Selective Primary Systemic Treatment for Operable Breast Cancer

A Randomised Trial

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1996

ABSTRACT

Surgical excision has been the method of choice for initial treatment of operable breast cancer, but is limited in its potential to produce cure. Postoperative systemic therapy prolongs survival, but kinetics theory and experimental data suggest it may be more effective if given preoperatively, with the added advantage of leaving the tumour as a marker of treatment progress. Important questions regarding the efficacy of primary systemic treatment (PST), its effects on known prognostic indicators, and its influence on surgical and psychological morbidity remain to be answered. These were addressed in this thesis.

171 women aged 27-69 with operable ($T_{2-3}N_{0-1}M_0$) breast cancers 31-85 mm in diameter were randomised over 68 months, 86 to conventional treatment (CONV) and 85 to PST. In CONV, surgery was followed by tamoxifen, except for node-positive premenopausal women who received 6 cycles of cyclophosphamide, methotrexate and 5-fluorouracil. PST was started after tumour oestrogen receptor (ER) measurement. Patients with ER>19 *f*mol/mg were treated by goserelin if premenopausal or with tamoxifen if postmenopausal. Response was assessed by weekly examination. Sequential mammography and ultrasound, and serum CA 15-3 and $HMFG_2$ measurements were studied as alternative means of monitoring response. Non responding patients and all patients with ER<20 *f*mol/mg were treated with 6 cycles of cyclophosphamide, doxorubicin and prednisolone (CAP). Surgery followed 12-16 weeks of PST. The first part of the trial included 79 patients with tumours >40 mm, all of whom underwent mastectomy. The second part allowed tumours >30 mm, and breast conservation was an option.

The first 79 patients were studied for morbidity. All toxicity was recorded. Psychological morbidity was assessed by means of the Hospital Anxiety and Depression, and the Mental Adjustment to Cancer questionnaires, completed before, during and after treatment. Surgical morbidity was recorded prospectively according to a pre-defined protocol.

170 evaluable patients have been followed up for a median of 37 months and have sustained 53 events. No survival difference has emerged. Axillary lymph nodes, ER and tumour response have emerged as independent indicators of prognosis. Systemic therapy produced significant changes in tumour characteristics but post treatment prognostic data was qualitatively similar to conventionally gathered information.

Patients experienced increased anxiety during PST, but psychological adjustment was similar after completion of all treatment. Despite longer treatment for PST, quality adjusted survival was identical to that found for CONV. Surgical morbidity was similar for both groups.

Ultrasound proved a highly effective method for measuring tumour size and response to primary systemic therapy. Tumour marker levels were generally low and did not reflect response.

The present package of primary systemic treatment is a safe and effective method for treating operable breast cancer, does not lead to excess morbidity, and offers the advantages of a response based approach to therapy.

ACKNOWLEDGEMENTS

This work was supported by a grant from the Scottish Hospital Endowments Research Trust, with additional funds from the Sarah Percy Fund and the Hartwell Foundation. The work was carried out at the University Department of Clinical Surgery, The Royal Infirmary, Edinburgh and at the Edinburgh Breast Unit, Western General Hospital, Edinburgh. The Co-operation of the patients, nursing, administrative and ancillary staff is gratefully acknowledged.

I am greatly indebted to my supervisor, Mr. U. Chetty, Clinical Director, Edinburgh Breast Unit, for giving me the opportunity to carry out this work, for supporting me throughout the work, for teaching me many of the surgical techniques used in this study, for reading and commenting on this manuscript, and for his unreserved help, advice and time whenever needed.

I would like to thank the head of the University Department of Clinical Surgery, Professor D. C. Carter, for his continuing interest in the work. Thanks are also due to Mr. J. M. Dixon, Edinburgh Breast Unit, for much stimulating discussion and many fresh ideas, particularly in relation to the study of surgical morbidity. Professor W. R. Miller, University Department of Clinical Oncology, also gave me many ideas and helpful advice for which I owe him appreciation.

The oncological treatment of patients took place under the care of Dr. R. C. F. Leonard, University Department of Clinical Oncology. I am indebted to him for helping me understand the concepts underlying primary systemic treatment, for advice on assessment of treatment toxicity, for advice regarding the study of tumour markers, and for reviewing the introductory chapters of this thesis.

Dr. T. J. Anderson, University Department of Pathology, was in overall charge of pathological reporting for the study. I am particularly grateful to him for facilitating the detailed examination of tumour specimens in accordance with the protocol of the size study. Oestrogen receptor measurements were performed under the direction of Dr. R. A. Hawkins, Lister Research Laboratories, The Royal Infirmary, Edinburgh. I am grateful to Dr. Hawkins for help and ideas regarding the interpretation of oestrogen receptor results. Dr. J. S. Walsh, Consultant Radiologist, Edinburgh Breast Unit, taught me the techniques for tumour size measurement by ultrasound, and helped greatly with the size study. Advice regarding the study of psychological morbidity and choice of questionnaires was given by Dr. G. Masterton, Consultant Psychiatrist, The Royal Edinburgh Hospital. Dr. J. E. Roulston, Consultant in Clinical Chemistry, provided the facilities for tumour marker assays, and Dr. J. Fisken gave me practical help in carrying out the assays. Dr. J. E. Prescott, University Department of Medical Statistics provided statistical advice.

The trial administration took place at the Scottish Cancer Trials Office, and I am specially grateful to Dr. Helen Stewart for help and advice regarding the collection and analysis of the data.

Above all I wish to express my deepest gratitude to my wife, Nita, whose patients, encouragement, and unwavering support made the completion of this thesis possible.

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Abbreviation	Full term
χ^2	Chi squared
A.P.	Anxious preoccupation
ANX.	Anxiety
AVO.	Avoidance
BMI	Body Mass Index
C.I. /CI	Confidence Interval
CAF	Cyclophosphamide, Adriamycin, 5-Fluorouracil
CAP	Cyclophosphamide, Adriamycin, Prednisolone
CHEMO	Cytotoxic chemotherapy
CHOP	Cyclophosphamide, Adriamycin, Vincristine, Prednisolone
CMF	Cyclophosphamide, Methotrexate, 5-Fluorouracil
Conv	Conventional treatment
DEP.	Depression
Diam	Diameter
DNA	Deoxyribonucleic Acid
EORTC	European Organisation for Research and Treatment of Cancer
e/ exp.	exponential
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ECAP	Failed Endocrine therapy followed by Cyclophosphamide, Adriamycin, Prednisolone
ENDO	Endocrine therapy
ER	Oestrogen receptor levels
EREIA	Oestrogen Receptor Enzyme Immuno-Assay
ERICA	Oestrogen Receptor Immuno -Cytochemical Assay
EVM-MTV	Epirubicin, Vincristine, Methotrexate: 3 cycles followed by Mitomycin, Thiotepa and Vindesine 3 cycles
Exact	Fisher's Exact Test
F.S.	Fighting Spirit
FAC	Same as CAF

Abbreviation	Full term
FAT.	Fatalism
FEC	5-Fluorouracil, Epirubicin and Cyclophosphamide
FSH.	Follicle Stimulating Hormone
GCAP	Failed Goserelin, followed by Cyclophosphamide, Adriamycin, Prednisolone
GI	Gastrointestinal
GOS	Goserelin (Zoladex)
H.H.	Hopelessness / Helplessness
H.R.	Hazard Ratio
HAD scale	Hospital Anxiety and Depression Scale
HMFG	Human Milk Fat Globules
ICRF	Imperial Cancer Research Fund
LD flap	Latissimus Dorsi Myocutaneous Flap
LH	Luteinizing Hormone
LHRH	Luteinizing Hormone Releasing Hormone
Ln	Natural Logarithm
Log	Base 10 logarithm
MAC scale	Mental Adjustment to Cancer Scale
MAN	Manual occupational social Class
N/EVCF	Mitoxantrone or Epirubicin, Vindesin, Cyclophosphamide and 5-Fluorouracil
NON MAN	Non-manual occupational social class
NSABP	National Surgical Adjuvant Breast and Bowel Project
p	The probability of a result having occurred by chance
PEM	Polymorphic Epithelial Mucin
Post op	Post operative
Pre op	Pre operative
PPV	Positive Predictive Value
PST	Primary Systemic Treatment
Q-TWiST	Quality adjusted Time Without Symptoms of recurrence or Toxicity of treatment
ρ	Spearman's correlation coefficient

Abbreviation	Full term
R^2	Adjusted square of the correlation coefficient for multiple correlation
r^2	Square of the correlation coefficient
recon	Breast reconstruction
Resp	Response
RT/ XRT	Radiotherapy
Rx	Treatment
S.D.	Standard Deviation
SE/SEM	Standard Error of the Mean
ST	systemic Therapy
Stat	The statistic for test
Surv	Survival
TAM	Tamoxifen
TCAP	Failed Tamoxifen followed by Cyclophosphamide, Adriamycin, Prednisolone
TNM	The Tumour, Node, Metastases system of staging cancer
TWiST	Time Without Symptoms of recurrence or Toxicity of treatment
U (Units)	(in relation to oestrogen receptors): | mol/mg cytosol protein
U (Units)	(In relation to CA 15-3 and $HMFG_2$): Arbitrary units
UICC	International Union Against Cancer
VTMF±A	Vinblastine, Thiotepa, Methotrexate and 5-Fluorouracil ± Adriamycin
WHO	World Health Organisation

THE OVERALL PLAN OF THE THESIS

The treatment of breast cancer remains a complex and rapidly evolving area of medicine. Developments in molecular biology and pharmacology promise to open new avenues of treatment for future investigation, but much remains to be done with drugs and techniques already available.

Selective primary systemic therapy is an attempt to optimise the way in which existing treatments are administered. Previous experience with this treatment has been greatly encouraging, but questions regarding efficacy, morbidity and the optimum method of administration remain to be answered. This thesis aims to explore answers to some of these questions.

This thesis is arranged in three parts. The rationale, and the theoretical background to the use of primary systemic treatment are described in the first part (chapters 1 & 2). In the second part (chapters 3-8) the protocol and results of a randomised clinical trial addressing the questions of efficacy and morbidity are described and discussed. An important objection to primary systemic treatment - loss of prognostic indicators - is addressed through analyses specific to the primary systemic treatment group of patients. The question of the optimisation of tumour monitoring during primary systemic therapy is addressed in the final part (chapters 9-11).

The rationale

The use of systemic therapy as the initial treatment for breast cancer represents a significant departure from the norms of breast cancer treatment.

The first chapter describes the theoretical principles which support the use of systemic therapy as initial treatment in breast cancer. The second chapter describes the clinical applications of primary systemic therapy and summarises the results reported by others in relation to its use.

Plan of the trial

The results from a sequential series of patients treated by selective primary systemic therapy hinted at substantial potential benefits. Its actual efficacy can only be established by testing the new treatment against conventional therapy in a randomised trial.

A new mode of therapy, particularly if it proves to be of marginal survival benefit, cannot be evaluated simply on the basis of its effects on survival. The true value of a treatment must be decided by weighing potential benefits against the relative costs of treatment in terms of the patient's quality of life and other associated morbidity.

Randomised studies

The study uses a randomised design to ask four questions about primary systemic treatment. This part of the thesis spans over chapters 3 to 8, and is the largest part of the thesis.

Is primary systemic treatment better at treating cancer?

The protocol for a randomised trial of selective primary systemic treatment versus conventional treatment is described in chapter 3. Treatment outcomes are compared in chapter 4, and the value of prognostic indicators with particular reference to the effects of primary systemic therapy are described in chapter 5. Results are summarised and discussed in chapter 6.

Is quality of life adversely affected?

The psychological well-being of patients in the two arms of the trial is compared in chapter 7. Results are presented. The survival results are re analysed, taking into consideration quality of life issues.

Does primary systemic therapy affect surgical outcome?

In chapter 8 the patients in the main trial are studied to assess whether primary systemic treatment increases surgical complication rates following mastectomy. Results are presented and discussed.

Optimising the method

Even if primary systemic treatment proves to be no better than conventional therapy, provided that it is no worse, the practical advantages it offers particularly in terms of allowing response assessment may still make it the treatment of choice in certain patients. It is therefore important that tumour response could be measured accurately.

In the chapters 9-11, the use of ultrasound and serological tumour markers as methods of improving the efficacy of tumour monitoring during primary systemic treatment are investigated and ways of optimising the monitoring regime are explored.

Concluding remarks

The main findings of the thesis are summarised, and whole thesis issues are discussed in the final chapter. This chapter also includes suggestions for the future research.

PART I

BACKGROUND

CHAPTER 1

1. Treatment of Breast Cancer and Failure of Treatment

1.1 THE IMPACT OF BREAST CANCER

1.1.1 Breast cancer incidence

In 1993, breast cancer resulted in the deaths of 1280 Scottish women. This represents 5% of all female deaths and 26% of female cancer related deaths in Scotland (Registrar General for Scotland: 1994). The incidence of breast cancer in Scotland rose by 18% between 1982 and 1991, giving Scottish women a 7.3% life time risk of developing breast cancer (Scottish health statistics: 1993), Figure 1-1]. The age adjusted breast cancer mortality rate of 47.4 per 100,000 of the female Scottish population is amongst the highest in the world, being surpassed only by the rate in the rest of the British Isles (Boring *et al:* 1994).

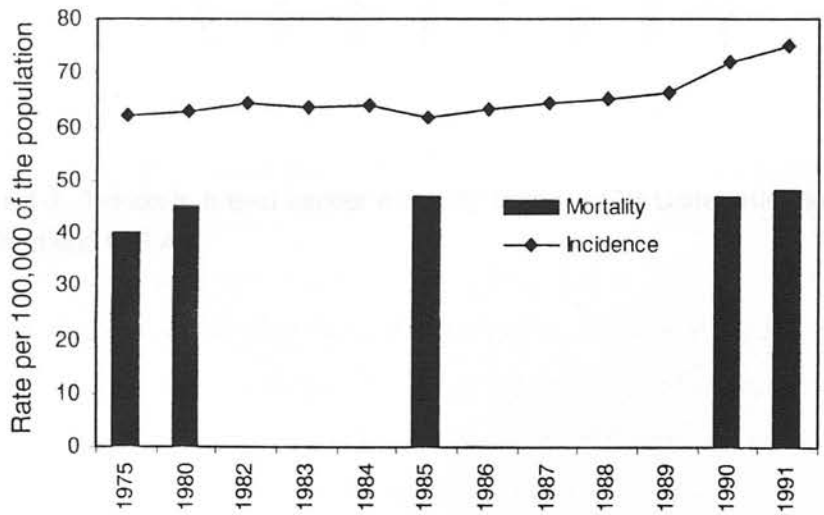

Figure 1-1: Changes in incidence and mortality from breast cancer in Scotland between 1975 and 1991

1.1.2 Breast cancer mortality

Despite increasingly radical operations and the more recent use of systemic therapy, there has been little change in breast cancer mortality over the past 40 years, with crude mortality remaining at around 40-50 per 100,000 of total population per year. [Figure 1-2 (W.H.O. 1994)].

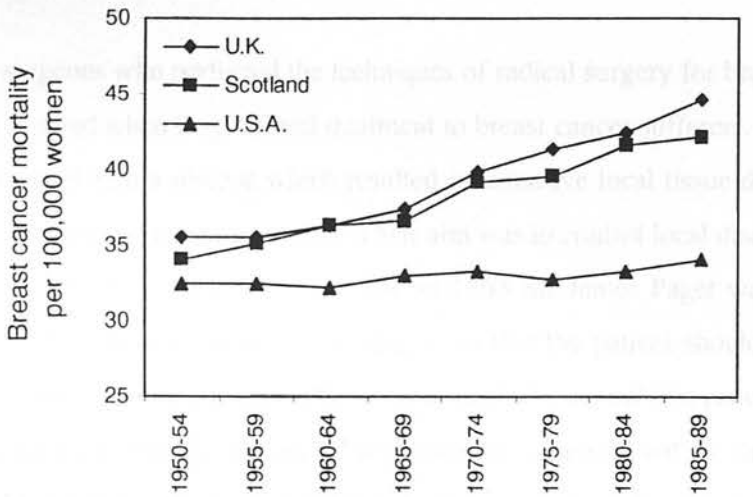

Figure 1-2: Trends in breast cancer mortality (all ages) for United Kingdom, Scotland and U.S.A.

1.2 LOCOREGIONAL TREATMENT OF BREAST CANCER

Surgery has an important place in the treatment of breast cancer, and other treatment modalities such as radiotherapy and systemic therapy have traditionally been regarded as aids to the main treatment. The role of locoregional treatment of breast cancer in achieving a cure will be explored in this section.

1.2.1 The evolution of surgery for breast cancer

The pioneering surgeons who perfected the techniques of radical surgery for breast cancer had very clear aims in mind when they offered treatment to breast cancer sufferers. Surgeons such as Halsted were faced with a disease which resulted in extensive local tissue destruction, and eventually killed the patient from metastases. Their aim was to control local disease in order to palliate the symptoms of their patients. As early as 1863 Sir James Paget wrote: "I am not aware of a single clear instance of recovery, that is, as that the patient should live for more than 10 years free from the disease. In deciding for or against removal of a cancerous breast in any single case, we may, I think, dismiss all hope that the operation will be the final remedy for the disease." [quoted in (Haagensen: 1971)]. Surgery was the only technique available to the early cancer clinicians. By adapting the principles of lymphatic spread expounded by his contemporaries such as Sir William Banks (Banks: 1887), William Halsted of Baltimore had already been able to develop the surgical techniques such that local recurrence rates fell from the 60-80% reported by the surgical authorities of his time such as Volkmann and Billroth, to a mere 6% (Halsted: 1894). But even Halsted was under no illusions about the potential for cure which his operation of radical mastectomy offered the patient: "unfortunately the tumour must first be recognised by the patient, and a scirrhous cancer large enough to attract her attention has quite surely already gone afield" (Halsted: 1907).

There were only two avenues open to Halsted and his contemporaries in search of an improvement in cure rates. One was earlier surgery and the other, more radical surgery (Halsted: 1913; Halsted: 1907). The first was out of the hands of the surgeon. The second dominated the treatment of breast cancer for the first seven decades of the twentieth century. Local eradication to prevent local progression and stop the formation of metastases was

regarded as the most important aspect of treatment, and expediency of surgical removal was emphasised.

The increasing use of systemic therapy in the latter half of the century has provided an alternative approach to breast cancer treatment. Nevertheless, systemic treatment has largely been seen as an aid to surgery which is still regarded as the main treatment, hence the term "adjuvant".

1.2.2 Curability by locoregional therapy alone

Halsted stressed the importance of accurate staging and the systematic collection of data; however a direct comparison between untreated and locoregionally treated groups of patients is unethical. The contribution of locoregional treatment to survival can therefore only be extrapolated from indirect studies.

