate, for example remove 'and company name' if access is not required outside of the NHS)
   I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from [company name], from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
   b. Statement one should be updated to refer to the revised version number and date of the information sheet.

However, the Committee would be grateful for a more complete response on the following points:

- At the meeting the Committee asked how the statistics had been decided. You explained that you have held discussions with a statistician who had advised on the type of tests she will need to do and the number of participants that would be required. The Committee asked if any written feedback had been given. You explained that you had written feedback from the annual review which was carried out in October 2008. The Chair noted the annual review form submitted, but did not think that it answered the statistical elements queried by the Committee. The statistics are mentioned briefly but there did not seem to be any evidence of discussion with the University. Please submit further evidence of statistical review, for example a letter from the Statistician who has advised you.

- The consent form should have a box next to each statement for the participant to initial.
  Please note, that this was not included in the Committee's previous letter and is therefore not a mandatory requirement for approval. However, is being suggested as it is considered best practice.

Any further revised document submitted should be given a revised version number and date
The 60 day clock for issue of a final ethical opinion on this application will re-start when the Committee has received a response on the outstanding points.

09/H0402/12 Please quote this number on all correspondence

Yours sincerely

Miss Jeannie D McKie
Committee Co-ordinator
Email: jeannie.mckie@nottspct.nhs.uk

Copy to:	*Prof Paul Whiting, De Montfort University* *R&D Department for NHS care organisation at lead site - UHL*

National Research Ethics Service
Leicestershire, Northamptonshire & Rutland Research Ethics Committee 2
1 Standard Court
Park Row
Nottingham
NG1 6GN

Telephone: 0115 8839428
Facsimile: 0115 9123300

27 March 2009

Mrs Annie Law
Practitioner/Lecturer
University Hospitals of Leicester NHS Trust
Cancer Services
Leicester Royal Infirmary
Leicester
LE1 5WW

Dear Mrs Law

Full title of study: **Identification of risk factors for Palmar-Plantar erythema**
REC reference number: **09/H0402/12**

Thank you for your letter of 20 March 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA). The favourable opinion for the study applies to all sites involved in the research. There is no requirement for other Local Research Ethics Committees to be informed or SSA to be carried out at each site.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission at NHS sites ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

APPENDIX 3.9 UHL R & D APPROVAL

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & DEVELOPMENT

Director: **Professor D Rowbotham**
Assistant Director: **John Hampton**
R&D Manager: **Carolyn Maloney**

Research & Development Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226

29/05/2009

Mrs Annie Law
University Hospitals of Leicester NHS Trust
Cancer Services & Clinical Haem
Leicester Royal Infirmary
Leicester
Leicester General Hospital
LE1 5WW

Dear Mrs Annie Law

Ref: UHL 10715
Title: Identification of risk factors for Palmar-Plantar Erythema
Project Status: Project Approved
End Date: 31/10/2011

I am pleased to confirm that with effect from the date of this letter, the above study now has Trust Research & Development permission to commence at University Hospitals of Leicester NHS Trust.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

Document Name	Version Number	Date
GP/Consultant information sheets	1.0	08.10.08
Protocol	1.0	08.01.09
CF	3.0	18.03.09
PIS	3.0	04.03.09

Please Note: Annie Law is the only person approved to work on this study; other study staff will be added at a later dated as a non-substantial amendment.

Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.

We are aware that undertaking research in the NHS comes with a range of regulatory responsibilities. Attached to this letter is a reminder of your responsibilities during the course of

APPENDIX 3.10 AMENDMENT TO PROTOCOL

University Hospitals of Leicester NHS
NHS Trust

Mrs Annie Law
Practitioner/Lecturer
Directorate of Cancer Services & Clinical Haematology
Leicester Royal Infirmary
University Hospitals of Leicester NHS Trust
Leicester, LE1 5WW
Tel: 0116 2586178
Email: annie.law@uhl-tr.nhs.uk

Date: 17th February 2010

Re: Amendments to protocol following initial data collection

Committee name: Leicestershire, Northamptonshire & Rutland No 2
Ref no: 09/H0402/12

During the data collection phase and following further discussions with colleagues, a few minor amendments to the protocol are required. The overall aims and objectives of the research have not changed.

1. **Retrospective notes review**
   Following a review of the numbers of patients in one calendar year who received each type of chemotherapy detailed in the sample group, namely, Capecitabine, 5FU, Docetaxel or Caelyx and discussion with colleagues on the incidence of PPE in each group, a decision was made to restrict the notes review to patients who had received Capecitabine or infusional 5FU only. The number of notes reviewed has to be increased to 400 to capture a full calendar years data.

2. **Prospective data collection**
   The sample group for the prospective data will be reduced to include patients receiving Capecitabine monotherapy only.
   The rationale for this change is that from the retrospective data 50% of patients who received this regime developed symptoms of PPE, with approximately 25% at grade 3. In patients receiving Capecitabine in combination with radiotherapy or other cytotoxic agents, and those receiving infusional 5FU the incidence of PPE was less than 10% and mostly only mild in nature.
   Since the principal investigator is the sole data collector, redefining the focus of the sample group would ensure the amount of data being

collected at one time remains manageable within the time frame allocated to the study.

This communication is to keep the ethics committee informed of developments in this study which is progressing as planned with these amendments. It is also to seek agreement of these amendments by the chair of the ethics committee.

Yours faithfully

Annie Law

NHS

National Research Ethics Service

Leicestershire, Northamptonshire & Rutland Research Ethics Committee 2

1 Standard Court
Park Row
Nottingham
NG1 6GN

Tel: 0115 8839428
Fax: 0115 9123300

01 March 2010

Mrs Annie Law
Practitioner/Lecturer
University Hospitals of Leicester NHS Trust
Cancer Services
Leicester Royal Infirmary
Leics
LE1 5WW

Dear Mrs Law

Study title:	**Identification of risk factors for Palmar-Plantar erythema.This research is in 2 phases;1. Identification of risk factors for Palmar-Plantar erythema.2. Develop and validate a PPE risk assessment tool.This application is for phase 1 and further ethical approval will be made for phase 2.**
REC reference:	**09/H0402/12**
Protocol number:	**1.0**
Amendment number:	**1**
Amendment date:	**17 February 2010**

Thank you for your letter of 17 February 2010, notifying the Committee of the above amendment.

The amendment has been considered by the Vice-Chair.

The Committee does not consider this to be a "substantial amendment" as defined in the Standard Operating Procedures for Research Ethics Committees. The amendment does not therefore require an ethical opinion from the Committee and may be implemented immediately, provided that it does not affect the approval for the research given by the R&D office for the relevant NHS care organisation.

Documents received

The documents received were as follows:

Document	Version	Date
Notification of a Minor Amendment	1	17 February 2010

This Research Ethics Committee is an advisory committee to East Midlands Strategic Health Authority.
The National Research Ethics Service (NRES) represents the NRES Directorate within the National Patient Safety Agency and Research Ethics Committees in England

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & DEVELOPMENT

Director: **Professor D Rowbotham**
Assistant Director: **Dr David Hetmanski**
R&D Manager: **Carolyn Maloney**

Research & Development Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

Direct Dial: (0116) 258 8351
Fax No: (0116) 258 4226

01/04/2010

Mrs Annie Law
University Hospitals of Leicester NHS Trust
Room 339, Knighton Street Offices
Leicester Royal Infirmary
Infirmary Square
Leicester
LE1 5WW

Dear Mrs Annie Law

Ref: UHL 10715
Title: Identification of risk factors for Palmar-Plantar Erythema
Project Status: Project Approved
End Date: 31/10/2011

Thank you for submitting documentation for *Non-Substantial Amendment 1 dated 17.02.2010*, for the above study.

I confirm that the amendment has the approval of the University Hospitals of Leicester NHS Trust R&D Department and may be implemented with immediate effect.

The documents received are as follows:

Document Name	Version Number	Date
Notification of Minor Amendment	1	17.02.2010
Ethics Acknowledgement Letter		01.03.2010

Please be aware that any changes to these documents after approval may constitute an amendment. The process of approval for amendments should be followed. Failure to do so may invalidate the approval of the study at this trust.

Please ensure that all documentation and correspondence relating to this amendment are filed appropriately in the relevant site file.

Yours sincerely

Carolyn Maloney
R&D Manager

APPENDIX 4.1 CAPECITABINE DOSE MODIFICATION MANUFACTURERS RECOMMENDATIONS

Toxicity NCI grades	**Dose changes within a treatment cycle**	**Dose adjustment for next cycle/dose** **(% of starting dose)**
• *Grade 1*	Maintain dose level	Maintain dose level
• *Grade 2*		
-1st appearance	Interrupt until resolved to grade 0-1	100%
-2nd appearance		75%
-3rd appearance		50%
-4th appearance	Discontinue treatment permanently	Not applicable
• *Grade 3*		
-1st appearance	Interrupt until resolved to grade 0-1	75%
-2nd appearance		50%
-3rd appearance	Discontinue treatment permanently	Not applicable
• *Grade 4*		
-1st appearance	Discontinue permanently *or* If physician deems it to be in the patient's best interest to continue, interrupt until resolved to grade 0-1	50%
-2nd appearance	Discontinue permanently	Not applicable

NB For hand-foot syndrome grade 4 does not apply.