The impact of locoregional therapy on survival may be assessed in four principal ways as follows:

1. The course of untreated breast cancer

2. The long term follow-up of patients treated by locoregional therapy only

3. The results of less radical locoregional measures

4. The results of earlier detection and treatment by screening

1.2.2.1 Untreated breast cancer

Survival from untreated breast cancer has been studied using retrospective analysis of data on patients presenting before surgery was widely available. These series estimate survival from the time the tumour had been first noticed by the patient (Bloom *et al:* 1962; Wade: 1946; Daland: 1927; Greenwood: 1926; Wyard: 1925; Lazarus-Barlow and Leeming: 1924). The median survival without treatment has been estimated at 2.3-2.7 years, but survival can range from a few months to over 15 years (Bloom *et al:* 1962). In the studies by Daland and Wade,

the survival curves for untreated patients are plotted alongside those of the patients treated by radical mastectomy, calculated from the time of diagnosis. The curves are parallel, although separated in favour of the treated group, suggesting that surgery acts as a debulking procedure without provoking a biological cure (Wade: 1946; Daland: 1927).

1.2.2.2 Survival following locoregional treatment

By the middle part of this century, long term follow-up data on women treated for breast cancer were becoming available. Initial studies of large number of breast cancer sufferers suggested that despite extensive local measures, the majority of patients eventually died of metastatic disease (Brinkley and Haybittle: 1968), an observation which was confirmed as the total duration of follow-up became longer (Brinkley and Haybittle: 1984; Brinkley and Haybittle: 1975).

It is now clear that even 35 years following locoregional therapy, women who have survived breast cancer will have an age adjusted all cause mortality risk which is between 1.5 to 2.5 times, and a risk of death from breast cancer which is 15 to 25 times greater than that expected for the general population (Haybittle: 1991).

Data such as these provide strong evidence that locoregional therapy alone is not enough to provide a biological cure for breast cancer.

The ratio of the number of deaths from breast cancer to the number of cases registered four years earlier is about 0.65 (Haybittle: 1991). This suggests that as many as 1/3 of all patients treated by local measures will not experience any recurrence from breast cancer within their life time (Haybittle: 1991). Even if this group have subclinical breast cancer at the time of death from another cause, they must be considered as having achieved a personal "cure".

1.2.2.3 The extent of local therapy

1.2.2.3.1 Extended radical mastectomy

Extended radical mastectomy, to include removal of the internal nodes was devised because of dissatisfaction with the results of Halsted's operation (Valagussa *et al:* 1978; Haagensen and

Stout: 1942). A large randomised clinical trial has clearly shown that more radical surgery does not result in longer disease free or overall survival (Lacour *et al:* 1983).

1.2.2.3.2 Modified radical mastectomy

The removal of the pectoralis major is a highly mutilating component of Halsted's operation, resulting in marked cosmetic deformity and significant impairment of arm function (Budd *et al:* 1978; Pollard *et al:* 1976). The observation by Gray that the deep fascia is poor in lymphatics led Patey to argue that the removal of the pectoralis major was not necessary for adequate local clearance of the tumour (Patey and Dyson: 1948). Handley reviewed the outcome of over 200 Patey's modified radical mastectomies and demonstrated that the results were no different to those achieved in historical controls following Halsted's operation (Langlands *et al:* 1980; Handley: 1964). Patey's operation has the advantage of having significantly less associated morbidity compared with the radical mastectomy (Feigenberg *et al:* 1977).

The efficacy of modified radical mastectomy has been clearly demonstrated in controlled series (Baker *et al:* 1979) and in two randomised clinical trials which have shown identical disease free and overall survival rates for the two operations (Maddox *et al:* 1987; Turner *et al:* 1981).

1.2.2.3.3 Breast conservation

Removal of the tumour, without removal of the breast, followed by radiotherapy to treat remaining breast and axillary disease has been tested in a number of large clinical trials. This much less radical approach results in a greater proportion of local recurrences but the disease free and overall survival times for the patients remain unaffected (Veronesi *et al:* 1981; Fisher *et al:* 1989; Stewart *et al:* 1989; Osteen and Smith: 1990).

1.2.2.3.4 The effects of incomplete local treatment

1.2.2.3.4.1 Inadequate radiotherapy

Mastectomy, without axillary dissection can potentially leave tumour tissue in the axilla.

Two trials of simple mastectomy and radiotherapy versus radical mastectomy have found superior survival results for the radical mastectomy group, particularly in groups of patients with early stage tumours (Berstock *et al:* 1985; Hayward and Caleffi: 1987; Langlands *et al:* 1980). The dose of radiotherapy used in these trials is considered inadequate by today's standards. When the axilla is adequately treated by radiotherapy or by surgical clearance on recurrence, the distant disease free and overall survival rates are the same as those expected for radical mastectomy (Cuzick *et al:* 1987; Fisher and Wolmark: 1985).

In another trial of 960 patients undergoing modified radical mastectomy with or without radiotherapy, the risk of developing distant metastases was smaller in node-positive patients who had received radiotherapy. On multivariate analysis the increased risk of distant metastases appeared to be completely explained by the 5 fold increase in the risk of local recurrence experienced by the no-radiotherapy group. The model therefore indicated that local recurrence does increase the risk of distant metastases (Arriagada *et al:* 1995).

Overall, early adequate axillary treatment, and in particular adequate radiotherapy (Levitt: 1994), may prevent future relapse in 5-10% of patients (Harris and Osteen: 1985).

1.2.2.3.4.2 Breast conservation trials

Following treatment for breast conservation, patients who developed local recurrence appeared to be at significantly increased risk of systemic relapse (Fisher *et al:* 1991). Other breast conservation trials however, despite showing a much greater incidence of local recurrence in non-irradiated breasts, have failed to show a disadvantage in terms of distant disease free or overall survival (Osborne *et al:* 1992; Abner *et al:* 1993; Kurtz *et al:* 1988). The number of patients are however relatively small, and many received systemic therapy following local recurrence which may have altered the course of systemic disease.

1.2.2.3.5 The benefits of screening

In the trials of more versus less radical surgery it is often the subgroups of patients with the earliest stages of the disease who derive maximum benefit from the more radical operations (Osborne and Borgen: 1990; Hayward and Caleffi: 1987; Langlands *et al:* 1980).

Early detection and surgical ablation of cancer may potentially eliminate all malignant cells before they have acquired metastatic potential. Detection methods are more likely to diagnose indolent tumours (length bias) and apparent improvements in results following early detection may simply reflect the time it would have taken a tumour to become clinically apparent (lead time bias). These problems have been addressed in the seven randomised trials of population screening for breast cancer (Buzdar: 1990; Frisell *et al:* 1991; Miller *et al:* 1992; Miller *et al:* 1992; Nystrom *et al:* 1993; Shapiro: 1994; Andersson *et al:* 1988; Tabar *et al:* 1992; Roberts *et al:* 1990). Taken together, these trials have clearly shown that early detection of breast cancer using mammographic screening can result in a reduction in the odds of breast cancer mortality of the order of 25-40% at 12 years of follow-up (Shapiro: 1994). The majority of tumours detected in these programmes were treated by locoregional measures alone, and these screening trials provide the strongest body of evidence in support of the notion that timely and adequate locoregional therapy can alter the natural history of breast cancer (Tabar *et al:* 1992a).

1.2.3 The place of locoregional therapy

1.2.3.1 Locoregional control

The main aim of local treatment should be adequate locoregional control. Modified radical mastectomy can be regarded as the standard against which other treatments must be compared. Many tumours may be treated by modern breast conservation techniques with acceptable results.

1.2.3.2 Systemic control

Locoregional therapy is most likely to achieve total cancer control in the earliest stages of the disease. Inadequate eradication of cancer cells in the breast and the axilla has a detrimental effect not only on locoregional outcome, but also on survival. Ever more radical locoregional measures however do not produce improved survival.

1.3 THE ROLE OF SYSTEMIC THERAPY

Most clinically palpable breast cancers will not be cured by locoregional treatment alone. The role of systemic therapy in the treatment of breast cancer will be considered in this section.

1.3.1 The evolution of systemic treatment

1.3.1.1 Systemic treatment for systemic disease

It is intuitive to use systemic treatment to treat widespread cancer. Beaston's use of ovarian ablation to produce remission in a patient with disseminated breast cancer is one of the earliest attempts at the systemic treatment of breast cancer (Beaston: 1896). Various forms of surgical and medical hormonal manipulations have been used in the treatment of metastatic breast cancer, and can induce remission in more than a third of unselected cases, and in up to half of the patients with oestrogen receptor positive disease (Buzdar: 1990).

The majority of patients however do not respond to endocrine manipulation, and many of those who initially respond would eventually become hormone resistant (Wong and Henderson: 1994). Breast cancer can be sensitive to a large number of single agents but these can produce clinically significant remission in only 20 to 30% of cases (Hortobagyi: 1994). Standard regimes of multi-agent chemotherapy with combinations of cyclophosphamide, 5-fluorouracil, and either methotrexate or doxorubicin can produce response rates of 35 to 80% in previously untreated patients (Hayes *et al:* 1995), and are now widely used in treatment of metastatic breast cancer (Wong and Henderson: 1994). Further progress in the treatment of metastatic cancer is being made with the use of new cytotoxic agents such as taxoids (Piccart: 1995), and dose intensive treatment regimes (Steward: 1995).

1.3.1.2 Adjuvant systemic treatment

The high remission rates achieved with endocrine therapies and chemotherapeutic agents in advanced breast cancer (Hortobagyi: 1995), combined with the evolving knowledge of tumour

kinetics (see below), paved the way for the use of systemic treatment in early breast cancer for the treatment of micro metastasis.

Hormonal ablation, single agent cytotoxic chemotherapy and multi-agent chemotherapy have all been tested as adjuvants to the locoregional treatment of early breast cancer and a large body of controlled data is available to quantify their benefits. The data have been summarised by the Early Breast Cancer Trialists' Collaborative Group (1992) and their main findings are presented below.

1.3.2 The results of systemic therapy in early breast cancer

1.3.2.1 The meta-analysis of clinical trials

In January 1992, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) published the results of a meta-analysis of 133 randomised clinical trials starting before 1985 and investigating many aspects of the systemic treatment of early breast cancer . Detailed data from 74652 women included in these trials were collated and collectively analysed on the basis of intention to treat (Early Breast Cancer Trialists' Collaborative Group. 1990). Their conclusions are based on 23956 deaths and 31299 recurrences in this group of patients. The main points relevant to the present study are summarised below.

1.3.2.2 Results of tamoxifen

Forty two sets of results from 40 randomised trials of tamoxifen versus no tamoxifen, including 30081 patients were analysed with a minimum ten year period of follow-up.

1.3.2.2.1 Recurrence free survival

Tamoxifen produces an overall reduction of 25% in the annual odds of recurrence. This is an average for the entire ten years. The size of the benefit is greatest during the first five years, with survival curves tending to become parallel thereafter.

1.3.2.2.2 Overall survival

Tamoxifen produces a reduction of 17% in the annual odds of death. Unlike the benefits seen for recurrence, the survival benefit is sustained for the entire follow-up period with the survival curves continuing to diverge at ten years.

1.3.2.2.3 Duration of tamoxifen treatment

Tamoxifen was given for less than 2 years in 12 trials, average of two years in 23 trials, and for longer than two years in 7 trials. The recurrence and survival benefits were heterogeneous between the three groups with longer duration of tamoxifen producing the maximum benefit. Thus the subgroup of women who received tamoxifen for longer than two years experienced an annual reduction in the odds of recurrence estimated at 38% and in the odds of death estimated at 24%.

1.3.2.2.4 Age at randomisation

There were significant differences in the size of the overall benefits from tamoxifen between different age groups. In this respect age, rather than menopausal status appeared to be the critical factor. For women aged less than 50 the reduction in the annual odds of recurrence and death were 12 and 6% respectively. The survival benefit in this age group was not statistically significant. In women over the age of 50 the magnitude of the recurrence benefit was in the order of 30% and survival benefit of 20%.

1.3.2.2.5 The effect of axillary nodal involvement

The overall magnitude of the reduction in the odds of death was the same for node-negative and node-positive patients.

1.3.2.2.6 Oestrogen receptor status

The influence of oestrogen receptor (ER) levels on response to tamoxifen has been reported in individual studies of metastatic (Bezwoda *et al:* 1991; Rosner *et al:* 1989) and primary breast cancer (The International Breast Cancer Study Group. 1990; Singh *et al:* 1988; Rutqvist *et al:* 1989; Rose *et al:* 1985). These observations were confirmed in the EBCTCG

meta-analysis. Oestrogen receptor positive (ER •10 U) and ER negative (<10 U) women benefited from tamoxifen although the size of the benefit in the ER positive women was approximately twice that seen in ER negative patients.

1.3.2.2.7 Summary of tamoxifen results

All breast cancer patients benefit from the use of tamoxifen. The maximum benefit accrues from the use of tamoxifen for over two years, and ER positive patients older than 50 are likely to experience the largest benefit.

1.3.2.3 Results of ovarian ablation

Results were available from 10 of 12 trials identified and comprised data from 3072 women, and were analysed separately for women aged under 50 (1746 patients) and those aged over 50 (1326 patients). At a follow-up of 15 years there was no benefit in terms of recurrence free or overall survival to the women older than 50 who received ovarian ablation. The results for younger women are presented below.

1.3.2.3.1 Recurrence free survival

There was a 26% reduction in the annual odds of recurrence over the 15 year follow-up period, with the main divergence occurring in the first ten years.

1.3.2.3.2 Overall survival

The reduction in the annual odds of death was 25% following ovarian ablation, and the effect was sustained throughout the 15 year follow-up period

1.3.2.3.3 The effect of axillary nodal involvement

The number of events in the node-negative group were too small for reliable analysis. Nevertheless it did appear that the reduction in the annual odds of recurrence and death was greatest among node-negative women, although the absolute benefits were still greater amongst node-positive women who had the highest risk of recurrence and death.

1.3.2.3.4 The effect of cytotoxic chemotherapy

The magnitude of the reduction in the odds of recurrence and death attributable to ovarian ablation was slightly reduced when patients received concurrent chemotherapy, but this reduction did not reach significance. In these younger women, ovarian ablation and cytotoxic chemotherapy had effects on survival which were largely independent of each other.

1.3.2.3.5 Summary of ovarian ablation results

Ovarian ablation has no measurable benefit in women aged 50 or older. In the younger age groups ovarian ablation produces a sustained reduction in the odds of recurrence and survival. Its effects are independent of cytotoxic chemotherapy, and may be most substantial in node-negative women.

1.3.2.4 Cytotoxic chemotherapy

Results were available on 18403 women treated in 47 randomised trials of some form of chemotherapy versus no chemotherapy. Because of the wide variation in the regimes used, the trials were grouped according to treatment to calculate the true magnitude of the chemotherapy effect. Multi-agent chemotherapy, given for more than one month had the largest survival benefit when compared with single agent regimes or regimes of shorter duration. The analysis therefore concentrated on the results of ten years of follow-up in 11041 women treated in 31 trials of prolonged multi-agent chemotherapy comprising 32 separate comparisons.

1.3.2.4.1 Recurrence free survival

At ten years of follow-up multi-agent chemotherapy resulted in a 28% reduction in the annual odds of recurrence. Most of this reduction was achieved in the first five years, with survival curves being parallel thereafter.

1.3.2.4.2 Overall survival

Chemotherapy produced a 16% reduction in the annual odds of death. The effect was sustained throughout the ten years of follow-up and the survival curves may be continuing to diverge after ten years.

1.3.2.4.3 The effects of the chemotherapy regime

The CMF[1] regime was used in 11 comparisons on its own and in a further 7 comparisons in conjunction with other drugs. A variety of other multi-agent chemotherapy regimes were used in the remaining studies. There was no significant difference in the magnitude of the benefit observed using different multi-agent chemotherapy regimes.

1.3.2.4.4 Duration of treatment

Multi-agent chemotherapy continued for more than a month produces a greater reduction in the annual odds of recurrence and death compared with treatments of less than one month's duration. The magnitude of the benefit for chemotherapy given for about 6 months however is the same as the benefit derived with more prolonged treatment.

1.3.2.4.5 Age at randomisation

Information could be reliably analysed up to the age of 70. All age groups derive benefit from chemotherapy. Women aged less than 50 appear to experience the largest reduction in odds of recurrence (36%) and death (25%). Women aged between 60 and 70 however still experience a substantial reduction in the odds of recurrence of the order of 20% and in odds of death of about 10%.

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[1] CMF: Cyclophosphamide, Methotrexate and 5-Fluorouracil

1.3.2.4.6 The effect of axillary nodal involvement

The magnitude of the reduction in the annual odds of recurrence or death is essentially the same for node-positive and node-negative women, although clearly both the absolute risks, and therefore the absolute benefits are much higher in node-positive patients.

1.3.2.4.7 Summary of trials of prolonged multi-agent chemotherapy

All patients can potentially derive benefit from chemotherapy although patients younger than 50 derive greater benefit. More benefit can be accrued by giving chemotherapy for more than one month, but prolongation beyond about six months is of no further advantage.

1.3.3 Improving the results

The EBCTCG overview leaves no doubt that systemic therapy can prolong survival from breast cancer. Nevertheless substantial proportions of patients continue to suffer recurrence and die from breast cancer despite full locoregional and systemic therapy.

There are important theoretical reasons which indicate that available treatments can be used in such a way as to kill more cancer cells. This subject will be considered in the next section.

1.4 FAILURE OF SYSTEMIC TREATMENT

Systemic treatment has been able to alter the natural history of breast cancer, but available techniques leave a substantial proportion of patients with residual disease which eventually causes systemic recurrence and death.

The failure of systemic therapy can be attributed to three general reasons:

1. Failure of systemic agents to reach target cells
2. Unfavourable tumour kinetics: failure to attack target cells at their most vulnerable
3. Biochemical resistance of individual cells to the systemic agents

Often all three of these mechanisms can act together to result in the eventual recurrence of cancer. The contribution of each resistance mechanism to eventual treatment failure will be considered below.

1.4.1 Reaching Target Cells

1.4.1.1 Possible mechanisms of failure

1.4.1.1.1 Pharmacological sanctuaries

The systemic administration of drugs aims to achieve therapeutic drug concentrations in all areas of the body where tumour cells may be present. Under some circumstances the antineoplastic agents may be physically unable to reach all their target cells. One such situation is the presence of malignant cells in pharmacological sanctuaries such as the central nervous system, where they are protected from the actions of some drugs by the blood/brain barrier (Whitehouse and Kay: 1979).

1.4.1.1.2 Poor blood supply

Another example of relatively protected cells are those at the centre of large tumour masses with a relatively poor blood supply, where the drug may have to diffuse through several cell layers (Hanna, Jr. *et al:* 1983). *In vitro* experiments using the multicellular spheroid model have shown that most of the drug is concentrated in the outer layers, leaving the central cells relatively protected (Sutherland *et al:* 1971) .

1.4.1.2 Relevance to breast cancer

In practice these factors are likely to have little influence on the final outcome of systemic treatment. Most recurrences of breast cancer happen in tissues with a good drug distribution such as bone marrow, lung and liver (Gompel and van Kirkem: 1983). Drug diffusion is only likely to be a significant problem in tumours of great bulk, in which there will be other much more compelling reasons for incurability (Goldie and Coldman: 1984).

1.4.2 The Influence of tumour kinetics

One of the defining characteristics of a neoplasm is that its growth rate exceeds that of normal tissues (Willis: 1952). Early experiments using *in vivo* labelling of solid tumours with tritiated thymidine demonstrated that there is little difference in the cycle times of normal and malignant cells. The faster growth rate of cancers compared with normal tissue is entirely explained by the presence of a greater proportion of proliferating cells (Young and DeVita: 1970). Cancers, however, by no means consist entirely of dividing cells as demonstrated by experiments involving prolonged continuous infusions of tritiated thymidine which demonstrated that certain subpopulations of malignant cells never take up the label (Mendelsohn: 1962).