APPENDIX 4.2 VARIABLES ENTER INTO LOGISTIC REGRESSION MODELS AND REMOVED. DETAILS OF MISSING CASES

Purposeful entry and model reduction retrospective data PPE pre cycle 4 all data		
Variables entered	**Variables remaining**	**Missing cases**
Metastatic spread	CrCl 3gps	PPE after cycle 4 = 27
Regime 3gps	Bilirubin	Bilirubin = 5
CrCl 3gps	Previous radiotherapy	ALP = 5
Bilirubin	Age	CrCl = 3
Previous radiotherapy	Weight loss	
Age		**Total = 40**
ALP		
Performance status		
Weight loss		
Season start		
Notes; gps = groups; CrCl = creatinine clearance; ALP = alkaline phosphatase		

Purposeful entry and model reduction retrospective data PPE pre cycle 4 Capecitabine monotherapy		
Variables entered	**Variables remaining**	**Missing cases**
Gender	Gender	PPE after cycle 4 = 13
Inflammatory conditions	Inflammatory conditions	Bilirubin = 3
Tumour 2gps	Season start	ALP = 3
Season start	ALP	CrCl = 1
CrCl 3gps	Metastatic spread	
ALP		**Total = 20**
Metastatic spread		
Bilirubin		
Albumin		
Notes; gps = groups; CrCl = creatinine clearance; ALP = alkaline phosphatase		

Purposeful entry and model reduction prospective data PPE pre cycle 4		
Variables entered	**Variables remaining**	**Missing cases**
Alcohol	Alcohol	PPE after cycle 4 = 13
Diabetes	Inflammatory conditions	
Inflammatory conditions	Metastatic spread	**Total = 13**
Metastatic spread	Cool hands	
Cool hands	Performance status 3gps	
Performance status 3gps	Age	
Season start	BMI	
Age	CrCl	
BMI		
ALB		
CrCl		
Notes; gps = groups; BMI = Body mass index; ALB = albumin; CrCl = creatinine clearance;		

APPENDIX 5.1 SUMMARY OF CAPECITABINE MONOTHERAPY TRIALS

NB when the trial is a comparison of Capecitabine monotherapy and another agent only the sample who received Capecitabine are reported here.

Authors	Type of study & country	Dose & schedule	N	TS	Age M Range	G	TSC	PPE all grades No (%)	PPE grade 1 No (%)	PPE grade 2 No (%)	PPE grade 3 No (%)	D No (%)	S No (%)	NV No (%)	F No (%)	DR No (%)
Abushullaih et al (2002)	Observational study of data from 2 RCTs Single institution USA	1250mg/m^2 bd for 14 days 7 days rest	41	CRC	63 25-79	M = 30 F = 11	Cap trial grading	28 (68.3)	5 (17.9)	20 (71.4)	3 (10.7)	NR	NR	NR	NR	17 (41.5) 16 for PPE
Bashey et al (2001)	Retrospective report USA	1250mg/m^2 bd for 14 days 7 days rest	10	MBC	47 NR	F = 10	NCI	8 (80)	3 (30)	4 (40)	1 (10)	4 (40)	NR	2 (20)	5 (50)	NR
Barrios et al (2010)	Multicenter, randomized open-label phase III (SUN 1107) 119 centres worldwide	1250mg/m^2 bd for 14 days 7 days rest 1000mg/m^2 in > 65 yrs	240	HER2 neg MBC	53 Mean 25-80	F = 240	NCI	146 (16)	NR	NR	38 (16)	81 (34)	20 (8)	95 (39)	49 (20)	35%
Blum et al (1999)	Multicentre single arm phase II trial 25 centres USA & Canada	1255mg/m^2 bd for 14 days 7 days rest	162	MBC	55.8 Mean (26-78)	F = 162	NCIC	91 (56.2)	23 (14.3)	52 (32.1)	16 (9.9)	88 (54.3)	15 (9.3)	144 (88.9)	59 (36.4)	NR
Blum et al (2001)	Multicentre Single arm Phase II trial 11 centres North America & 1 French centre	1255mg/m^2 bd for 14 days 7 days rest	74	MBC	52.5 Mean (29-77)	F = 74	NCIC	46 (62.2)	NR	NR	16 (21.6)	43 (62.2)	25 (33.8)	41 (55.4)	17 (23.0)	37 (50)