Many treatment schedules are designed around assumptions about the growth characteristics of cancers. Exponential and Gompertzian functions are able to explain the growth behaviour of most human cancers, but have very different implications for treatment scheduling. The fine detail is also important, as not all drugs are able to kill all cancer cells at all times. These points are considered below.

1.4.2.1 Exponential growth kinetics

1.4.2.1.1 The fractional cell kill model

In 1964 Skipper and colleagues put forward a mathematical model to explain the behaviour of cancer cells in response to chemotherapy. This still forms the basis for much of the thinking behind the design of cancer therapeutic protocols. The model is based on data from the study of the murine leukaemia L1210 cells (Skipper *et al:* 1964). Three sets of observations form the basis for Skipper's "fractional cell kill" or "log-kill" model for the action of antineoplastic agents.

1.4.2.1.1.1 Exponential growth

The growth pattern of this leukaemia closely approximates an exponential curve, thus the tumour burden increases by a constant fraction over time, and death occurs when a relatively constant lethal number of cells is reached (DeVita *et al:* 1969).

1.4.2.1.1.2 Dose response relationship

Skipper observed that when a specified tumour burden was given a fixed dose of chemotherapy, a fixed prolongation in survival was obtained. Furthermore, cells surviving following treatment followed a re-growth curve which was identical to that of the untreated cells. Given these observations Skipper was able to estimate the number of cells killed from the length of prolongation in survival.

1.4.2.1.1.3 Fractional Kill

The third, rather surprising, observation was that the prolongation of survival obtained by a fixed dose of drug was not influenced by the size of the initial tumour burden. This clearly indicated that a fixed dose of chemotherapy does not, as might have been expected, kill a fixed number of cells, but that it kills a fixed fraction of cells.

1.4.2.1.2 Implications for treatment

Skipper's fractional cell kill model has a number of important treatment implications. Based on principles derived from his theoretical model Skipper was able to design treatment protocols which could produce cure even in advanced tumours (Skipper *et al:* 1964).

1.4.2.1.2.1 Dose is important

Because of the observed dose response relationship, it is clear that dose is important in producing the maximum cell kill. Skipper proposed the use of multi-agent chemotherapy as a way of achieving greater total dose of drug within the limits of toxicity for each individual agent.

1.4.2.1.2.2 The inverse rule

The probability of cure is inversely related to the initial tumour burden. Thus chemotherapy given in the setting of early disease for a tumour such as breast cancer, which was observed to respond in the advanced case (Cooper: 1969), is predicted to produce a high probability of cure.

Reducing the initial tumour bulk by removing the primary would be a way of reducing initial tumour burden and hence increasing the probability of cure. This model therefore supports the concept that systemic therapy should follow local tumour eradication.

1.4.2.2 Gompertzian growth kinetics

Many of the modern chemotherapeutic treatment regimes have been formulated based on Skipper's fractional cell kill model. This model is based on observations on systems with exponential growth characteristics, and does not take into consideration the consequences of the natural death of tumour cells. In many cancers, including breast cancer, the growth rate is not constant but varies in proportion to the tumour bulk. Exponential kinetics do not adequately explain the growth of these tumours.

In 1825 Gompertz described an equation for actuarial analysis in human populations (1825). His equation was later proposed by Winsor as a growth curve (1932). The Gompertzian

function describes a mode of growth in which exponential growth is accompanied by an exponential retardation in the rate of growth (Figure 1-3). This Gompertzian function describes the growth of many solid tumours much more accurately than the exponential function (Laird: 1969; Laird: 1964).

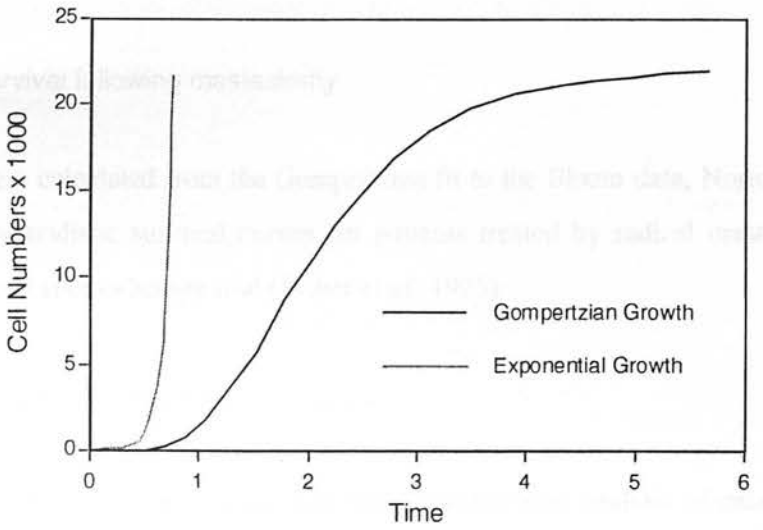

Figure 1-3: The Gompertzian growth function.

The Gompertzian plot is represented by the equation: $y=\exp[{}^{A}/_{\alpha}(1-e^{-\alpha x})]$ where A is the growth constant and α represents the retardation constant and x and y are the plot axis. In this representation $\alpha=0.1A$.. In the case where α tends to zero, the equation simplifies to the exponential curve represented by the equation: $\mathbf{y=\exp(Ax)}$

1.4.2.2.1 Gompertzian growth of breast cancer

Norton, using data from three separate sources, has put forward a compelling argument for the Gompertzian growth of human breast cancer (Norton: 1988).

1.4.2.2.1.1 Untreated breast cancer

In the nineteenth century non-intervention was regarded as acceptable treatment for breast cancer. Detailed follow-up data on 250 women with histologically proven breast cancer managed in this way at the Central Middlesex hospital were published by Bloom & colleagues in 1962 . Norton used these data to construct a survival curve for untreated breast cancer, and showed that Gompertzian function describes this curve with a very high degree of accuracy.

1.4.2.2.1.2 Survival following mastectomy

Using parameters calculated from the Gompertzian fit to the Bloom data, Norton was able to construct highly realistic survival curves for patients treated by radical mastectomy in the NSABP* adjuvant chemotherapy trial (Fisher *et al:* 1975).

1.4.2.2.1.3 Growth of "missed" breast cancers

Additional support for Gompertzian growth was provided from analysis of data published by Hanser on cancers detected on the second round of a mammographic screening programme, which had, on retrospective review, also been present on mammograms done during the first round (Heuser *et al:* 1979). Twenty three patients had measurable tumour growth on mammography. The change in tumour volume was used to calculate the Gompertzian growth constant for each cancer. The probability distribution for actual Gompertzian growth constants was calculated using parameters obtained using the Bloom data. The calculated constants perfectly fitted the probability distribution curve, confirming that the mammographic tumours had indeed increased in size in a Gompertzian fashion.

While the growth of these tumours can be explained by more complex mathematics such as the stochastic growth model proposed by Speer and colleagues (1984), the relative simplicity of the Gompertzian model has allowed it to be used as a basis for models for predicting cell kill and drug resistance.

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* NSABP: National Surgical Adjuvant Breast and Bowel Project

1.4.2.2.2 The behaviour of tumours showing Gompertzian growth

Skipper's original equation does not accurately predict the behaviour of Gompertzian growing tumours. Norton and Simon (1986) have proposed a modification of Skipper's equation, thus generalising it to systems with changing growth fractions. Cell kill as predicted by this modification is proportional to the instantaneous growth fraction, as well as the dose of drug administered. When the growth fraction is constant, as in exponential growth, the Norton-Simon model simplifies back to the Skipper model (Norton and Simon: 1986).

1.4.2.2.3 Implications of Gompertzian growth for treatment

This kind of modelling would predict that the rate of tumour regression would decrease with shrinking tumour volume. The prolongation in survival produced by a given dose of drug will no longer be constant, but will depend on the position of the initial tumour on its Gompertzian growth curve. This has important implications for adjuvant therapy. Thus in direct contradiction to Skipper's inverse rule, a regime producing even complete clinical regression in an advanced tumour, may not be able to eradicate the same tumour in the adjuvant setting. Treatment will fail to produce cure in the absence of any form of cellular resistance (Norton and Simon: 1986; Norton: 1990).

1.4.2.3 The importance of the cell cycle

The differential sensitivity of proliferating and non-proliferating cells forms a fundamental assumption underlying the construction of mathematical models to predict the effects of anticancer agents.

The position of cancer cells within the cell cycle is an important factor in determining sensitivity to chemotherapy. In general, proliferating cells are much more sensitive to the actions of anticancer agents than non-proliferating cells (Lamerton: 1972; Valeriote and van Putten: 1975). Bruce and his colleagues (1966) studied the action of a wide variety of antineoplastic agents on the proliferative capacity of normal haematopoietic stem cells and transplanted lymphoma cells. They showed that antineoplastic agents can be divided into two broad categories of "cycle specific" and "phase specific". Both classes of drugs killed many more neoplastic cells than they did normal cells (Bruce *et al:* 1966). This was shown to be

because significantly larger fractions of the normal cells were outside the cell cycle in the G_0 resting state (Bruce and Meeker: 1967; Bruce *et al:* 1969).

1.4.2.3.1 Cycle specific agents

Cycle specific agents are drugs such as cyclophosphamide which produce exponential dose-response curves. This indicates that once cells have left the resting phase, they would become susceptible to the action of these drugs in all the phases of the cell cycle.

1.4.2.3.2 Phase specific agents

The second group of agents includes drugs such as 5-fluorouracil. The dose-response curve for this group of drugs reaches a plateau, indicating that dividing cells which are outside specific phases of the cell cycle are no longer susceptible to the action of these drugs.

1.4.2.4 The clinical relevance of kinetic resistance

That kinetic resistance is important in the clinical setting is borne out by the fact that the remission rate in tumours recurring for the first time is often very similar to the rate observed in cancers treated *de novo* by the same drugs (Kardinal *et al:* 1988; Fisher *et al:* 1979). Nevertheless, subsequent recurrences eventually do become resistant to treatment, and it is the uncontrolled growth of such biochemically resistant cells which will bring about the demise of the patient. Treatment strategies designed to minimise the probability of overgrowth with resistant cells will therefore have the greatest likelihood of affecting a cure.

1.4.3 Biological cellular drug resistance

Tumours are sensitive to the effects of chemotherapeutic agents to varying degrees. Malignant melanoma represents an example of a tumour which may be regarded as intrinsically resistant to chemotherapy. Breast cancer, on the other hand often responds to initial treatment, but will, with subsequent recurrence acquire drug resistance.

1.4.3.1 The origins of drug resistance

The question of whether resistance is truly acquired (i.e., it develops as a consequence of exposure to drug), or it is pre-existent and is simply selected out by chemotherapy was first addressed in bacteria by Luria and Delbrück's (1943) classic fluctuation analysis experiment. This is now regarded as the main tool for dealing with a heritable property that is acquired by a stochastic mechanism.

Luria and Delbrück exposed subcultures obtained from a number of sublines of the same bacterium to a bacteriophage, and after a specified period, determined the number of resistant bacteria in each subculture. If resistance had developed as a result of exposure to the bacteriophage the variance in the number of resistant bacteria should have been the same between sublines and subcultures. In fact the variance in the number of resistant colonies between the sublines was much greater than that seen between the subcultures, indicating that resistance had developed at a variable time before exposure to the bacteriophage (Figure 1-4).

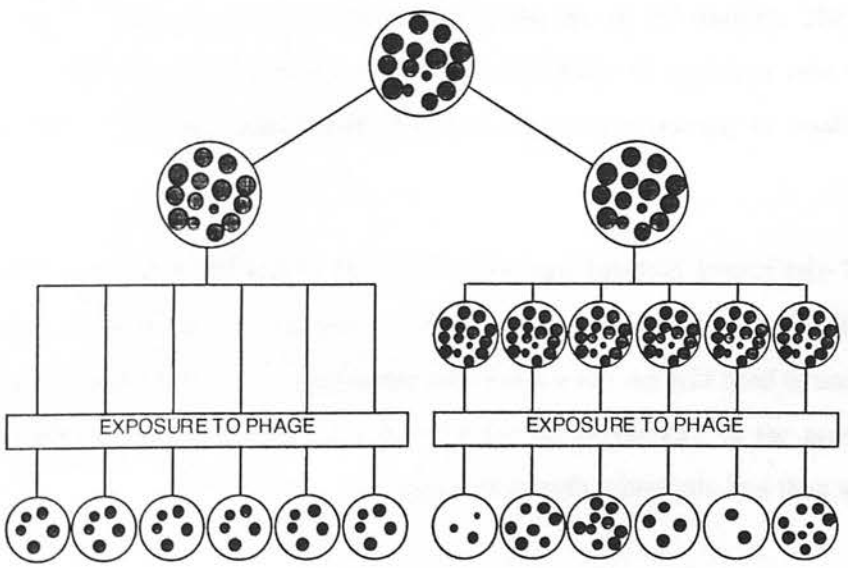

Figure 1-4: Illustration of Luria and Delbrück's fluctuation analysis experiment.

Nine years later Law applied the same fluctuation analysis method to study anti-folate resistance in L1210 murine leukaemia cells, with identical results (Law: 1952). Similar results have been found in other experimental neoplastic systems (Ling: 1975; Poche *et al:* 1975). It is now accepted that resistance develops as a result of random spontaneous mutations during the developmental lifetime of the tumour before, and not as a result of, exposure to treatment.

1.4.3.2 Probability of developing the resistant phenotype

1.4.3.2.1 Exponentially growing tumours

In 1979 Goldie and Coldman proposed a mathematical model to predict the probability of a resistant phenotype emerging at a given time point in the life of the tumour by a process of random spontaneous mutation. The model assumes that all cells and their progeny are capable of dividing and that any mutant resistant cells will survive. According to this model emergence of resistance is dependent only on the underlying mutation rate, and the total number of cells present at any given time, regardless of the growth function of the tumour. The model also predicts that the change from a low probability of resistance to a high probability of resistance takes place over a relatively short critical period in the life of the tumour. The fractional growth required for this transformation is constant regardless of mutation rate or starting tumour size. Faster mutation rates simply result in the process starting at smaller tumour sizes.

The probability function is defined by the Goldie-Coldman equation $y=\exp[-\alpha(x-1)]$, Where y=probability of no resistance, x = number of cells and α = mutation rate. The shape of the probability plot remains constant. It can be calculated that a tumour will need to undergo a 60 fold increase in size (log growth = 1.77) in order for the probability of the presence of a resistant cell to rise from 0.05 to 0.95. This degree of growth represents less than six tumour doublings (Figure 1-5).

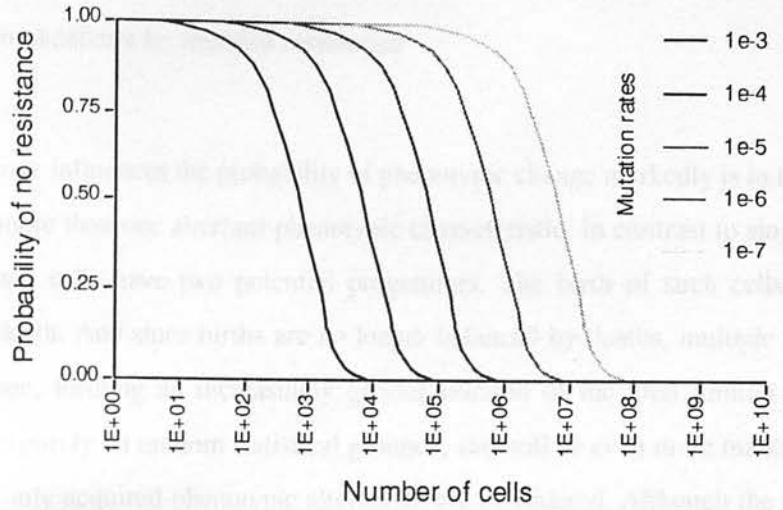

Figure 1-5: The probability of curability (no resistant cells) at different mutation rates for growth with no cell loss

1.4.3.2.2 Modification for Gompertzian growth

The assumption that all mutations are stable and that no loss of cells takes place is unrealistic. In 1983 Goldie and Coldman published a generalisation of their earlier model to account for the probability of cell death . When cell death is zero the modified model simplifies back to the original. For death rates greater than zero the change from low to high probability of resistance takes place at progressively smaller volumes. In practical terms the model predicts that in real tumours where cells can die as well as be born, the probability of resistance does not relate to the tumour size *per se*, but rather to the number of doublings it has undergone in order to reach a given size. A tumour with high death rate reaches a given size after many more doublings than a tumour with a smaller death rate, and will have a greater probability of resistance at that size.

1.4.3.2.2.1 Implications for single resistance

In the case of a single resistant phenotype, death rate has only a small influence on probability of resistance, since the increased probability of resistance at higher death rates is to some extent balanced by the correspondingly increased chance of the emergent resistant cells becoming extinct.

1.4.3.2.2.2 Implications for multiple resistance

Where death rate influences the probability of phenotypic change markedly is in the emergence of cells with more than one aberrant phenotypic characteristic. In contrast to single resistance, doubly resistant cells have two potential progenitors. The birth of such cells is no longer balanced by death. And since births are no longer balanced by deaths, multiple resistant cells will accumulate, forming an increasingly greater fraction of the total tumour burden. This effect happens purely on random statistical grounds, and will be even more marked when three or more randomly acquired phenotypic alterations are considered. Although the probability of multiple resistance will always be smaller than that for any single character, the shape of the probability curve will remain similar to that found for the most simple case. The critical mass for the change from low to high probability of multiple resistance however will be much more sensitive to death rates. The final consequence is that tumours with high rates of cell loss will display a much greater degree of heterogeneity at a given size than the more rapidly growing tumours with smaller death rates.

This hypothesis provides a stochastic explanation for the very high level of heterogeneity observed in most solid tumours (Fidler *et al:* 1978; Nowel: 1976; Chow and Greenberg: 1980).

1.4.3.3 Implications of cellular resistance

1.4.3.3.1 The incurable tumour

The shape of the probability curve, notwithstanding any resistance mechanisms the tumour may have inherited from its normal ancestors, indicates that no matter how refractory a tumour may eventually become, there is a period in its life during which time the probability of resistance is low and the tumour potentially curable. The change from the curable to the incurable state can take place over a relatively short period of time, perhaps a few weeks.

1.4.4 Success with systemic therapy

1.4.4.1 Cellular resistance is the key

In this section three reasons for failure of systemic treatment have been examined. Hidden cancer cells, and kinetic failures could in theory be overcome by more treatment when they eventually manifest themselves. The theory does not work because of cellular resistance. Thus large tumour masses may be less curable because they may have already reached the critical size for incurability. A tumour recurrence after a "kinetic" failure may be refractory to chemotherapy because by the time it becomes clinically apparent it has acquired multiple levels of biochemical drug resistance.

1.4.4.1.1 Curing micro metastases

The reason systemic treatment is necessary at all is that tumours metastasise.

The rapid change from the curable to the incurable stage has important implications for the treatment of micro metastases in the adjuvant setting. Micro metastases may have a size distribution which is below the level at which probability of cure is lost, and may be particularly susceptible to the actions of antineoplastic agents (Goldie: 1987). Here timing of treatment will be of crucial importance to outcome. Treatment should be started as early as possible since even short delays are likely to result in loss of curability.

Any protocol design must take account of the mechanisms for metastasis and the behaviour of metastatic deposits. This subject will be considered next.

1.5 THE PROCESS OF METASTASES

1.5.1 The nature of metastases

Metastasis, the growth of a tumour arising from a primary but at a site distant from the primary is the unequivocal hallmark of malignant neoplasia. Metastatic deposits appear to arise from single cells which have randomly expressed a pre-existent metastatic phenotype. The evidence is reviewed below.

1.5.1.1 Single cell origin

Experiments using radiation induced chromosomal markers in a murine model have demonstrated that metastatic deposits arise from the growth of a single metastatic cell and that each deposit has a different progenitor cell. This holds true even after the direct intravascular injection of multicellular cell clumps (Talmadge *et al:* 1982).

1.5.1.2 Stochastic nature of the metastatic process

Metastatic deposits are established at the culmination of a series of sequential steps, the failure of any of which can result in the failure of the entire process (Fidler: 1990; Poste and Fidler: 1980).

The question whether the metastatic steps are completed by random chance, or ability to metastasise is a genetically acquired phenotype has been addressed by Fidler and his colleagues. They showed that metastatic ability can be selected and enhanced by passaging metastatic lung nodules through syngenic mice (Fidler: 1973). Mice were injected with cultured melanoma cells in a step analogous to the "phage exposure" step of the classical fluctuation analysis experiment of Luria and Delbrück (1943). Analysis of variance of the number of metastatic deposits established that the ability to form metastases was not a consequence of random release into the blood stream, but was a genetically acquired pre-existent phenotype (Fidler and Kripke: 1977). These results were confirmed by other experimenters, using different cell lines (Fidler and Hart: 1982; Chambers *et al:* 1981) and *in*

vivo using spontaneously metastasising experimental tumours (Neri *et al:* 1982). Attempts are now being made to identify some of the genetic events underlying the metastatic phenotype (Poste *et al:* 1982).

1.5.1.3 Critical mass for metastasis

The application of the Goldie-Coldman model (Goldie and Coldman: 1979; Coldman and Goldie: 1983) to the metastatic process predicts that there will be a critical size below which the presence of metastases is improbable, and that the likelihood of metastasis will dramatically increase once this size is reached. This prediction has proved correct in experimental systems (Hill *et al:* 1984) and is borne out clinically by the observation that some cancers appear clinically cured by locoregional therapy alone.

1.5.1.4 Metastasis and drug resistance

Harris and colleagues have calculated mutation rates for the acquisition of the metastatic phenotype in murine tumours. The rates appear much greater than those estimated for development of drug resistance (Harris *et al:* 1982; Hill *et al:* 1984). This has been suggested as an indication of the genetic instability of the metastatic phenotype, resulting in the rapid development of other abnormal phenotypic features such as drug resistance (Cillo *et al:* 1987; Nowel: 1976). However experimental systems designed to estimate the rate of development of resistance in cells which acquire the metastatic phenotype, suggest that metastatic ability and drug resistance evolve independently of each other at different rates (Jang and Hill: 1991; Damen *et al:* 1989). It is therefore theoretically possible for the expression of metastatic potential to predate the expression of drug resistance. Thus a metastatic deposit could still retain a low probability of drug resistance. Since the main bulk of early tumours is formed by the primary, it is likely to be the number of cells in this which determines the probability of resistance for its micro metastases.

1.5.2 Interactions between primary tumour and its metastases

1.5.2.1 Shared regulatory mechanisms

The Gompertzian growth pattern suggests that the growth of cancer while abnormal, is nevertheless subject to some form of control. The idea that any growth inhibition is simply the result of the failure of supply of oxygen and nutrients to an otherwise exponentially growing collection of cells (Burton: 1966), is unlikely to be correct since such failure would be expected to result in sudden and rapid growth retardation. The progressive slow-down which characterises Gompertzian growth of solid tumours (Laird: 1969) is similar to the pattern of growth seen in many normal tissues (Laird and Howard: 1966; Laird *et al:* 1965), suggesting that specific regulatory mechanisms are involved. Although metastatic deposits rapidly acquire marked heterogeneity both with individual deposits and between different deposits (Poste *et al:* 1982), it is still likely that they continue to share at least some regulatory mechanisms with each other and with their parent tumour. If this is the case metastatic deposits will not act as independently growing new tumours. Rather the cells making up the tumour and its metastases will behave like a single growing population.

1.5.2.2 Effects of removing the primary on the growth of metastases

1.5.2.2.1 Tumour excision accelerates metastatic growth

Partial or complete removal of an experimental tumour results in the accelerated growth of metastatic deposits. This was first observed during the early part of this century (Tadenuma and Okonogi: 1924; Tyzzer: 1913), and later experiments repeated the observation (Schatten: 1958b). Increase in the rate of metastatic growth was shown to be independent of the effects of anaesthesia or surgical trauma (Schatten: 1958a). Numerous investigators have since confirmed that non-curative excision results in increased growth of residual tumour or any metastatic deposits (Gunduz *et al:* 1979; Ketcham *et al:* 1961; Ketcham *et al:* 1959; Simpson-Herren *et al:* 1976).

That this is not merely an epi-phenomenon observed as a result of longer survival following tumour debulking has been shown using kinetic studies with tritiated thymidine labelling.

These have established that following partial excision there is an increase in the size of the tumour growth fraction (Gunduz *et al:* 1979; Simpson-Herren *et al:* 1976), produced by recruitment of resting cells into the cell cycle (Fisher *et al:* 1983b).

1.5.2.2.2 Inhibition of post excisional growth spurt

The accelerated growth following excision of the primary can be inhibited by the re-implantation of the tumour (Gorelik *et al:* 1978; DeWys: 1972). The inhibition is tumour specific: re-implantation of an unrelated tumour fails to influence metastatic growth (Gorelik *et al:* 1978). That actual growth stimulatory substances are also involved is suggested by the observation that in some models, serum from a mouse which has had its tumour removed, is able to stimulate tumour growth in a second mouse, or in cultured cancer cells. No such effect is seen following sham surgery (Fisher *et al:* 1989a). The post excisional growth spurt can be abolished in experimental animals by preoperative chemotherapy (Fisher *et al:* 1989d; Fisher *et al:* 1983d), and to a lesser extent by preoperative radiotherapy (Fisher *et al:* 1986).

1.5.2.2.3 Rapid tumour growth after ablation of related non-malignant tissue

Substances have been characterised which regulate the growth and regeneration of normal tissues, including hepatocytes, renal cells and colonic mucosal cells (Iversen: 1991). Similar molecules have been implicated in the regulation of growth in tumours (Herlyn and Malkowicz: 1991).

The essential similarity between the regeneration response of normal tissue and the post excisional growth spurt seen in cancer is emphasised by the observation that growth of experimental tumours can be stimulated in a tissue specific manner by ablation of related *normal* tissue (Fidler: 1991). Thus cancers from a gastro-intestinal origin undergo growth stimulation in animals with regenerating livers following hepatectomy. Hepatectomy has no effect on the growth of renal cancers, which are however stimulated following removal of a normal kidney (Fidler: 1991).

1.5.2.2.4 Application to breast cancer

Breast cancer represents a prime example of a tumour in which growth is regulated by complex interactions between systemic hormones (Brunner: 1990) and tumour derived growth stimulatory and growth inhibitory peptides. Many of these have been characterised. Growth promoters include insulin-like growth factors IGF-I and II (Yee *et al:* 1989; Yee *et al:* 1988), transforming growth factor alpha (TGF-α) (Bates *et al:* 1988) and epidermal growth factor (EGF) (Osborne *et al:* 1980). Growth inhibitory substances such as the transforming growth factor beta (TGF-ß 1 and 2) (Zugmaier *et al:* 1989; Knabbe *et al:* 1987) and the mammary derived growth inhibitor (Grosse *et al:* 1991; Grosse and Langen: 1990) also play an important role in the regulation of breast cancer growth.

Although the precise nature of the interactions between these mechanisms is not known, it is very likely that accelerated metastatic growth may be a consequence of primary tumour excision in at least some breast cancers.

1.5.3 Implications for treatment of breast cancer

Expedient removal of the primary tumour early in its life can potentially result in cure as the cancer may not as yet have acquired metastatic potential. This is borne out by the success of the breast screening trials (see section 1.2.2.3.5), and is undoubtedly the correct treatment for very early cancers.

The situation for larger tumours which have already formed micro metastatic deposits is entirely different. Here early removal may in certain circumstances be actually detrimental, and a strong argument may be made for the use of systemic therapy before local excision. This argument will be put forward in the next section

1.6 PRIMARY SYSTEMIC TREATMENT OF BREAST CANCER

Operable breast cancer has conventionally been treated by some form of surgical excision followed, in appropriate cases, by systemic therapy given as an adjuvant to surgery. In the light of the foregoing discussion it may be more appropriate to view breast cancer as a complex systemic disease, which should in the first instance be treated by systemic means. Reversing the conventional sequence of treatment offers several potential advantages which may render breast cancer more curable.

1.6.1 Potential advantages of primary systemic treatment

1.6.1.1 Theoretical advantages

1.6.1.1.1 Favourable Kinetics

Most patients with operable breast cancer at the time of diagnosis have tumours which are on the steepest part of the Gompertzian growth curve (Brown *et al:* 1984). Locoregional treatment will significantly reduce the total body burden of cancer cells. Residual cells, in the form of micro metastatic deposits will return to the initial slow growth phase of the Gompertzian curve and will be difficult to eradicate purely for kinetic reasons.

Systemic therapy before tumour excision will treat micro metastatic disease when it is kinetically most vulnerable. With response, the tumour will eventually reach a kinetically refractory size, but residual cells are most likely to be located in the part of the tumour with greatest initial number of cells, i.e., the primary tumour, and will be eliminated by "adjuvant surgery".

1.6.1.1.2 Avoidance of delay

A tumour, and in particular its metastases can progress from a curable to an incurable state over a short critical period of time. This critical time period may be made even shorter by the "tumour regeneration" response caused by surgical excision of the primary tumour. Primary

systemic treatment eliminates any delay which may otherwise be introduced by the time required to complete locoregional therapy. Furthermore it may abolish the tumour regeneration response in any residual cancer cells.

1.6.1.2 Practical advantages

1.6.1.2.1 Assessment of response

Micro metastatic deposits are by definition clinically undetectable. Surgical excision removes the only means by which the response of the tumour to systemic treatment may be assessed. Primary systemic treatment will allow optimisation of treatment regimes based on observed tumour response (Goldie: 1987; Fisher *et al:* 1990; DeVita, Jr. 1983). In addition, the final degree of response may be used to evaluate the patient's final prognosis (Hortobagyi *et al:* 1988; Jacquillat *et al:* 1991; Jacquillat *et al:* 1990). Application of response based treatment regime is one of the most important practical advantages offered by primary systemic treatment, and accurate measurement of tumour response must be regarded as critical to its success.

1.6.1.2.2 Easier locoregional control

The regression of the primary breast tumour in response to systemic therapy has been regarded by some as a way of increasing breast conservation rates (Singletary *et al:* 1992; Schwartz *et al:* 1994; Bonadonna *et al:* 1990).

1.6.2 Potential disadvantages of primary systemic treatment

The potential advantages of primary systemic treatment should be balanced against the possible disadvantages of delaying surgical excision.

1.6.2.1 Theoretical disadvantages

1.6.2.1.1 Risk of further metastases

Stochastic theory predicts that metastases develop over a short critical time period. A delay in surgical excision runs the risk of allowing localised disease to establish micro metastases.

In practice, since metastatic potential develops very early in the history of the tumour, this is likely to be a significant consideration only in very early cancers such as those detected on screening.

1.6.2.1.2 Kinetic considerations

Very large cancers may have reached the plateau part of the Gompertzian growth curve and be refractory to treatment without initial debulking. In practice this situation is only likely to arise in very advanced disease and is not likely to apply to operable breast cancer (Brown *et al:* 1984).

1.6.2.2 Practical disadvantages

1.6.2.2.1 Loss of full pathological information

Histological and biochemical information normally available from examination of the surgical specimen will only become available after completion of systemic therapy, and may not represent the true nature of the tumour. Pre-treatment tumour biopsy and axillary sampling can to some extent overcome this problem, although it may also reduce some of the expected benefits of primary systemic therapy.

1.6.2.2.2 Surgical considerations

A period of what is often toxic treatment can result in compromised immune defences and wound healing. This may have serious consequences for the morbidity experienced by the patient following surgery.

1.6.2.2.3 Psychological considerations

The diagnosis of breast cancer represents a major life event for the patient, and facing the potential of loss of life can be associated with major adverse psychological reactions. Primary systemic therapy requires that the patient should live with the tangible component of her cancer for an extended period of time. It may be speculated that this, combined with the added anxiety of not knowing whether the tumour is going to respond to treatment could have further adverse effects on her psychological well-being.

1.6.3 Weighing up the options

Primary systemic therapy can potentially make a contribution to the successful treatment of women with breast cancer. The remainder of this document describes a study carried out to assess the extent of this contribution.

CHAPTER 2

2. Clinical Applications of Primary Systemic Treatment

2.1 APPLICATIONS IN TUMOURS OTHER THAN BREAST CANCER

In a limited number of tumours primary systemic treatment has proven of value both in preserving function and in improving survival, and is regarded as standard treatment.

2.1.1 Sarcomas

In Ewing's sarcoma and osteogenic sarcoma, primary treatment has resulted in greatly improved rates of limb salvage, and considerable gains in disease free survival in the 70-80% of patients who show complete response to initial treatment (Picci *et al:* 1994; Eilber and Rosen: 1989; Smith *et al:* 1991; Jurgens *et al:* 1988). In these tumours primary systemic therapy is now considered standard treatment. Similarly in soft tissue sarcomas primary systemic treatment, although of no proven value in increasing survival, can ease surgical resection, particularly when the tumour is in the vicinity of neurovascular bundles (Eilber *et al:* 1990).

2.1.2 Carcinomas

2.1.2.1 Head and neck tumours

In the treatment of head and neck tumours primary systemic therapy, although not yielding any definite survival advantage, has proved of great value in allowing preservation of anatomical function, and in simplifying locoregional therapy (Urba and Wolf: 1991). This has resulted in functional laryngeal and pharyngeal preservation in up to two third of patients treated in this way (Dimery and Hong: 1993).

2.1.2.2 Anal squamous cell carcinoma

In the treatment of squamous carcinoma of the anal canal, a combination of chemotherapy and radiotherapy can produce over 90% response rates (Nigro *et al:* 1989; Cummings *et al:* 1991), resulting in preservation of function.

2.1.2.3 Other epithelial cancers

Unfortunately the role of primary systemic treatment is least clear in the treatment of the common epithelial cancers. The use of combinations of radiotherapy and chemotherapy have been reported to produce clinical response without any obvious advantage in overall outcome in lung (Ginsberg: 1993; Murren and Buzaid: 1993), bladder (Scher: 1993; Walther: 1993), cervical (Jones: 1993; Potish and Twiggs: 1993), oesophageal (Kelsen *et al:* 1990; Fink *et al:* 1994), gastric (Ajani *et al:* 1991; Alexander *et al:* 1993) and pancreatic cancer (Douglass: 1993).

2.2 LOCALLY ADVANCED BREAST CANCER

Local eradication has traditionally been regarded as the main method of treatment for tumours apparently confined to the breast (Bonadonna: 1989). For early breast cancers good local control can generally be achieved by well established techniques of surgery and radiotherapy, the main debate focusing on ways of minimising the extent of local therapy (Mansfield *et al:* 1991; Hayward and Caleffi: 1987; Fisher *et al:* 1985; Atkins *et al:* 1972). There are nevertheless a significant number of breast cancers which although not metastatic at presentation, will be regarded as "locally advanced", a term referring to a heterogeneous group of patients including those with tumours classified under the TNM classification (UICC: 1987) as T3, T4, or N2. Eleven to 29% of breast cancers have been reported to present in a locally advanced state (McWhirter: 1955; Haagensen: 1971).

2.2.1 Local treatment

Although resection of locally advanced tumours is technically possible, surgery is associated with a high rate of relapse and short survival (Ackland *et al:* 1985; Haagensen: 1971; Haagensen and Stout: 1943). Radiotherapy can achieve better local control (Baillet *et al:* 1993; Fletcher: 1971), but survival remains short, most patients relapsing with distant metastases (Zucali *et al:* 1976; Rubens *et al:* 1977). The overall survival of a group of 9055 such patients treated with a combination of surgery and radiotherapy was 33% at five years and 22% at ten years. The results in the special subgroup of inflammatory cancers were even poorer, 97% being dead at five years (Hortobagyi: 1990).

2.2.2 The influence of systemic treatment

With the publication of 1992 overview of adjuvant breast cancer trials (Early Breast Cancer Trialists' Collaborative Group: 1992) the case for systemic therapy in early breast cancer can now be regarded as proven. By extrapolation the need for some form of systemic treatment in locally advanced breast cancer is assumed (Ragaz *et al:* 1991).

In the case of the special subgroup of patients with inflammatory breast cancer, systemic treatment has produced five year survival rates of 30-50%. Compared with survival rates of 2-3% reported with locoregional therapy alone this is such a pronounced improvement that the need for direct comparisons between systemic therapy and no-systemic therapy groups has been eliminated (Jaiyesimi *et al:* 1992).

This is not the case with the more common forms of non-inflammatory locally advanced breast cancer. Systemic therapy for this disease produces five year disease free survival rates of 30-60%, being only slightly better than those reported with local therapy alone (Hortobagyi: 1990). Nevertheless in view of the observed improvements, and the findings of adjuvant trials in early breast cancer, studies which do not include some form of systemic treatment are now regarded as ethically unjustified (Swain and Lippman: 1991).

2.2.2.1 Sequential series of systemic therapy

The success of multi-agent chemotherapy regimes in producing remissions in significant numbers of patients with metastatic breast cancer (Greenspan: 1966; Carter: 1972), led in the early 1970's to the development of the concept of "combined modality approach" for the treatment of breast cancer (Carter and Soper: 1974). A large number of studies have been used to test different forms of systemic treatment for locally advanced breast cancer. Since the disease is by definition "inoperable" many studies have used systemic therapy as the primary treatment, with better locoregional control and reduced treatment related morbidity as a desirable by-product. The main treatment objective however remains to prolong survival. A representative sample of these studies are summarised in Table 2-1.

Most patients had truly inoperable cancers although a few patients with large but operable tumours (T3 by the current TNM classification) were also included. The initial reports from these series concentrated on the objective response rates, and the adequacy of local control following a combination of chemotherapy, radiotherapy and surgery, including breast conservation. Survival has frequently been longer than that seen with historical controls, but better data are provided by the few comparative studies available.