Authors	Type of study & country	Dose & schedule	N	TS	Age M Range	G	TSC	PPE all grades No (%)	PPE grade 1 No (%)	PPE grade 2 No (%)	PPE grade 3 No (%)	D No (%)	S No (%)	NV No (%)	F No (%)	DR No (%)
Brearley et al (2010)	Longitudenal prospective evaluation of data from 1 RCT Single centre USA	1250mg/m^2 bd for 14 days 7 days rest (12.3% had cap in combination regimes)	81	CRC (50) & MBC (31)	61 (26-83)	M = 29 F = 52	NCI	71 (87.7)	NR	NR	19 (27.2)	65 (80.2)	56 (69.1)	68 (84.0)	78 (96.3)	31 (38.3)
Cassidy et al (2002)	Evaluation study of safety from 2 phase III RCTs Multicentre	1250mg/m^2 bd for 14 days 7 days rest	596	CRC	64 23-86	NR	NCI C	319 53.5	NR	NR	54 17.1	284 47.7	145 24.3	226 37.9	126 21.1	278 46.6
Chua et al (2003)	Phase II single arm study China	1250mg/m^2 bd for 14 days 7 days rest	17	MNPC	46 29-71	M = 12 F = 5	NCI	10 58.8	4 23.5	4 23.5	2 12.0	2 12.0	8 47.0	8 47.0	NR	NR
El-Helw & Coleman (2005)	Phase II single arm trial of reduced dose	1000mg/m^2 bd for 14 days 7 days rest	57	MBC	48 Mean 20-73	F = 57	NCI	17 32	NR	NR	1 2.0	11 19.0	5 10.0	12 21.0	NR	11
Feliu et al (2005)	Study to assess the tolerability of Capecitabine in older people	1250mg/m^2 bd for 14 days 7 days rest	51	CRC	76 Mean 71-89	M = 31 F = 20	WHO	25.0	NR	10 20.0 G1&2	2 5.0	17 33.0	7.6 15.0	19 38.0	NR	NR
Fumoleau et al (2004)	Single arm open-label multicentre phase II study France	1250mg/m^2 bd for 14 days 7 days rest	126	MBC	54 30-80	F = 126	NCI C	89 71.0	NR	NR	19 21.0	60 48.0	60 48.0	31 25.0	NR	47 37.0 22 PPE
He et al (2011)	Evaluation study of metronomic chemotherapy in elderly patients China	500mg bd for 28 days 7 days rest	45	AGC	74.5 71-81	M = 33 F = 12	NCI	16 35.5	3 20.0	2 13.3	1 2.2	7 15.5	14 31.2	5 11.1	NR	0
Hennessey et al (2005)	Retrospective analysis USA	3 doses A = 1250mg/m^2 bd B = 1125mg/m^2 bd C = ≤ 1000 mg/m^2 bd	113	MBC	52.5 26-77	M = 1 F + 112	NCI	74	NR	NR	33	43	37	46	28	42 40.0
Hoff et al (2001)	Prospective randomised	1250mg/m^2 bd for	302	CRC	64 23-86	M = 181 F = 121	NCI C	NR	NR	NR	54 18.1	NR	NR	NR	NR	NR