	Treatment	No.	Resp	MS	Surv
(De Lena *et al:* 1978)	ST+RT	72	64%	30	20%
(De Lena *et al:* 1981)	ST+RT+ST	126	75%	42	36%
(Valagussa *et al:* 1983)	ST+S+ST	79	82%	68	51%
(Hortobagyi *et al:* 1983)	ST+RT±S+ST	52	94%	64	55%
(Hortobagyi *et al:* 1988)	ST+RT+S+ST	174	96%	66	55%
(Pierce *et al:* 1992)	ST+RT+S+ST	107	92%	39	43%
(Jacquillat *et al:* 1989b)	ST+RT+ST	98	91%	NR	64%
(Schaake-Koning *et al:* 1985)	±ST+RT+ST	73	71%	46	37%
(Schwartz *et al:* 1994)	ST+S+RT+ST	189	84%	NR	69%
(Campbell *et al:* 1988)	ST+S+RT	37	61%	24	50%(2yrs)
(Conte *et al:* 1987)	ST+S+ST	39	72%	NR	60%(3yrs)
(Perloff *et al:* 1988)	ST±S±R+ST	113	81%	39	NA
(Jacquillat *et al:* 1989a)	ST+RT+ST	75	75%	NR	58%
(Cocconi *et al:* 1990)	ST+S+ST+RT	49	67%	60	49%
(Rubens *et al:* 1980)	ST+RT+ST	12	67%	36	50%(3yrs)
(Lopez *et al:* 1990)	ST+S+ST	17	76%	56	41%
(Lynch *et al:* 1989)	ST+S+RT+ST	26	46%	NR	77%(2yrs)
(Rainer: 1993)	ST+S+ST±RT				
(Shanta and Krishnamurthi: 1991)	ST+RT+S	211			61%
(Frank *et al:* 1992)	S+RT+ST	113			54%
(Luboinski *et al:* 1991)	ST+S+ST	160			38%
(Heys *et al:* 1993)	ST+RT±S±ST	42	76%	NR	65%
(Balawajder *et al:* 1983)	ST+RT±S	53	NA	NA	42%

"±": allocation to study arms, ST: Systemic therapy; RT: radiotherapy; S: Surgery; NR: Not Reached, NA: Not available. Resp: proportion of responders, MS: Median survival in months, Surv: Proportion alive. Follow-up 5 years unless indicated in brackets

Table 2-1: Summary of studies using primary systemic therapy for locally advanced breast cancer. Only the relevant part of the study is quoted.

2.2.2.2 Comparisons with matched historical controls

In a comparative study 164 patients treated with radiotherapy and surgery alone were compared with 211 cases, treated during a later period with chemotherapy prior to radiotherapy and surgery. The five and ten year survival was better for the chemotherapy group, with 47% versus 61% at five years and 36% versus 44% at ten years (Shanta and Krishnamurthi: 1991).

2.2.2.3 Non-randomised matched controls

Two non-randomised studies with matched controls have also reported increased survival for patients receiving adjuvant therapy. In one study 47 patients having radiotherapy with or without mastectomy were compared with 53 patients who had been given induction chemotherapy. Mastectomy improved local control without changing the odds of survival, whereas chemotherapy resulted in an increased probability of survival at ten years (Balawajder *et al:* 1983). In another study 75 patients receiving different forms of radiotherapy alone were compared with 41 who had chemotherapy or hormonal manipulation following radiotherapy. More than half of the adjuvant group were disease free at four years, compared with less than one third of those who had received radiotherapy alone (Bruckman *et al:* 1979).

2.2.2.4 Randomised Trials

Three of five small randomised clinical trials comparing conventional or primary adjuvant systemic therapy against locoregional treatment alone have found a survival advantage for the systemically treated group. One trial of radiotherapy versus radiotherapy followed by adjuvant chemo/ or hormonal therapy containing a total of 87 patients, suggested significantly superior survival for patients receiving adjuvant treatment at a median follow-up of three years (Caceres *et al:* 1980). In another, 120 patients with large operable cancers (T3 N0-2 M0)

were randomised to post-mastectomy radiotherapy alone versus post-mastectomy chemotherapy, with and without radiotherapy (Grohn *et al:* 1984). At five year follow-up significantly greater numbers of patients receiving chemotherapy were still alive, with the best results obtained with combination of postoperative chemotherapy and radiotherapy (Klefstrom *et al:* 1987). A third randomised study allocated 209 patients to either receive mastectomy and radiotherapy (pre and postoperatively) alone, or to have pre and postoperative chemotherapy. Five year overall survival figures were significantly better for the chemotherapy group (Rainer: 1993).

Two randomised studies, both confined to patients with T4 cancers, however have failed to show any advantage for systemic therapy. In a study of 118 patients randomised to receive radiotherapy alone, or radiotherapy with preoperative, or postoperative chemo-hormonal adjuvant therapy, overall survival at a median follow-up of 66 months was identical for all groups at 37% (Schaake-Koning *et al:* 1985). The second study with 52 patients compared primary multi-agent chemotherapy followed by radiotherapy with radiotherapy alone. Actuarial survival at three years was identical for both groups, although patients given chemotherapy achieved a greater rate of full local control (Leonard *et al:* 1991).

In interpreting these studies it is important to note that the EBCTCG meta-analysis found that most randomised trials in early breast cancer were too small to be able to detect the advantage for systemic therapy with sufficient confidence, and that it was often those studies which detected an unusually high level of benefit which attained statistical significance (Early Breast Cancer Trialists' Collaborative Group. 1992). A similar situation is likely to exist with locally advanced breast cancer.

2.2.3 Studies designed to examine timing of systemic therapy

The timing of systemic treatment in relation to local therapy has been addressed in a number of small trials (Table 2-2). None have found primary systemic treatment to be inferior to treatment given after local therapy, and some have shown trends in favour of primary systemic

therapy. This coupled with the improvements in local control (Buzdar *et al:* 1993; Leonard *et al:* 1991) have made primary systemic therapy the treatment of choice for locally advanced breast cancer.

	Treatment	No.	Res	M S	Surv
(Olsen *et al:* 1986)	RT+ST	99		24	32%(4yrs)
	ST+RT+ST		76%	34	33%
(Schaake-Koning *et al:* 1985)	RT+ST	39		50	37%
	ST+RT+ST	34	71%	45	37%
(Rubens *et al:* 1980)	RT+ST	12		36	50%(3yrs)
	ST+RT+ST	12	50%	36	50%
(Lopez *et al:* 1990)	RT+ST	17	76%	15	6%
not randomised	ST+RT+ST	17	76%	56	41%

ST: Systemic therapy; RT: radiotherapy; S: Surgery; NR: Not Reached, NA: Not available. Resp: proportion of responders, MS: Median survival in months, Surv: Proportion alive. Follow-up 5 years unless indicated in brackets

Table 2-2: Randomised trials of primary locoregional therapy versus primary systemic treatment in locally advanced breast cancer

2.2.3.1.1 Main findings of primary systemic treatment studies

Three important points have emerged from treating locally advanced breast cancer with primary systemic therapy:

1. Tumour response to initial treatment correlates strongly with subsequent survival (Jacquillat *et al:* 1989b; Jacquillat *et al:* 1988b).

2. The best response rates are obtained with the least bulky tumours (Hortobagyi: 1990; Swain and Lippman: 1991).

3. Best survival figures are seen for patients with "operable" cancers (Pierce *et al:* 1992; Valagussa *et al:* 1990; Hortobagyi: 1994).

2.3 OPERABLE BREAST CANCER

The experience of using primary systemic treatment in locally advanced breast cancer provided strong evidence for the safety of the technique, both in terms of local control and survival (Singletary *et al:* 1992; Schwartz *et al:* 1994; Valagussa *et al:* 1990). This, combined with the observation that it is often the least bulky tumours which respond best to systemic therapy (Pierce *et al:* 1992; Hortobagyi: 1994; Valagussa *et al:* 1990) has been the starting point for attempts to extend the scope of this treatment to include women with earlier stages of the disease. With the proven efficacy of breast conservation (Fisher *et al:* 1989b; Veronesi *et al:* 1981b; Fisher *et al:* 1985b; Osteen and Smith: 1990b) patients with operable breast cancer can be surgically subdivided into those treatable by breast conservation and those requiring mastectomy. The latter group often have larger tumours with poor prognosis. Primary systemic treatment offers these women a chance to avoid mastectomy, and may improve their survival. These women have often been targeted in the studies of primary systemic treatment for breast cancer. Only studies which address the specific question of the efficacy of primary versus conventional systemic therapy are reviewed.

2.3.1 Sequential series

Primary systemic therapy has been used by the Milan group in patients with tumours over 3 cm in diameter (median 4.5 cm) since 1988 (Bonadonna *et al:* 1995; Bonadonna *et al:* 1993; Bonadonna *et al:* 1990; Bonadonna and Veronesi: 1991; Bonadonna *et al:* 1991). A total of 227 patients have been treated with cytotoxic chemotherapy using the CMF[1], FAC[2] and FEC[3] regimes. Tumour response was observed in 78% of patients. Complete pathological remission was seen in 3.5%, and disease progression in 2% of patients. The main objective of this study, which was to avoid mastectomy, was achieved in 201/227 patients with a local relapse rate at three years of 3.5%. Degree of response was found to be a predictor of relapse free survival,

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[1]CMF: Cyclophosphamide, Methotrexate and 5-Fluorouracil

[2]FAC: 5-Fluorouracil, Adriamycin (doxorubicin) and Cyclophosphamide

[3]FEC: 5-Fluorouracil, Epirubicin and Cyclophosphamide

with 52% of poor responders having relapsed at three years as compared with only 27% of responders (Bonadonna *et al:* 1993).

The French group, led by the late Claude Jacquillat, have reported the results of their programme of primary systemic treatment which has been running since 1980 (Jacquillat *et al:* 1991a; Jacquillat *et al:* 1990a; Jacquillat *et al:* 1989a; Jacquillat *et al:* 1989a; Baillet *et al:* 1989a; Jacquillat *et al:* 1988a). Their treatment programme includes patients with all stages of localised breast cancer, and is aimed at avoiding surgery altogether. Of the 250 patients whose treatment has been reported, 192 had operable breast cancer, and of these, 21 patients had small (T1) tumours. Patients were treated with cytotoxic chemotherapy with VTMF±A[1]. In addition 195 patients received tamoxifen. An overall pre-radiotherapy response rate of 75% was achieved with the best response (94%) in the smallest tumours. Response rates were significantly better in the subgroup given tamoxifen. Although the local recurrence rates were relatively high (13-19% according to stage), the overall survival figures were better than expected, with 80% of patients with node-positive operable disease alive at 5 years (Jacquillat *et al:* 1990). In a multivariate analysis of risk factors, initial tumour regression again emerged as an important predictor of final prognosis (Jacquillat *et al:* 1991b).

Calais and colleagues (1994) have reported the results of a series of 158 patients with large (mean tumour diameter: 5.6 cm) operable breast cancers treated with preoperative N/EVCF[2] regime. Clinical regression was achieved in over 60%, and was complete in 20%. Five year overall survival was 73.2% with responding patients surviving significantly longer than non-responding patients (Calais *et al:* 1994).

A series of 126 patients with all stages of operable breast cancer (94 were T2), treated by primary chemotherapy has been reported by Belembaogo and colleagues (1991). A response rate of 83% and a breast conservation rate of 85% was achieved. At a median follow-up of 30 months 7 patients (6%) had died (Belembaogo *et al:* 1992).

Ragaz and colleagues have reported a series of 43 patients with operable breast cancer treated with CMF (Ragaz *et al:* 1985). Survival at 2 years was 97%.

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[1]VTMF±A: Vinblastine, Thiotepa, Methotrexate and 5-Fluorouracil ± Adriamycin (doxorubicin)
[2]N/EVCF: Mitoxantrone or Epirubicin, Vindesin, Cyclophosphamide, and 5-Fluorouracil

Other studies in progress where no survival data has been reported include those by Sinn and colleagues (1994) who have observed clinical regression in 2/3 of 51 patients they treated with primary chemotherapy, and the sequential series of 40 patients with operable tumours over 3 cm reported by Lemaire and colleagues (1992) in whom half of the patients had a clinical response to chemotherapy.

2.3.2 Randomised Trials

The question of whether primary treatment can actually influence survival is currently being addressed by the NSABP[1] trial B-18 (Fisher and Wickerham: 1991). This is of a simple design, testing surgery followed by chemotherapy with doxorubicin and cyclophosphamide, against chemotherapy followed by surgery. All women aged over 50 will also receive tamoxifen. The results of this trial are awaited. The same question is being asked by the EORTC[2] 10902 trial of preoperative versus postoperative chemotherapy (van de Velde: 1993).

The Royal Marsden group have also been running a trial of pre and postoperative chemotherapy versus postoperative chemotherapy only. The trial includes 212 patients with tumours over 2 cm in diameter, 105 whom were randomised to receive primary systemic treatment. At 28 months follow-up the number of events have been too small for any conclusions about survival (Powles *et al:* 1995).

Two trials with published survival results, have indicated a benefit in favour of primary systemic treatment, although part of the advantage may be attributable to the more aggressive schedules used for primary therapy.

The trial by Scholl and colleagues included 390 evaluable patients 191 of whom had received primary FAC[3] chemotherapy (Scholl *et al:* 1994; Scholl *et al:* 1991; Scholl *et al:* 1991). Response rate was found to be significantly related to the actual drug dose given, and survival was better for responders compared with non-responders. At a median follow-up of 54 months

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[1]NSABP: National Surgical Adjuvant Breast Project
[2]EORTC: European Organisation for Research and Treatment of Cancer
[3]FAC: 5-Fluorouracil, Adriamycin (doxorubicin) and Cyclophosphamide

there was a survival advantage in favour of the primary systemic treatment group (Scholl *et al:* 1994).

In a second trial by Mauriac and colleagues (1991) 272 women with operable tumours of over 3 cm in maximum diameter were randomised to receive either 6 cycles of primary chemotherapy with EVM-MTV[1], or post-mastectomy chemotherapy to node-positive patients only. Node-negative patients were not given systemic treatment in the adjuvant arm of the study. One third of the 134 patients given primary treatment had complete tumour regression following chemotherapy, and a further third had partial responses. Oestrogen and progesterone receptor positive tumours were less likely to respond to cytotoxic chemotherapy. At a median follow-up of 34 months patients treated by primary systemic treatment had significantly better overall survival, although recurrence free survival was identical for both groups (Mauriac *et al:* 1991).

2.3.3 Application of Selective Primary Systemic Treatment

One of the important advantages offered by primary systemic treatment is the ability to use the observed tumour response to plan and modify treatment.

The Royal Marsden Group have used induction chemotherapy primarily as a method of treating a series of patients, the majority of whom had large tumours over 4 cm in diameter, with primary chemo and endocrine therapy (Smith *et al:* 1995; Smith *et al:* 1993; Mansi *et al:* 1989). Although their primary aim was to avoid mastectomy, the group has utilised the observed tumour response as a method of evaluating the effectiveness of different chemotherapy regimes. Thus an overall response rate of 69%, including 17% complete remission was improved to 98% (66% complete) with a regime including continuous infusion 5-fluorouracil (Smith *et al:* 1995).

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[1]EVM-MTV: Epirubicin, Vincristine, Methotrexate: 3 cycles followed by Mitomycin, Thiotepa and Vindesine: 3 cycles

2.3.4 Selective chemo-endocrine primary systemic treatment

2.3.4.1 Primary endocrine therapy

Systemic endocrine therapy has been generally neglected in trials of primary systemic treatment, where its use has usually been in conjunction with cytotoxics (Jacquillat *et al:* 1990), or following the completion of cytotoxic chemotherapy (Smith *et al:* 1993). Gazet and colleagues have used endocrine therapy for the treatment of locally advanced (Gazet *et al:* 1991) and early (Gazet *et al:* 1996) breast cancer. Response rates to endocrine therapy were found to be low for unselected patients (Gazet *et al:* 1991). When only patients with oestrogen receptor-rich tumours were given endocrine therapy over 40% responded, although the rate was still lower than the 60% achieved with cytotoxic chemotherapy (Gazet *et al:* 1996). Primary endocrine therapy has also been used for the treatment of postmenopausal patients by the Marsden group (Powles *et al:* 1995; Mansi *et al:* 1989).

2.3.5 The Edinburgh programme of selective chemo-endocrine therapy

2.3.5.1 Selection by response

The Edinburgh programme for primary systemic treatment was started in 1985. It is different from other series in that the main rationale was to use tumour response as a method of assessing the effectiveness of primary endocrine therapy and to base further treatment on the observed response (Kjellgren *et al:* 1989). In the initial stages of the programme endocrine therapy was used in all patients, with chemotherapy reserved for those whose tumours failed to respond. In the Scottish breast conservation trials, an upper limit of 4 cm was set for breast conservation (Stewart *et al:* 1989), and historically the programme was confined to patients with operable cancers over 4 cm in maximum diameter who were not suitable for the conservation trials. Endocrine therapy consisted of medical oophorectomy with goserelin for premenopausal patients and 4-hydroxy-androstenedione or tamoxifen for postmenopausal patients. Cytotoxic chemotherapy was given with cyclophosphamide, doxorubicin and vincristine, with prednisolone to protect the marrow (CHOP regime). Since the study of

response to treatment was one of the main aims of this study, tumour size was measured on a weekly basis after the start of the treatment, and response was defined as a consistent decrease in tumour size. No attempt at breast conservation was made following primary systemic therapy, the main outcome measure being survival.

2.3.5.2 Selection by oestrogen receptor levels

Of the first 43 unselected patients treated with endocrine therapy, 18 patients showed a response. The tumour progressed in 11 and was static in 14. Ten of the 11 progressing tumours had an oestrogen receptor (ER) level of less than 20 *f*mol/mg cytosol protein. All responding tumours had a level greater than this (Anderson *et al:* 1989). The protocol was therefore modified so as to give the low ER patients chemotherapy from the start.

2.3.5.3 Results of the initial series

In a sequential series, 88 patients were treated with the above protocol, including the 43 who were treated before the introduction of selection by oestrogen receptor status. Twenty four were given endocrine treatment only, 27 cytotoxics only and the remainder received endocrine treatment followed by chemotherapy. At the end of primary chemo-endocrine therapy 66 of the 88 patients achieved clinical response which was complete in 14 (16%) cases (Forrest and Anderson: 1991; Forrest *et al:* 1991; Anderson *et al:* 1991). At a median follow-up of 24 months 86% of the patients were alive (Anderson *et al:* 1991).

2.3.6 A randomised trial

The Edinburgh series has shown that the most appropriate adjuvant treatment for individual patients can be selected, by careful assessment and monitoring of tumours during primary systemic therapy. The approach offers an integrated treatment package for high risk operable breast cancer. The next section describes a randomised trial, started in 1990, and designed to compare this treatment package with what was considered to be best conventional therapy for breast cancer.

PART 2

RANDOMISED STUDIES

CHAPTER 3

3. Protocol for a Randomised Clinical Trial

3.1 AIMS AND OVERALL DESIGN

3.1.1 Aims

3.1.1.1 Primary aim

To assess the value of selected preoperative systemic therapy by comparing the local recurrence rate, distant disease free interval and survival of patients with large but operable breast cancers, randomised to treatment by either primary selected systemic therapy followed by mastectomy, or mastectomy and unselected adjuvant systemic therapy.