	phase III study 61 centres. 48 USA, 9 Canada, 2 Brazil, 2 Mexico	14 days 7 days rest													
Authors	**Type of study & country**	**Dose & schedule**	**N**	**TS**	**Age M Range**	**G**	**TSC**	**PPE all grades No (%)**	**PPE grade 1 No (%)**	**PPE grade 2 No (%)**	**PPE grade 3 No (%)**	**D No (%)**	**S No (%)**	**NV No (%)**	**F No (%)**	**DR No (%)**
Hoff et al (2004)	Phase II single arm study Single institute USA	1250mg/m^2 bd for 14 days 7 days rest	23	CRC	63 44-75	M = 18 F = 5	NCI C	20 87	NR	NR	3 13	17 74	4 17	7 30	9 39	NR
Hong et al (2004)	Phase II single arm study 4 centres Korea	1250mg/m^2 bd for 14 days 7 days rest	44	MGC	62 25-72	M = 35 F = 9	NCI	30 68.0	4 8.0 (G 1 & 2)	See G1	26 60.0	27.0	NR	27.0	NR	NR
Hyodo et al (2006)	Open-label multicentre phase II trial 11 centres Japan	1250mg/m^2 bd for 14 days 7 days rest	60	CRC	60 34-71	M = 33 F = 27	NCI	44 73.0	NR	NR	6 13.0	22 37.0	22 37.0	22 37.0	NR	32 53.0 PPE 19
Jakob et al (2002)	Open-label phase II study, Single Centre. Germany	1250mg/m^2 bd for 14 days 7 days rest	14	MBC	45.5 35-60	F = 14	NCI C	7 50.0	NR	NR	5 71.4	NR	5 35.7	9 64.3	NR	NR
Jenkins et al (2005)	Single centre phase II trial USA	1000mg/m^2 bd for 14 days 7 days rest	23	Cervix	NR	F = 23	NCI	NR	NR	NR	2	1 G3 only	NR	2 G5 only	7 G3 only	NR
Kaufmann et al (2010)	MONICA prospective non-randomized phase II trial 35 centres Germany	1000mg/m^2 bd for 14 days 7 days rest	161	MBC Her 2 neg	65 37-90	M = 1 F = 160	NCI	60 37.3	NR	NR	12 20.0	33 20.5	23 14.3	48 29.8	55 34.2	NR
Kim et al (2011)	Evaluation study Single centre Korea	1250mg/m^2 bd for 14 days 7 days rest	20	CRC	59 31-83	M = 14 F = 6	NCI	NR	NR	2 10.0	1 5.0	0	2 10.0	NR	NR	NR
Koizumi et al (2003)	Pilot phase II study. 14 centres. Japan	828mg/m^2 bd for 21 days 7 days rest	31	AGC	NR	M = 22 F = 9	NCI C	11 34.4	NR	NR	1 3.1	3 9.4	NR	NR	NR	NR

Authors	Type of study & country	Dose & schedule	N	TS	Age M Range	G	TSC	PPE all grades No (%)	PPE grade 1 No (%)	PPE grade 2 No (%)	PPE grade 3 No (%)	D No (%)	S No (%)	NV No (%)	F No (%)	DR No (%)
Kusama et al (2010)	Multicentre (23) phase II study Japan	828mg/m^2 bd for 21 days 7 days rest	50	MBC	52.5 35-75	F = 50	NCI C	33 66.0	17 51.5	7 21.2	9 27.2	10 20.0	11 22.0	13 26.0	NR	5 10.0 PPE = 4
Lee et al (2004)	Evaluation study. Single centre. Korea	1250mg/m^2 bd for 14 days 7 days rest	51	CRC	57 32-73	M = 31 F = 20	NCI C	18 35.3	NR	NR	3 16.6	8 15.7	10 19.6	9 17.6	NR	NR
Lee et al (2008)	Open- label randomized Multicentre phase II study. Korea	1250mg/m^2 bd for 14 days 7 days rest	46	AGC	71 66-78	M = 30 F = 16	NCI	26 59.1	8	15	3	16 36.4	24 54.5	22 50.0	NR	36.4
Leonard et al 2002	Named patient programme to assess efficacy & safety	1250mg/m^2 bd for 14 days 7 days rest	102	MBC	53 30-95	M = 3 F = 99	NCI	37 36.0	NR	NR	8 8.0	33.0	NR	24.0	NR	33.0
Lin et al (2006b)	Open-label phase II prospective trial. Single centre. Taiwan	1250mg/m^2 bd for 14 days 7 days rest	37	MBC	52 47-84	F = 37	NCI	7 19.0	NR	NR	NR	5 14.0	5 14.0	6 16.0	NR	NR
Lokich (2004)	Retrospective review USA	1000mg/m^2 bd for 14 days 7 days rest	19	CRC AGC GUT MBC	NR	NR	NR	0	0	0	0	0	0	0	NR	NR
Martinez-Trufero et al (2010)	Phase II study 5 centres Spain	1250mg/m^2 bd for 14 days 7 days rest	40	HNC	58.4 Mean 40-75	M = 40	NCI	15 37.5	11 73.3 G 1 & 2	NR	4 26.6	6 15.0	14 35.0	3 7.5	NR	NR
Miller et al (2005)	Randomized phase III trial 96 centres USA	1250mg/m^2 bd for 14 days 7 days rest	230	MBC	52 Mean 30-77	F = 230	NCI	NR	NR	77 35.8	52 24.2	57	11	NR	NR	NR
Morant et al (2004)	Phase II trial Single centre Switzerland	1250mg/m^2 bd for 14 days 7 days rest	25	MPC	70 54-85	M = 25	NCI C	NR	NR	4 16.0	4 16.0	4 16.0	2 8.0	8 32.0	NR	NR