3.1.1.2 Subsidiary aims

To compare the impact of primary systemic treatment on psychological and surgical morbidity with that seen with conventional therapy

3.1.2 Design of trial

A randomised design without stratification was used. The overall scheme of the trial is represented in Figure 3-1.

3.1.2.1 Registration, stratification and randomisation

All eligible patients were registered and the reason why those not randomised for therapy within the trial recorded.

3.1.2.1.1 Randomisation procedure

Randomisation was performed at the Scottish Cancer Trials Office from a list of random numbers. Eligibility for the trial was rechecked by the office and the patient allocated to an

arm of the trial. Copies of registration details, investigations, follow-up details and pathology reports were collected by the trials office.

3.1.2.2 Modification of the protocol

On 30 April 1992, a modified protocol was implemented to allow patients with smaller tumours to be included in the study. The details of the original protocol were for the most part unchanged. In the account that follows the original protocol is described. Where relevant, details of the modified protocol are provided under separate headings in boxed paragraphs.

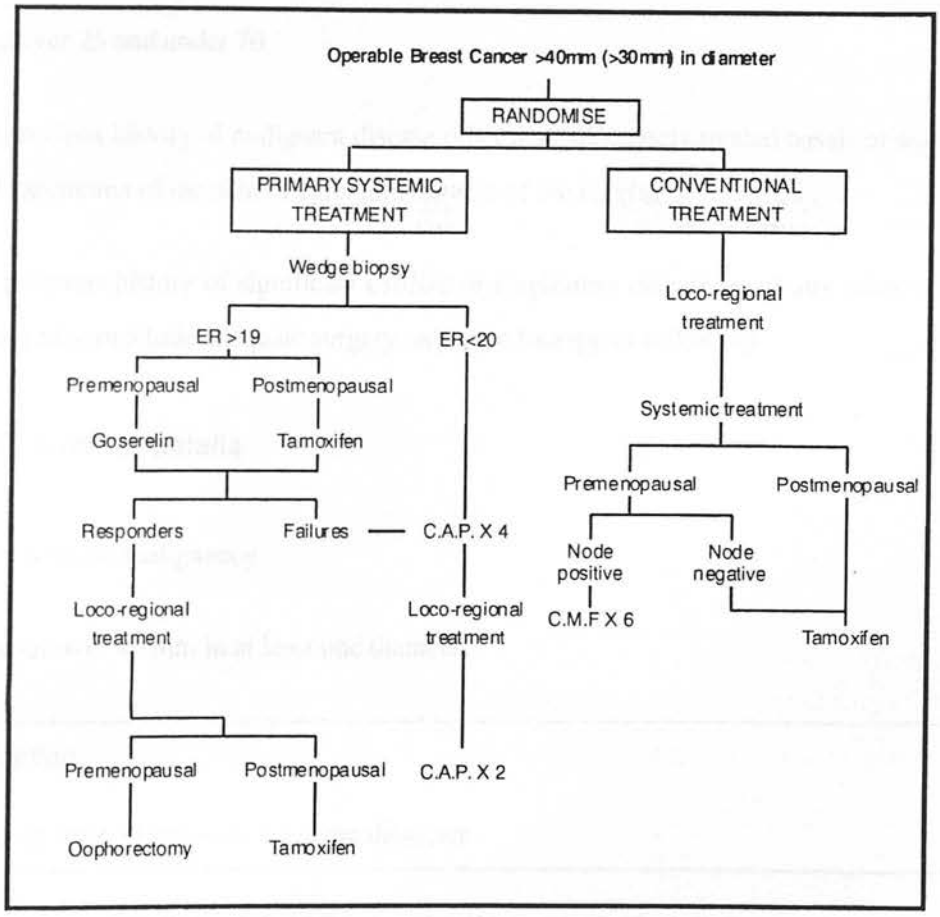

Figure 3-1: Scheme of the protocol for the randomised trial of conventional versus selective primary systemic treatment

3.2 PATIENT RECRUITMENT

3.2.1 Entrance criteria

The following criteria were used to define suitability for recruitment into the trial.

3.2.1.1 Personal history

1. Female patients only

2. Age over 25 and under 70

3. No previous history of malignant disease other than adequately treated basal- or squamous-cell carcinoma of the skin or carcinoma *in situ* of the cervix.

4. No previous history of significant cardiac or respiratory disease or of any other condition which may preclude adequate surgery, adjuvant therapy or follow-up.

3.2.1.2 Tumour details

1. Proven breast malignancy

2. Tumour over 40 mm in at least one diameter

Modification
2. Tumour over 30 mm in at least one diameter

3. Locally operable: T4 or N2 (TNM classification) tumours excluded

   a. No evidence of skin invasion by either tumour or lymph nodes

   b. No fixation to chest wall by tumour or nodes

c. No involvement of overlying skin by tumour or lymph nodes (Paget's disease of the nipple or tethering to the skin acceptable)

peau

d. No peu d' orange (small area directly over the tumour acceptable)

e. No inflammatory carcinomas

4. Tumour freely mobile within the breast with no clinically detectable fixation to pectoral muscle or fascia

5. No evidence of distant metastases

3.2.2 Exclusion criteria

1. Bilateral primary breast cancer

2. In-situ carcinoma only

3. Pregnancy, lactation or expressed intent for future pregnancy

4. High probability of inadequate follow-up (e.g.: overseas residents)

3.2.3 Pre-recruitment investigations

The following investigations were carried out in all potentially eligible patients to establish the diagnosis of invasive breast carcinoma and to exclude the presence of distant metastases prior to recruitment into the trial.

3.2.3.1 Diagnostic investigations

1. Fine needle aspiration cytology

2. Bilateral 2-view mammography

3.2.3.2 Investigations to exclude metastatic disease

3.2.3.2.1 Haematological investigations

Haematological investigations were carried out as part of routine clinical work up at the Department of Haematology, The Royal Infirmary, Edinburgh, EH3 9YW.

All patients had a full blood count and a measurement of erythrocyte sedimentation rate. Patients with abnormal results had bone marrow aspiration and trephine to exclude metastatic disease.

3.2.3.2.2 Biochemical investigations

Biochemical investigations were carried out as part of routine clinical work up at the Department of Clinical Chemistry, The Royal Infirmary, Edinburgh, EH3 9YW.

All patients had the following parameters measured: serum electrolytes, urea and creatinine, serum calcium and liver function tests. Abnormal results were appropriately investigated.

3.2.3.2.3 Radiological investigations

Radiological investigations were carried out under the care of Dr. J. S. Walsh, Consultant Radiologist, The Edinburgh Breast Unit, Western General Hospital, Edinburgh, EH4 2XU.

All patients underwent chest radiography, and a radio-isotope bone scan with radiographs of suspicious areas. Patients with abnormal liver function tests or other clinical indications of liver disease also had ultrasound scan or computerised tomography of the liver.

3.2.3.3 Determination of menopausal status

The menopausal status in patients who had previously had a hysterectomy without bilateral oophorectomy or whose last menstrual period was more than 3 months but less than 12 months earlier, was determined by the measurement of plasma oestradiol, oestrone, FSH and LH at the Regional Immunoassay Laboratories, The Royal Infirmary, Edinburgh, EH3 9YW.

Patients were classified as premenopausal or postmenopausal, according to the following definition:

3.2.3.3.1 Postmenopausal

Patients whose last menstrual period was at least 12 months previously or who had formerly had an unrelated bilateral oophorectomy or whose serum hormone levels indicated cessation of ovulation.

3.2.3.3.2 Premenopausal

Patients with a menstrual period within the preceding 3 months, or with hormone levels indicative of continuing ovulation.

3.2.3.4 Other investigations

3.2.3.4.1 Histological examinations

All examination and reporting of cytological and histological samples was carried out under the care of Dr. T. J. Anderson, Consultant Pathologist, The Edinburgh Breast Unit, Western General Hospital, Edinburgh, EH4 2XU.

3.2.3.4.2 Determination of oestrogen receptor levels

Oestrogen receptor determination was carried out by Dr. R. A. Hawkins at the Lister Research Laboratories, The Royal Infirmary, Edinburgh, EH3 9YW. Homogenised tissue was examined using a monoclonal antibody based enzyme immunoassay technique. The assay was obtained in a commercial kit (Abbot ER-EIA kit, Abbot diagnostics division, Abbot House, Norden Road, Maidenhead, Berkshire, SL6 4XF). The performance of the assay has been described previously both in this laboratory (Hawkins *et al:* 1987), and by other investigators (Jordan *et al:* 1986; Leclercq *et al:* 1986).

3.3 TRIAL OPTIONS

Patients were randomised to one of the following two options:

1. Primary systemic therapy followed by mastectomy

2. Conventional treatment with mastectomy followed by adjuvant systemic therapy

3.3.1 Primary systemic treatment

An incisional biopsy was performed to obtain tissue for measurement of oestrogen receptor (ER) levels. Systemic treatment was started depending on the tumour ER. Tumour regression was monitored and patients whose tumours failed to respond or progressed on endocrine therapy were given cytotoxic chemotherapy. Tumour progression on chemotherapy was managed by termination of systemic treatment and immediate mastectomy. Treatment details were as follows:

3.3.1.1 Initial biopsy

Local anaesthesia was used unless the patient requested general anaesthesia. A transverse incision placed directly over the tumour was deepened down to the surface of the tumour. A wedge of tumour was removed and sent fresh for histology and ER. The minimum acceptable quantity of tumour was removed, not exceeding 0.6 grams in total. The four quadrants of the tumour were marked using metal haemostatic clips before closure. Any excess tissue left over from ER or histological examination was stored in liquid nitrogen.

Patients who presented with obviously clinically malignant axillary lymph nodes, had a lymph node biopsy in preference to an incisional biopsy. A single enlarged node was removed through a "lazy S" incision.

3.3.1.2 Systemic therapy

This was started as soon as the invasive nature of the tumour had been established and ER values were available. Patients with ER equal or greater than 20 *f*mol/mg cytosol protein were initially treated by endocrine therapy.

All patients with ER less than 20 *f*mol/mg cytosol protein, and those patients whose tumours did not respond or progressed on endocrine treatment were given cytotoxic chemotherapy.

3.3.1.2.1 Endocrine therapy

Premenopausal patients were given a subcutaneous implant of goserelin, 3.6 mg, repeated once every 4 weeks for a total of 12 weeks. Those who responded were treated with bilateral oophorectomy at the time of mastectomy.

Postmenopausal patients were given tamoxifen 20 mg daily for 12 weeks, and those who responded were asked to continue tamoxifen after their mastectomy for five years or until recurrence, whichever was sooner.

3.3.1.2.2 Cytotoxic chemotherapy

Four cycles of treatment were given once every three weeks before mastectomy. Two further cycles were administered postoperatively, starting as soon as practicable after the mastectomy. Chemotherapy cycles were delayed by one week if the patients' white blood cell count remained less than 3 x 10^9/l when they were due for chemotherapy.

The following drugs were used for each cycle:

Cyclophosphamide	1g/m^2	single intravenous dose
Doxorubicin	50 mg/m^2	single intravenous dose
Prednisolone	40 mg	orally daily for five days

3.3.1.3 Measurement of response

3.3.1.3.1 Examination and tumour measurement

Patients were examined once a week for signs of disease progression in the breast or the axilla, and the tumour size was measured by callipers. Eight measurements were taken at 22.5° axes, and mean tumour diameter and tumour volume calculated. Initial tumour measurements were obtained at the time of entry into the study. Measurements were resumed four weeks after the initial tumour biopsy to avoid errors due to post-surgical swelling and continued for the duration of primary systemic treatment.

Patients also underwent weekly breast ultrasound examination and four weekly mammography during primary systemic treatment.

3.3.1.3.2 Response assessment

A probit plot was used to assess the distribution of values for "tumour volume". This was shown to be positively skewed and a logarithmic transformation of volume was used in assessment of response (section 10.3).

For each patient linear regression was used to assess the relationship between duration of primary systemic treatment as the independent variable against the natural logarithm of tumour volume as the dependent variable. Using the method of least squares, the slope and the intercept for the regression line were calculated, and the correlation coefficient determined. If the slope was negative and correlation significant at the 95% level, the tumour was classed as one which had responded to treatment.

3.3.1.4 Grading of tumour response

The degree of tumour response was assessed by calculating the proportional reduction in the product of two maximum tumour diameters, as defined by the criteria set out by the International Union Against Cancer (Hayward *et al:* 1977). Pre-treatment tumour diameter was estimated from a combination of clinical and radiological measurements, and post

treatment diameter was measured on the cut surface of resected tumour specimens as described in section 10.2.1.2.4.

3.3.1.4.1 Response categories

Six tumour response categories were defined as follows:

1. Complete pathological remission: no evidence of residual cancer on histological examination of the post treatment specimen

2. Complete clinical remission: no clinical or radiological evidence of residual tumour, but residual cancer cells identified in the tumour resection specimen

3. Clinical response: a reduction of 75% or more in the product of two maximum tumour diameters

4. Partial response: a reduction of 50% to 74% in the product of two maximum tumour diameters

5. Minimal response: a reduction of 25% to 49% in the product of two maximum tumour diameters

6. No response: a reduction of less than 25% in the product of two maximum tumour diameters

3.3.1.4.2 Tumour half life

A more detailed assessment of the way each tumour responded to treatment was obtained using the regression line fitted to the sequential tumour measurements. Time taken for the tumour to regress to half its original volume (tumour half life: $t_{\frac{1}{2}}$) was calculated from the slope of the regression line (m) using this equation: $t_{\frac{1}{2}} = \frac{\ln 2}{-m}$.

3.3.1.5 Locoregional Therapy

Modification

Suitable patients were allowed breast conservation as an option. The appropriate form of surgery and radiotherapy was decided before randomisation. The patients were assessed jointly by the responsible surgeon and radiation oncologist. A decision was made to treat the breast by mastectomy or by wide local excision of the tumour, depending on the clinical and mammographic appearance of the tumour, and taking into consideration patient preference. Following primary systemic treatment, if the tumour had regressed or was static, this original decision was adhered to regardless of the extent of tumour regression. If the tumour has progressed, the decision was revised according to the immediate preoperative findings.

3.3.1.5.1 Timing of locoregional therapy

Patients responding to primary endocrine treatment received locoregional therapy no later than 16 weeks after starting tamoxifen or goserelin.

Locoregional treatment followed the fourth cycle of cytotoxic chemotherapy, or an earlier cycle if it become clear that the tumour was failing to respond. Patients were allowed a recovery period of 3 weeks or until the white blood cell count was equal to, or greater than $3 \times 10^9/l$, whichever was later. Locoregional treatment took place within one week following this recovery period.

3.3.1.5.2 Surgical treatment

The breast was treated by total mastectomy in all patients. Skin margins were marked from the centre of any residual tumour mass. When a tumour was smaller than at presentation a margin equivalent to the original tumour radius plus 3 cm was required. If the tumour size had not changed or had increased, a 3 cm margin was allowed around the palpable tumour. Where achieving an adequate skin clearance precluded primary closure of the wound, a latissimus dorsi myocutaneous flap (LD flap) was used.

Modification

The breast was treated by wide local excision where appropriate. The breast was reassessed in the immediate preoperative period to confirm that breast conservation remained possible. The tumour was excised down to pectoral fascia, with a margin of normal breast tissue. When a tumour was smaller than at presentation the margin was planned according to the original size of the tumour. If the tumour size had not changed or had increased, the margin was planned around the palpable tumour.

The axilla was treated by a full level III axillary clearance.

All patients were offered primary breast reconstruction following mastectomy. A LD flap was used where this was needed to achieve skin closure, otherwise the patients were offered a subpectoral tissue expander.

The details of the mastectomy procedure are presented in section 8.2.3.

3.3.1.5.3 Radiotherapy

Patients with tumours which were clinically tethered to pectoral fascia or muscle were excluded from the trial. However if a tumour clinically judged to be free was found at surgery to be tethered to the pectoral fascia or muscle, breast reconstruction was not performed and radiotherapy was given to the skin flaps. Radiotherapy was also given if indicated from tumour histology.

Modification

Patients treated by wide local excision received postoperative radiotherapy to the breast.

In patients on endocrine treatment, radiotherapy was started as soon as practicable after surgery. In other patients, radiotherapy was delayed until after the completion of cytotoxic chemotherapy.

3.3.2 Conventional therapy

Conventional treatment consisted of primary locoregional treatment followed by adjuvant systemic therapy determined by the patient's menopausal status and axillary lymph node status.

3.3.2.1 Locoregional therapy

3.3.2.1.1 Confirmation of diagnosis

Prior to surgery, patients under the age of 50 received a core biopsy in addition to other diagnostic tests in order to confirm the presence of invasive malignancy. For patients over the age of 50 an unequivocal malignant report on the fine needle aspirate and on mammography were deemed adequate proof of malignancy.

Modification

Prior to surgery, patients under the age of 50 who required a mastectomy underwent a core biopsy in addition to other diagnostic tests in order to confirm the presence of invasive malignancy. For patients over the age of 50 or any patients being treated by breast conservation an unequivocal malignant report on the fine needle aspirate and on mammography were deemed adequate proof of malignancy.

3.3.2.1.2 Surgical treatment

A mastectomy and full level III axillary clearance was carried out as the initial treatment. The details of the operation and breast reconstruction were identical to that described for patients undergoing primary systemic treatment.

Modification

A mastectomy or a wide local excision was carried out along with a full level III axillary clearance as the initial treatment. The details of the operation and breast reconstruction were identical to that described for patients undergoing primary systemic treatment.

3.3.2.1.3 Radiotherapy

Indications for radiotherapy were as described for primary systemic treatment.

In endocrine treated patients radiotherapy was started as soon as practicable after surgery. Patients who required postoperative chemotherapy were started on radiotherapy after two cycles of chemotherapy had been administered. Chemotherapy was resumed 3 weeks after radiotherapy had been completed.

3.3.2.2 Adjuvant systemic treatment

3.3.2.2.1 Cytotoxic chemotherapy

Premenopausal patients who had one or more involved axillary lymph nodes were treated with cytotoxic chemotherapy. Six cycles of treatment were given once every three weeks. Chemotherapy cycles were delayed by one week if the patients' white blood cell count remained less than 3 x 10^9/l when they were due for chemotherapy.

The following drugs were used:

Cyclophosphamide	600 mg/m^2	Single intravenous dose
Methotrexate	50 mg/m^2	Single intravenous dose
5-fluorouracil	600 mg/m^2	Single intravenous dose

3.3.2.2.2 Endocrine therapy

Premenopausal patients with no axillary lymph node involvement and all postmenopausal patients regardless of axillary nodal status were treated with adjuvant tamoxifen 20 mg daily for 5 years or until first recurrence, whichever was sooner.

3.4 TREATMENT RELATED TOXICITY

3.4.1 Endocrine treatment

Any side effects reported by patients on endocrine treatment were recorded. Complications directly relating to surgical oophorectomy were also recorded.

3.4.2 Cytotoxic chemotherapy

Toxicity relating to cytotoxic chemotherapy was divided into four main categories as follows:

1. Gastrointestinal (GI) disturbances in the form of nausea and diarrhoea

2. Inflammation of mucous membranes (mucositis) including conjunctivitis

3. Alopecia

4. Myelosuppression

3.4.2.1 Grading of toxicity

Toxicity was recorded at the time of administering each cycle of chemotherapy on a scale of 0 to 3, defined as follows:

0: No manifestation, or very minor lasting less than 12 hours

1: Mild, lasting less than 48 hours

2: Severe side effects lasting up to 12 hours, moderate severity lasting up to 48 hours, or mild side effects lasting over 48 hours

3: Severe side effects lasting over 12 hours

3.4.2.2 Analysis of results

On completion of treatment, the mean score over the course of 6 cycles was calculated to obtain an average side effects score for the individual patient.

3.4.2.2.1 Dose intensity

Prolonged neutropenia was dealt with by reduction in the dose of cyclophosphamide and lengthening of the interval between chemotherapy cycles, resulting in an overall reduction in dose intensity. Actual dose intensity as a percentage of planned dose intensity was calculated and compared.

3.5 FOLLOW-UP AND ANALYSIS

3.5.1 Follow-up

Patients were seen at regular intervals during their breast cancer treatment as dictated by the requirements of specific treatment regimes.

3.5.1.1 Discharge to follow-up

Patients were discharged to follow-up once all cancer related treatment had been completed. For patients receiving cytotoxic chemotherapy this was when the patient had fully recovered from any immediate side effects of their final cycle of chemotherapy. For patients on endocrine treatment this was regarded as the time when the patient was first started on long term tamoxifen, or when the patient had fully recovered from any complications of surgery, whichever was later. If radiotherapy was the final adjuvant treatment, time of discharge was regarded as the time of full recovery from the effects of radiotherapy. Hospital visits for breast reconstruction were not regarded as cancer treatment.

3.5.1.2 Long term follow-up

Patients were reviewed once every three months for the first 2 years, once every four months in the third year, once every six months for the fourth and the fifth years and annually thereafter. All patients received annual two view mammograms of the untreated breast.

3.5.1.3 Treatment of recurrence

The choice of further treatment once a recurrence was detected was left entirely open to the discretion of the surgeons and oncologists involved in treatment at the time of recurrence.

3.5.2 Projected trial statistics

Projected trial statistics were determined in conjunction with Dr. R. J. Prescott, Department of Medical Statistics, University of Edinburgh Medical School, Teviot Place, Edinburgh, EH8 9AG.

3.5.2.1 Trial power

Based on previous studies (section 2.3), it was deemed reasonable to expect an overall survival of 50% at 5 years for conventionally treated patients. An absolute improvement in survival of the order of 15% was assumed to be the minimum desirable improvement for patients treated by primary systemic therapy.

At this level of risk reduction, it was calculated that 163 patients were needed in each arm of the trial in order to provide 75% power to detect the difference at the 5% level of statistical significance. Based on previous experience of the Edinburgh Breast Unit, it was estimated that this number could have been recruited within 5 years.

3.5.2.2 Interim analysis

Distant disease free survival and overall survival were analysed at six monthly intervals. A statistically significant survival difference at the 1% level was regarded as the threshold for the termination of the trial.

3.5.3 Ethical considerations

The details of the protocol and the ramifications of all possible treatments were explained to eligible patients at two separate interviews conducted jointly by a nurse counsellor and a doctor. Patients were required to give written consent before being randomised to an arm of the trial.

The protocol was approved by the "Medicine/ clinical oncology ethics of medical research sub-committee" of the Lothian Health Board.

Modification

The modified protocol was independently approved by the "Medicine/ clinical oncology ethics of medical research sub-committee" of the Lothian Health Board.

3.5.4 Analysis of results

All analyses were performed using the statistical software package Stata 4.0 for Windows, Stata Corporation, 702 University Drive East, College Station, Texas 77840 USA.

3.5.4.1 The first part of the trial

Data for the trial are presented on the basis of intention to treat and actual treatments received. Details of statistical methods are specified within the text of the results section.

3.5.4.1.1 Survival analysis

Life tables were used to plot Kaplan-Meier survival curves. The hazard ratio, and its significance were calculated using univariate Cox's regression (Cox: 1972). The results were analysed on the basis of intention to treat and separately on the basis of actual treatments given. Survival outcome was death from all causes.

3.5.4.2 Results including patients treated in the modified protocol

The results of the entire trial, including all patients recruited after the protocol was modified are reported separately. Patient and tumour characteristics are described in so far as is relevant to the interpretation of the survival results. Detailed toxicity data, and response data for patients in the primary systemic treatment arm are not reported.

3.5.4.3 Assessment of prognostic indicators

Prognostic factors were analysed on all trial patients including those treated after the modification of the trial protocol.

Cox's proportional hazard model (Cox: 1972) was used to assess the importance of tumour and patient characteristics in predicting overall survival. For the purpose of analysing prognostic indicators, only deaths from breast cancer were considered. Data from patients dying of other conditions were treated as censored observations. The following factors were considered in the analysis:

1. Age at randomisation

2. Clinical tumour diameter at the time of diagnosis

3. Actual number of involved axillary lymph nodes

4. Initial tumour oestrogen receptor levels, normalised by log transformation

5. Initial tumour differentiation, classed as poor, moderate or well

6. Actual treatment received classed as Primary systemic or Conventional

Factors which proved significant with $p<0.15$ on univariate analysis were included in the multivariate model.

Significant prognostic factors were further analysed by dividing them into categorical variables, and plotting Kaplan-Meier survival curves for each category. Details are described in the results section.

3.5.4.3.1 The significance of the ERICA assay

3.5.4.3.1.1 Methods

As part of an ongoing investigation, a portion of cells from the initial diagnostic fine needle aspirate were assayed for oestrogen receptors using an ϕEstrogen Receptor Immuno-Cytochemical Assay (ERICA). Assays were performed by Kathryn Sangster and Dr R. A. Hawkins at the Lister Research Laboratories, The Royal Infirmary, Edinburgh, EH3 9YW. A commercial kit was used for the assays (Abbot ER-ICA kit, Abbot diagnostics division, Abbot House, Norden Road, Maidenhead, Berkshire, SL6 4XF). The details of the assay and its characteristics have previously been reported by Dr Hawkins' group (Hawkins *et al:* 1988;

Hawkins *et al:* 1987), and by other investigators (Flowers *et al:* 1986; Cavailles *et al:* 1987; Weintraub *et al:* 1987; McClelland *et al:* 1987).

3.5.4.3.1.2 Analysis

The results were reported as the proportion of cells staining for ER. Patients had been classed as ER positive or ER negative according to the initial oestrogen receptor content of their tumour as determined by the enzyme immuno-assay. This was set as the standard against which ERICA measurements were compared.

To determine the relationship between ERICA values and patient oestrogen receptor status, the patients were categorised to ERICA negative and ERICA positive using a series of cut off values. The number of ER negative and ER positive patients correctly identified by the ERICA negative and ERICA positive categories were determined and the "positive predictive value[1]" for each cut off level calculated. In addition the relative overall survival for the two ERICA categories was calculated for each cut off level using Cox's regression.

The following cut off values were investigated: 0/1, 1/2, 2/3, 3/4, 4/5, 7/8, 10/11, 14/15, 19/20, 29/30, 39/40, 49/50.

3.5.5 Results specific to the primary systemic treatment group

3.5.5.1 Post treatment prognostic indicators

Cox's proportional hazard model (Cox: 1972) was used to assess the importance of post treatment tumour characteristics in predicting overall survival. Only deaths from breast cancer were considered. The following tumour factors, assessed on specimens obtained after the completion of primary systemic therapy, were studied:

1. Actual number of involved axillary lymph nodes without consideration of any pre-treatment information on lymph nodes

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[1] Positive Predictive value = [(Number identified as POSITIVE by both ER and ERICA)+(Number identified as NEGATIVE by both ER and ERICA)]/ (total number of patients)

2. Post treatment tumour oestrogen receptor levels, normalised by log transformation

3. Post treatment tumour differentiation, classed as poor, moderate or well

Factors which proved significant with a probability of <0.15 on univariate analysis were included in the multivariate model.

Significant prognostic factors were further analysed by dividing them into categorical variables, and plotting Kaplan-Meier survival curves for each category. Details are described in the results section.

3.5.5.2 Tumour response and survival

The patients were divided into "fast responders" and "slow responders" by comparing individual tumour half lives with the median value for tumour half life. Patterns of response were found to be different for endocrine and cytotoxic treatments. The fast and the slow responders for the two treatment categories were therefore determined separately.

3.5.5.2.1 Categorisation of non-responders

Patients who failed to respond to endocrine treatment and subsequently received cytotoxic chemotherapy were considered along with chemotherapy only patients. Tumour behaviour during the endocrine phase of treatment was discounted for this group of patients and tumour half life based on regression during the cytotoxic therapy phase.

Patients who failed to respond to cytotoxic chemotherapy, (i.e.: had a regression slope which was not significantly different from zero) by definition had a tumour half life of "infinity".

3.5.5.2.2 Allocation to response categories

The median half life for each treatment category was determined. Patients with tumour half lives shorter than or equal to the median half life for their treatment category were classed as "fast responders" while those with longer half lives were classed "slow responders".

3.5.5.2.3 Analysis of survival in relation to response

Cox's proportional hazard model was used to assess the influence of tumour response in relation to distant disease free and overall survival. The following patient characteristics were considered:

1. Menopausal status, classed as pre or postmenopausal

2. Mean tumour diameter at the time of diagnosis

3. Axillary nodal involvement, classed as node-positive or node-negative

4. Oestrogen receptor status, classed as ER<20 and ER>19

5. Tumour differentiation, classed as poor, moderate or well differentiated

6. Tumour response categorised as "slow" or "fast"

Factors which on univariate analysis where significant with $p<0.15$ were included in the multivariate model.

3.5.5.3 Relationship between tumour characteristics and the rate of response

The distribution of tumour half lives was examined using a probit plot and was found to be near normal. A model was constructed using multiple regression analysis to assess the contribution of patient and tumour characteristics to the speed of response as measured by tumour half life. The following characteristics were examined:

1. Menopausal status, classed as pre or postmenopausal

2. Tumour diameter at the time of diagnosis

3. The natural logarithm of the actual oestrogen receptor levels

4. Tumour differentiation, classes as poor, moderate or well differentiated

Since axillary nodal status was determined following the completion of primary systemic treatment, it could potentially have been affected by regression and it was not entered into the model.

CHAPTER 4

4. Results of the Main Trial

4.1 RESULTS RELATING TO THE FIRST PART OF THE TRIAL

4.1.1 Recruitment and compliance

4.1.1.1 Recruitment

The first patient was recruited into the pilot study on 31 January 1990. The pilot was closed on 29 April 1992. In the 27 month period of the study 559 breast cancer patients were treated at the Edinburgh Breast Unit, 86 of whom fulfilled the criteria for entry into the trial. One patient with mental disability was deemed unable to provide informed consent and was not approached.

Eighty five patients were counselled regarding the trial. Six patients refused to enter the trial and were treated in a conventional manner. A total of 79 patients were recruited into the study and randomised in accordance with trial protocol.

4.1.1.2 Treatment allocation and compliance

Thirty nine patients were allocated to the conventional arm of the trial and 40 women were randomised to receive primary systemic treatment (PST).

4.1.1.2.1 Major protocol violations

There were 5 major protocol violations with the trial as follows.

4.1.1.2.1.1 Primary systemic treatment

There were 3 protocol violations in this arm of the trial. Two patients who were initially allocated to receive PST later requested conventional therapy. One of these patients had made her request after undergoing a wedge biopsy, and was given 3 weeks of tamoxifen before mastectomy. In a third patient initial wedge biopsy failed to confirm the presence of invasive

carcinoma, and a complete tumour excision was carried out to establish the diagnosis. This patient was subsequently treated conventionally.

4.1.1.2.1.2 Conventional treatment

There were two major protocol violations in this arm. One patient requested and after discussion with the local ethics committee, she was treated according to the primary systemic therapy protocol by initial chemotherapy. This patient was put on long term tamoxifen following mastectomy.

The second patient was a 64 year old postmenopausal woman who was treated by initial mastectomy. Her mastectomy specimen contained ductal carcinoma *in situ* only with no evidence of invasive disease. This patient has not been given any form of systemic treatment and has been excluded from further analysis. She remains alive and well after 56 months of follow-up.

4.1.1.2.2 Minor protocol violations

There were 4 minor protocol violations two of which occurred in patients who already had major protocol violations as explained above.

The third patient was recruited into the PST arm of the study having been started on goserelin 3 weeks earlier for a gynaecological condition. Goserelin was subsequently continued when it was shown to have been the appropriate treatment for the patient's breast cancer. The final patient was premenopausal and was treated by chemotherapy in the PST arm but failed to respond to treatment. She was put on long term tamoxifen postoperatively.

4.1.1.3 Reporting of results

Seventy eight patients were eligible for analysis. Forty were allocated to PST and 38 to conventional treatment. 40 were treated conventionally and 38 by PST.

4.1.2 Patient and tumour characteristics

4.1.2.1 Patient characteristics

4.1.2.1.1 Age

The cohort of 78 patients had a mean age of 51 years (range 31-69). The age distribution between the two arms by intention to treat and by actual treatments are shown in Table 4-1. There was no significant difference in age distribution between the two arms of the trial.

	Conventional	PST	t=	p=
By intention to treat	50.9 (31-69)	51.1 (33-69)	-0.09	0.93
By actual treatments given	51.4 (31-69)	50.6 (33-69)	0.35	0.73

Mean age and age range. Student's t-test with 76 degrees of freedom

Table 4-1: Age distribution of patients in the first part of the trial

4.1.2.1.2 Menopausal status

Menopausal status was clear on the basis of history alone in 75 patients, and was determined from serum hormone estimates in a further 3. There were 41 premenopausal patients and 37 postmenopausal patients in the entire cohort. The numbers of pre and postmenopausal patients in each arm of the study are shown in Table 4-2. The distribution of pre and postmenopausal patients between the two treatment groups was not significantly different.

	Conventional		PST		
	Pre	Post	Pre	Post	p=
By intention to treat	19	19	22	18	0.821
By actual treatments given	19	21	22	16	0.375

Proportions compared using Fisher's exact test

Table 4-2: Menopausal status for patients in the first part of the trial

4.1.2.2 Tumour characteristics

4.1.2.2.1 Tumour diameter

The distribution of tumour size by intention to treat is shown in Figure 4-1. The median tumour diameter for the entire cohort of patients was 45 mm, with a range of 41 to 85 mm.

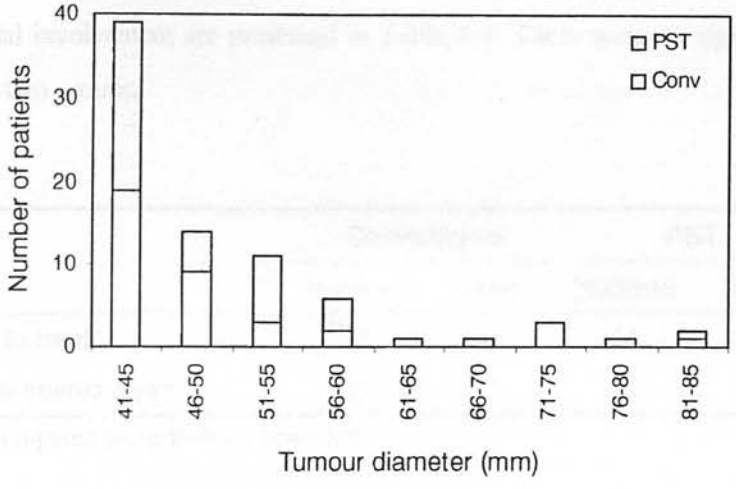

Figure 4-1: Tumour size distribution for patients in the first part of the trial

The median and range of tumour sizes for patients in each arm of the trial are presented in Table 4-3. There were no significant differences.

	Conventional	PST	z=	p=
By intention to treat	46 (41-85)	46 (41-83)	0.55	0.58
By actual treatments given	47 (41-85)	45 (41-83)	-0.74	0.46

Median and range of tumour sizes. Mann-Whitney U test

Table 4-3: Tumour size for patients in the first part of the trial

4.1.2.2.2 Axillary lymph node involvement

Following primary axillary clearance a median of 17 (range 3-33) nodes were recovered. This was not significantly different from the median of 14 (range 4-29) nodes recovered when axillary clearance followed primary systemic treatment (z= -0.84, p= 0.40, Mann-Whitney U test). Five patients treated by PST had histological evidence of axillary nodal metastases prior to start of treatment. On subsequent axillary clearance, two of these patients had no residual axillary involvement. These two patients were nevertheless classed as "node-positive".

In total, 46 patients had evidence of axillary metastases. The proportion of patients with any axillary nodal involvement are presented in Table 4-4. There were no significant differences between the two groups.

	Conventional		PST		
	Involved	Free	Involved	Free	p=
By intention to treat	23	15	23	17	0.821
By actual treatments given	23	17	23	15	0.821

Proportions compared using Fisher's exact test

Table 4-4: Number of patients with axillary metastases

The median and range of the number of involved axillary nodes for patients with involved axillae are presented in Table 4-5. Patients treated conventionally had a significantly greater number of involved axillary nodes compared with patients treated with PST.

	Conventional	PST	z=	p=
By intention to treat	8 (1-23)	3 (1-13)	-2.41	0.016
By actual treatments given	7 (1-23)	3 (1-13)	-2.34	0.019

Median and range of the numbers of involved nodes. Mann-Whitney U test

Table 4-5: Number of involved nodes amongst node-positive patients

4.1.2.2.3 Oestrogen receptors

Initial oestrogen receptor (ER) estimates were available on tumour samples from all 78 patients, obtained at mastectomy or by incisional biopsy. The median and range of ER values are presented in Table 4-6. There was no significant difference in initial ER values between the two arms of the trial.

	Conventional	PST	z=	p=
By intention to treat	22 (2-233)	19.5 (0-552)	-0.23	0.814
By actual treatments given	22 (2-233)	19.5 (0-522)	0.27	0.787

Median and range of initial ER values in fmol/mg cytosol protein. Mann-Whitney U test

Table 4-6: Initial oestrogen receptor values

The distribution of ER values by treatment intention is shown in Figure 4-2.

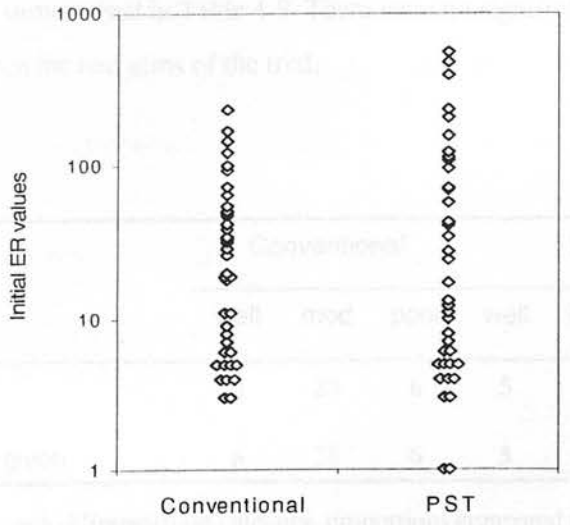

Figure 4-2: Distribution of tumour ER values.

4.1.2.2.4 *Tumour histological type and grade*

The number of patients with ductal and lobular cancers, and with special types are summarised in Table 4-7. The proportions of different type of cancer were similar for the two groups.