Authors	Type of study & country	Dose & schedule	N	TS	Age M Range	G	TSC	PPE all grades No (%)	PPE grade 1 No (%)	PPE grade 2 No (%)	PPE grade 3 No (%)	D No (%)	S No (%)	NV No (%)	F No (%)	DR No (%)
Muller et al (2010)	Phase I pilot study 10 centres Germany	1000mg/m^2 bd for 14 days 7 days rest or 1250mg/m^2 bd for 14 days 7 days rest	10 26	EBC	49 37-64 55 35-67	F = 10 F = 26	NR	NR 13 50.0	NR 5 38.4	NR 4 30.8	1 4 30.8	NR 5 19.0	NR 14 54.0	NR 21 81.0	NR 16 52.0	NR NR
Muss et al (2009)	Cancer & Leukaemia Group B (CALGB) 49907 trial Single centre USA	1000mg/m^2 bd for 14 days 7 days rest	307	EBC	65-69 (110) 70-79 (183) ≥ 80 (14)	F = 307	NCI	NR	NR	NR	47 16.0	20 7.0 G 3 & 4	3 1.0 G 3 & 4	6 2.0 G 3 & 4	15 5.0 G 3 & 4	NR
Oevemann et al (2000)	Phase II Single centre Germany	1000mg/m^2 bd days 1-5 of weeks 5-8	30	MRC	60 38-73	M = 24 F = 6	WHO	7 23.3	5 71.4	2 28.6	0	17 56.6	11 36.6	15 50.0	14 46.6	NR
Osako et al (2007)	Retrospective review Japanese	828mg/m^2 bd for 21 days 7 days rest	102	MBC	56.1 Mean 29-85	F = 102	NCI	47 46.0	26 55.3	15 32.0	6 12.7	23 23.0	7 7.0	31 30.0	28 27.0	27 26.0
O'Shaughnessy et al (2001)	Randomized open-label phase II trial Multicentre (23) USA	1255mg/m^2 bd for 14 days 7 days rest	62	MBC	69 54-83	F = 62	NCIC	26 43.0	9 34.6	8 30.8	9 34.6	30 48.0	18 29.0	35 56.0	11 18.0	21 34.0
Otterson et al (2004)	Phase II multicentre trial USA	1250mg/m^2 bd for 14 days 7 days rest	27	Meso	70 40-81	M = 19 F = 7	NCI	NR	NR	NR	3 12.0	3 12.0 G3	2 8.0 G3	2 8.0 G3	3 12.0 G3	NR
Pagliaro et al (2006)	Phase II trial Single centre USA	1250mg/m^2 bd for 14 days 7 days rest	15	MRC	59 38-75	M = 13 F = 2	NCI	7 47.0	7 100 G 1 & 2	NR	NR	6 40.0	3 20.0	2 13.0	NR	3 20.0
Park et al (2009)	Retrospective review Single centre Japan	1250mg/m^2 bd for 14 days 7 days rest	38	CRC	Mean 67.9 (M) 71.3 (F)	M = 24 F = 14	WHO	NR	NR	NR	17 44.7	NR	NR	NR	NR	13 34.2

Authors	Type of study & country	Dose & schedule	N	TS	Age M Range	G	TSC	PPE all grades No (%)	PPE grade 1 No (%)	PPE grade 2 No (%)	PPE grade 3 No (%)	D No (%)	S No (%)	NV No (%)	F No (%)	DR No (%)
Patt et al (2004)	Retrospective analysis Single centre USA	1000mg/m^2 bd for 14 days 7 days rest	63	HCC CBT	62 28-85	M = 37 F = 26	NR	23 37.0	NR	NR	NR	11 17.4	6 9.5	12 19.0	9 14.3	1 1.6
Pierga et al (2004)	Retrospective review Multicentre (32) France	1250mg/m^2 bd for 14 days 7 days rest	197	MBC	56 31-88	M = 2 F = 195	NCI	96 54.0	NR	NR	29 16.0	62 36.0	34 19.0	54 31.0	NR	63 32.0
Reichardt et al (2003)	Phase II multicentre study (10) Germany	1250mg/m^2 bd for 14 days 7 days rest	136	MBC	56 32-77	F = 136	NCI C	75 55.0	31 42.0 G1 & 2	NR	9.7 13.0	38 28.0	20 15.0	46 34.0	NR	NR
Rischin et al (2004)	Phase II multicentre (6) trial Australia	1250mg/m^2 bd for 14 days 7 days rest	35	OC	58 26-76	F = 35	NCI	15 43.0	3 20.0	6 40.0	6 40.0	12 35.0	6 18.0	20 58.0	5 14.0	NR
Saif (2005)	Retrospective meta-analysis phase II/III studies	1250mg/m^2 bd for 14 days 7 days rest	603	NR	NR	NR	NR	NR	NR	NR	102 17.0	NR	NR	NR	NR	NR
Santini et al (2006)	Open-label nonrandomized dose escalation Phase 1 study Single centre Italy	1750mg/m^2 - 3000 mg/m^2 ¼ of the dose 0800hrs, ¼ of the dose 1800hrs and ½ dose 2300hrs for 14 days 7 days rest	27	CRC MBC AGC PC Other	68 49-88	M = 9 F = 18	NCI C	13 48.1	3 23.1	7 53.8	3 23.1	13 48.1	10 37.0	11 40.7	20 74.1	NR
Scheithauer et al (2003)	Open-label randomized phase II study Multicentre (164) international	1250mg/m^2 bd for 14 days 7 days rest	993	CRC	62 25-80	M = 536 F = 457	NCI C	616 62.0	NR	NR	179 29.0	457 46.0	218 22.0	357 36.0	228 23.0	417 42.0
Seymour et al (2011)	Open-label, randomized factorial trial (MRC FOCUS2) Multicentre 61 centres in UK	1000mg/m^2 bd for 14 days 7 days rest	115	CRC	73 49-84	M = 68 F = 47	NR	NR	NR	24 21.0 G2 & 3	11 10.0	23 21.0 G2 & above	6 5.0 G2 & above	15 13.0 G2 & above	40 36.0 G2 & above	NR

Authors	Type of study & country	Dose & schedule	N	TS	Age M Range	G	TSC	PPE all grades No (%)	PPE grade 1 No (%)	PPE grade 2 No (%)	PPE grade 3 No (%)	D No (%)	S No (%)	NV No (%)	F No (%)	DR No (%)
Sharma et al (2006)	Phase II of fixed dose Capecitabine 3 centres Australia	1000mg/m^2 bd for 14 days 7 days rest	55	CRC	72 42-86	M = 35 F = 20	NCI	NR	NR	12 22.0 G2 & 3	6 11.0	19 34.0 G2 & 3	8 15.0 G2 & 3	6 11.0 G2 & 3	15 27.0 G2 & 3	16 29.0
Son et al (2009)	Study to determine the incidence and response to treatment of PPE Single centre Korea	1250mg/m^2 bd for 14 days 7 days rest	84	CRC	62 29-78	M = 51 F = 33	NR	65 77.4	33 50.7	22 33.8	10 15.5	8 9.5	7 8.3	29 34.5	NR	NR
Spicer et al (2005)	Phase II study Single centre UK	1250mg/m^2 bd for 14 days 7 days rest	14	MPC	68 Mean 41-82	M = 14	WHO	NR	NR	7 50.0 G1 & 2	1 7.0	4 29.0	7 50.0	7 50.0	NR	NR
Sun et al (2009)	Retrospective study Single centre USA	1000mg/m^2 bd for 14 days 7 days rest	28	CRC PC CBT AGC	59 Mean 38-81	M = 14 F = 14	NCI	20 71.0	NR	19 67.8 G1 & 2	1 3.6	6 21.0	2 7.0	1 4.0	16 57.0	11 28.0 8 PPE
Talbot et al (2002)	Phase II open-label randomised trial Multicentre international	1255mg/m^2 bd for 14 days 7 days rest	22	MBC	52 33-67	F = 22	NCIC	4 18.0	NR	NR	2 50.0	9 41.0	5 23.0	10 46.0	6 27.0	5 2 PPE
Twelves et al (2005)	Randomised trial Multicentre international	1250mg/m^2 bd for 14 days 7 days rest	995	CRC	62 25-80	M = 537 F = 458	NCIC	597 60.0	NR	NR	169 17.0	458 46.0	219 22.0	358 36.0	229 23.0	418 42.0

Authors	Type of study & country	Dose & schedule	N	TS	Age M Range	G	TSC	PPE all grades No (%)	PPE grade 1 No (%)	PPE grade 2 No (%)	PPE grade 3 No (%)	D No (%)	S No (%)	NV No (%)	F No (%)	DR No (%)
Van Cutsem et al (2000)	Randomized Phase II open-label multicentre trial International (21 centres)	3 treatment groups A – 1331mg/m^2/day continuously B - 2510mg/m^2/day for 14 days, 7 days rest C – 1657 mg/m^2/day for 14 days, 7 days rest + leucovorin 60mg	A 39 B 34 C 35	CRC	A 62 44-83 B 64 36-82 C 65 41-78	A M = 26 F = 13 B M = 24 F = 10 C M = 22 F = 13	NCI C	NR	39 36.0	45 41.6	48 44.4	G1 51 47.2 G2 47 43.5 G3 31 28.7	G1 23 21.3 G2 6 5.5 G3 6 5.5	G1 83 76.8 G2 53 49.1 G3 12 11.1	G1 41 37.9 G2 24 22.2 G3 3 2.7	NR
Van Cutsem et al (2001)	Randomized Phase III open-label multicentre trial International (59 centres)	1250mg/m^2 bd for 14 days 7 days rest	297	CRC	64 29-84	M = 169 F = 128	NCI C	144 48.5	NR	NR	48 33.3	149 50.2	65 21.9	167 56.2	NR	81 27.3
Van Cutsem et al (2004)	Integrated data from two large randomised phase III multicentre trials	1250mg/m^2 bd for 14 days 7 days rest	603	CRC	64 23-86	M = 362 F = 241	NCI C	323 53.5	NR	NR	NR	288 47.7	146 24.3	228 37.9	NR	NR
Vasey et al (2003)	Phase II open-label trial single centre (UK)	1250mg/m^2 bd for 14 days 7 days rest	29	OC	57 38-78	F = 29	NCI	18 62.0	NR	NR	4 22.0	17 59.0	9 31.0	17 59.0	12 41.0	7 24.1
Venturini et al (2007)	Open-label multicentre study 14 countries	1250mg/m^2 bd for 14 days 7 days rest	631	MBC	54 47-91	F = 631	NCI C	219 34.7	67 30.6	104 47.5	48 21.9	188 29.8	52 8.2	169 26.8	57 9.0	172 27.3 PPE 13.6
Wenzel et al (2002)	Prospective study single centre Austria	1250mg/m^2 bd for 14 days 7 days rest	26	RCC	58 47-76	M = 19 F = 7	WH O	NR	5 19.2	4 15.4	2 7.7	1 3.6	3 11.5	8 30.8	NR	NR
Wist et al (2004)	Open-label non-randomized compassionate study	1250mg/m^2 bd for 14 days 7 days rest	48	MBC	55 35-74	F = 48	NCI C	NR	NR	NR	17 35.0 G2&3	11 23.0	NR	NR	NR	29.0

Authors	Type of study & country	Dose & schedule	N	TS	Age M Range	G	TSC	PPE all grades No (%)	PPE grade 1 No (%)	PPE grade 2 No (%)	PPE grade 3 No (%)	D No (%)	S No (%)	NV No (%)	F No (%)	DR No (%)
Wolf et al (2006)	Single arm nonrandomized phase II trial Multicentre USA	1000mg/m^2 bd for 14 days 7 days rest	41	OC FTC PerC	56 27-77	F = 41	NCI	NR	NR	NR	11 27.0	4 10.0	NR	NR	19 46.0 G3	17 41.5 Most PPE
Yun et al (2010)	Evaluation study of outcome after cessation or dose reduction single centre Korea	1250mg/m^2 bd for 14 days 7 days rest	173	CRC	A <65 96 ≥65 42 B <65 18 ≥65 17 C <65 105 ≥65 50	A M = 92 F = 46 B M = 22 F = 13 C M = 105 F = 50	NCI C	114 65.9	NR	84 48.5 G!&2	18 10.4	161 93.1	162 93.6	149 86.1	172 99.4	42

Notes;
TS = tumour site, AGC – Advanced Gastric Cancer, CBT – Cancer of the biliary tree CRC – Colorectal Cancer, EBC – Early Breast Cancer, FTC – Fallopian tube Cancer, GUT – Genitourinary tumours, HCC – Hepatocellular Cancer, HNC – Head & Neck cancer, MBC – Metastatic Breast Cancer, Meso – Mesothelioma, MGC – Metastatic gastric cancer, MNPC – Metastatic Nasopharyngeal Cancer, MPC – Metastatic Prostate Cancer, MRC – Metastatic Renal Cancer, OC – Ovarian Cancer, PC – Pancreatic cancer, PerC – Peritoneal Cancer, RCC – Renal Cell Carcinoma
Age M = age median
G = gender
TSC = Toxicity scoring system, NCI – National Cancer Institute common toxicity criteria for adverse events, NCIC – National Cancer Institute of Canada common toxicity criteria for adverse events
D = Diarrhoea
S = Stomatitis
NV = Nausea and/or vomiting
F = Fatigue
DR = Dose reduction due to adverse events
NR = not reported