	Conventional	PST	p=
Ductal carcinoma, no special type	31	33	
Ductal carcinoma, special types	1	3	0.604
Lobular carcinoma	6	4	

Proportions compared using Fisher's exact test

Table 4-7: Tumour histological types in the first part of the trial

Tumour differentiation was recorded as "poor", "moderate" or "well". The number of patients in each category are summarised in Table 4-8. There were no significant differences in tumour differentiation between the two arms of the trial.

	Conventional			PST			
	well	mod	poor	well	mod	poor	p=
By intention to treat	6	26	6	5	29	6	0.938
By actual treatment given	6	28	6	5	27	6	1.000

Number of patients in each differentiation category. proportions compared using Fisher's exact test

Table 4-8: Distribution of tumour differentiation categories

4.1.3 Treatments and toxicity

4.1.3.1 Delay to start of treatment

For patients treated conventionally, treatment was regarded to have been started on the date the patient underwent a mastectomy. In the primary systemic treatment group start of treatment was recorded as the date the first dose of appropriate drug was administered. The requirement for initial incisional biopsy in the primary systemic treatment group did not significantly delay start of treatment compared with conventionally treated patients. The biopsy was performed a median of one day (range: 0-11) after randomisation. Treatment was started a median of 13 days following randomisation to conventional treatment (range 1-35), compared with a median of 14 days (range: 7-34) following randomisation to primary systemic treatment (χ^2=1.23, p=0.27 Log rank test).

4.1.3.2 Delay to the start of systemic treatment

Delay in starting systemic treatment can in theory have a deleterious effect on survival. An important objective in using primary systemic treatment is to minimise this delay. Every effort was made to start systemic therapy in conventionally treated patients as soon as possible following mastectomy.

The median time to the start of systemic treatment was 14 days (range: 7-34) for the patients treated by primary systemic therapy, significantly shorter than the median of 35 days (range: 14-85) for conventional treatment χ^2=37, p<0.0001, Log rank test).

4.1.3.3 Overall duration of hospital cancer treatment

Patients were discharged to long term follow-up when all cancer treatment was completed, and any associated complications dealt with. Additional hospital attendance for breast reconstruction was not included in the overall duration of hospital cancer treatment.

Duration of treatment for each group is shown in Table 4-9. Overall, primary systemic treatment was significantly more protracted than conventional therapy. This was particularly

noticeable in patients receiving primary endocrine treatment. When cytotoxic chemotherapy was the treatment given, overall duration of treatment for conventional and primary systemic treatment was similar.

	Conventional	PST	χ^2=	p=
All patients (n=78)	41 (21-262)	168 (96-271)	8.7	0.003
Cytotoxic treatment only (n=34)	184 (91-262)	176 (96-227)	0.67	0.41
Endocrine treatment only (n=44)	35 (21-89)	140 (112-271)	32.3	0.0001

Treatment duration in days: median (range), compared using log-rank test

Table 4-9: Duration of cancer treatment

4.1.3.4 Actual treatments received

4.1.3.4.1 Conventional treatment group

Of the 39 patients randomised to this arm of the trial 37 received postoperative adjuvant systemic treatment. Treatment details appear in Table 4-10. One patient with ductal carcinoma *in situ* only, was not systemically treated, and a second patient was treated using primary chemotherapy with the CAP regime, followed by postoperative adjuvant tamoxifen.

	Premenopausal	Postmenopausal	Total
Tamoxifen	3	19	22
CMF chemotherapy	15	0	15
None	*1*	*0*	*1*
Primary CAP chemo	*1*	*0*	*1*
Total number of patients	20	19	39

Number of patients given each treatment. Italics indicate protocol violations.

Table 4-10: Details of adjuvant systemic treatment received by patients in the conventional arm of the study

4.1.3.4.2 Primary systemic treatment

Thirty seven of the 40 patients randomised to this arm received preoperative systemic therapy. Treatment details are listed in Table 4-11. Three patients who were treated by conventional adjuvant systemic treatment received postoperative tamoxifen.

	Premenopausal	Postmenopausal	Total
Primary tamoxifen alone	0	7	7
Primary goserelin alone	7	0	7
Primary CAP alone	12	6	18
Failed tamoxifen followed by CAP	0	3	3
Failed goserelin followed by CAP	2	0	2
conventional tamoxifen	*1*	*2*	*3*
Total number of patients	22	18	40

Number of patients given each treatment. Italics indicate protocol violations.

Table 4-11: Details of primary systemic treatment

4.1.3.4.3 Treatment differences

Overall, systemic treatment was administered to 40 patients according to the conventional treatment protocol and to 38 patients according to the protocol for primary systemic treatment. Patients treated according to the primary systemic treatment protocol were significantly more likely to receive cytotoxic chemotherapy compared with conventionally treated patients: 15 of the conventionally treated patients and 24 patients given primary systemic treatment received cytotoxic chemotherapy (p=0.025, Fisher's exact test). This difference was accounted for by the provision of cytotoxic chemotherapy for some postmenopausal patients in the primary systemic treatment protocol. None of the 21 conventionally treated postmenopausal patients received cytotoxic chemotherapy compared with 9 of the 16 postmenopausal patients completing primary systemic treatment (p=0.000, Fisher's exact test).

4.1.3.5 Treatment related toxicity

4.1.3.5.1 Endocrine treatment

Endocrine treatment was well tolerated with minimal associated morbidity.

4.1.3.5.1.1 Tamoxifen

Thirty five patients received tamoxifen. Two of 3 premenopausal patients and one postmenopausal patient experienced menopausal symptoms with tamoxifen. Treatment was temporarily discontinued in one postmenopausal patient because of a transient rash. None of the patients experienced serious side effects.

4.1.3.5.1.2 Goserelin and oophorectomy

Nine patients received goserelin. All experienced significant menopausal symptoms, and 1 complained of problems with the implantation site. Seven patients subsequently had an oophorectomy. None experienced significant morbidity in relation to the oophorectomy which was performed at the same time as the mastectomy.

4.1.3.5.2 Cytotoxic chemotherapy

All patients receiving cytotoxic chemotherapy experienced significant toxicity. In particular all patients developed myelosuppression following each cycle of chemotherapy. This was generally mild and always resolved but was the main reason for dose reduction or delay in treatment resulting in reduced dose intensity of chemotherapy.

4.1.3.5.2.1 Comparison between toxicity of CAP and CMF regimes

Fifteen patients were treated with CMF as compared with 24 who received CAP. Patients treated with CAP had a median age of 49.5 (range: 33-69), significantly older than the median age of 44 (range: 31-50) for those patients given CMF (p=0.025, Mann-Whitney U test).

Median toxicity scores and the proportion of planned dose intensity are summarised in Table 4-12. Prolonged neutropenia was less frequent with the CAP regime, and 18 (75%) of 24

patients received 90% or more of the full planned dose of CAP in the allotted time compared with 5 (33%) of 15 patients who were given CMF. However nausea and mucositis were more common with CAP. Total alopecia was universal in patients given CAP, whereas only one patient in the CMF group lost all hair and four others experienced minor degrees of hair loss.

	CAP (n=24)	CMF (n=15)	z=	p=
GI symptoms	1.55 (0-3)	1.0 (0-3)	2.23	0.02
Mucositis	0.5 (0-2)	0 (0-1.6)	1.19	0.23
Alopecia	3.0 (3)	0 (0-3)	5.70	0.0001
% Planned dose intensity	100 (83-100)	83 (68-100)	2.58	0.01

Median (range) of toxicity grades. Values compared using Mann Whitney U test

Table 4-12: Severity of side effects produced by the CAP and CMF regimes

4.1.4 Follow-up and survival

The main outcome measure for this trial was overall survival. The survival results are presented in this section. Kaplan-Meier survival curves are presented along with the text. Life tables relating to each survival curve are provided in the appendix. The reference to the relevant life table is given in the text.

4.1.4.1 Entire cohort of patients

The cohort of 78 patients have been followed up for a median of 65 months from the time of entry until the time of analysis (range: 51 to 77 months). The median follow-up until death or censoring has been 57 months (range: 6-77). All patients have been seen according to protocol, and there have been no loses to follow-up.

4.1.4.1.1 Local recurrence

Four patients have been treated for locoregional recurrence. All patients had been treated in a conventional manner by initial surgery. One had been randomised to primary systemic treatment, but received an initial mastectomy, because of difficulty in establishing diagnosis.

4.1.4.1.2 Systemic recurrence

There have been 36 systemic recurrences of breast cancer amongst the 78 patients treated within the trial. The Kaplan-Meier curve for distant disease free survival for the entire cohort is represented in Figure 4-3 (Table 14-1).

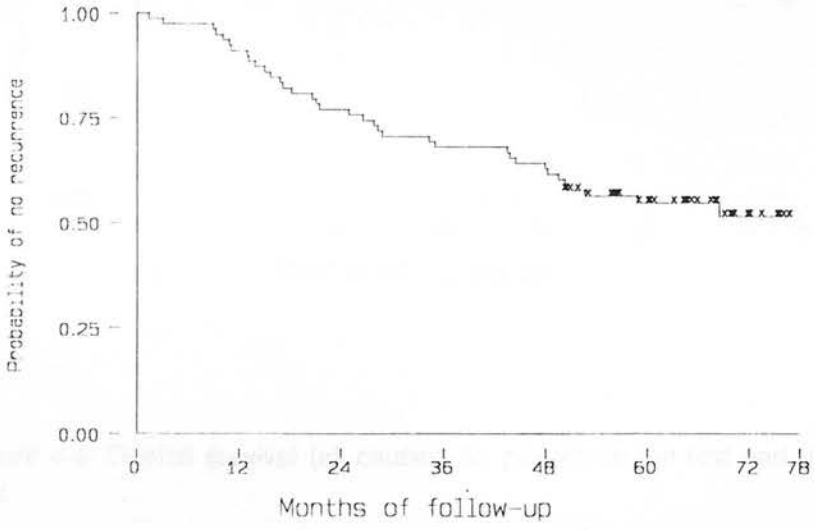

Figure 4-3: Distant disease free survival for patients in the first part of the trial

4.1.4.1.3 Deaths

There have been 33 deaths in the entire cohort of 78 patients. Thirty one patients died from metastatic breast cancer.

Two patients were free of breast cancer at the time of death. One died as a result of acute myocardial infarction. The second patient died as a result of a mixed mesodermal tumour of myometrial origin, disseminated to the peritoneal cavity.

The Kaplan-Meier all cause overall survival curve is shown in Figure 4-4 (Table 14-2).

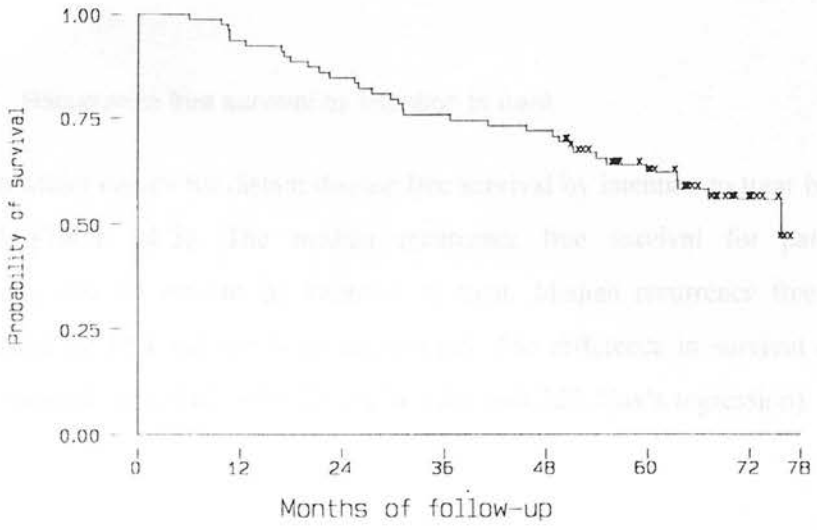

Figure 4-4: Overall survival (all causes) for patients in the first part of the trial

4.1.4.2 Survival by treatment category

4.1.4.2.1 Systemic recurrence

The number of patients suffering systemic recurrence in each arm of the trial are presented in Table 4-13. The difference in the proportion of patients with recurrence is not significant.

	Conventional		PST		
	well	recurred	well	recurred	p=
By intention to treat	18	20	24	16	0.364
By actual treatments given	20	20	22	16	0.505

Proportions compared using Fisher's exact test

Table 4-13: Number of patients with systemic recurrence in the first part of the trial

4.1.4.2.1.1 Recurrence free survival by intention to treat

The Kaplan-Meier curves for distant disease free survival by intention to treat is presented in Figure 4-5 (Table 14-3). The median recurrence free survival for patients treated conventionally was 53 months by intention to treat. Median recurrence free survival for patients treated by PST has not been reached yet. The difference in survival curves is not significant (hazard ratio: 0.67, 95% C.I.: 0.34-1.28, p=0.225, Cox's regression).

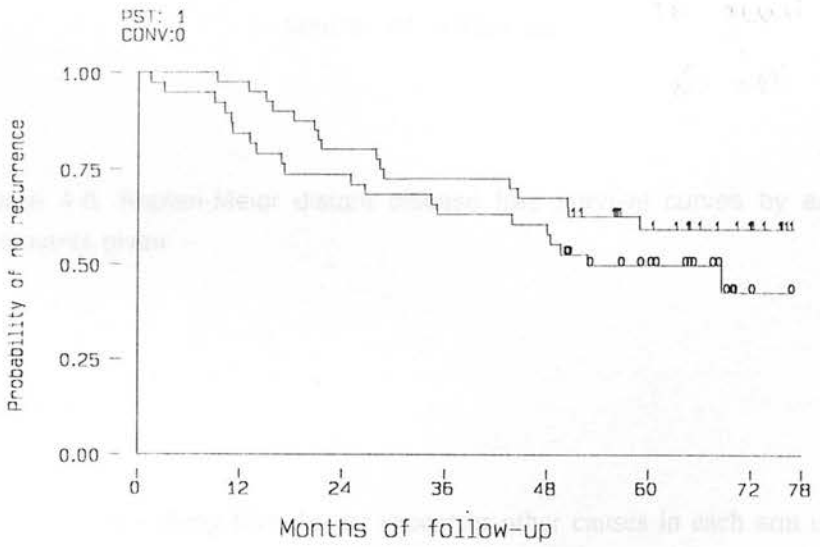

Figure 4-5: Kaplan-Meier distant disease free survival curves by intention to treat

4.1.4.2.1.2 Recurrence free survival by actual treatments given

The distant disease free survival according to actual treatments given is presented in Figure 4-6 (Table 14-4). The median recurrence free survival for patients treated conventionally was 69 months by actual treatments received. Median recurrence free survival for patients treated by PST has not been reached yet. There is no significant difference between the curves (hazard ratio: 0.76, 95% C.I.: 0.39-1.47, p=0.419, Cox's regression).

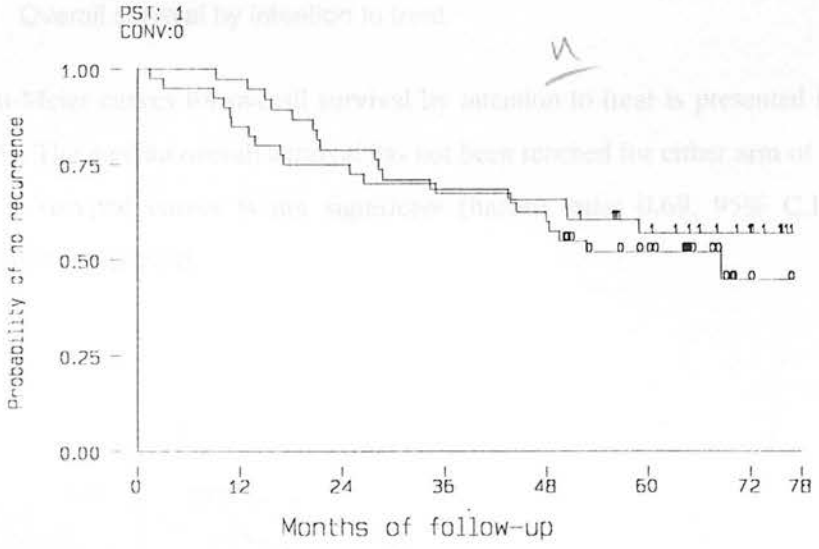

Figure 4-6: Kaplan-Meier distant disease free survival curves by actual treatments given

4.1.4.2.2 Deaths

The number of patients dying form breast cancer or other causes in each arm of the trial is presented in Table 4-14. The difference in the proportion of patients who have died in each arm of the trial is not significant. Survival is analysed on the basis of mortality from any cause.

	Conventional			PST			
	Alive	Dead	D (df)	Alive	Dead	D (df)	p=
By intention to treat	20	17	1	25	14	1	0.739
By actual treatment given	22	17	1	23	14	1	0.821

D (df): died free of breast cancer. Proportions compared using Fisher's exact test

Table 4-14: Number of patients who have died in the first part of the trial

4.1.4.2.2.1 Overall survival by intention to treat

The Kaplan-Meier curves for overall survival by intention to treat is presented in Figure 4-7 (Table 14-5). The median overall survival has not been reached for either arm of the trial. The difference in survival curves is not significant (hazard ratio: 0.69, 95% C.I.: 0.35-1.37, p=0.285, Cox's regression).

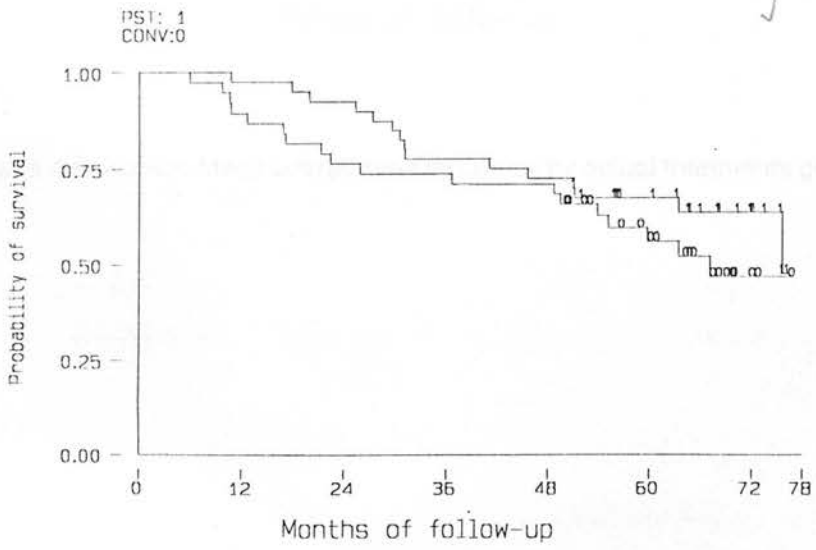

Figure 4-7: Kaplan-Meier overall survival curves by intention to treat for patients in the first part of the trial

4.1.4.2.2.2 Overall survival by actual treatments given

The overall survival according to actual treatments given is presented in Figure 4-8 (Table 14-6). The median survival for either for of treatment has not been reached yet. There is no significant difference between the curves (hazard ratio: 0.77, 95% C.I.: 0.39-1.53, p=0.451, Cox's regression).

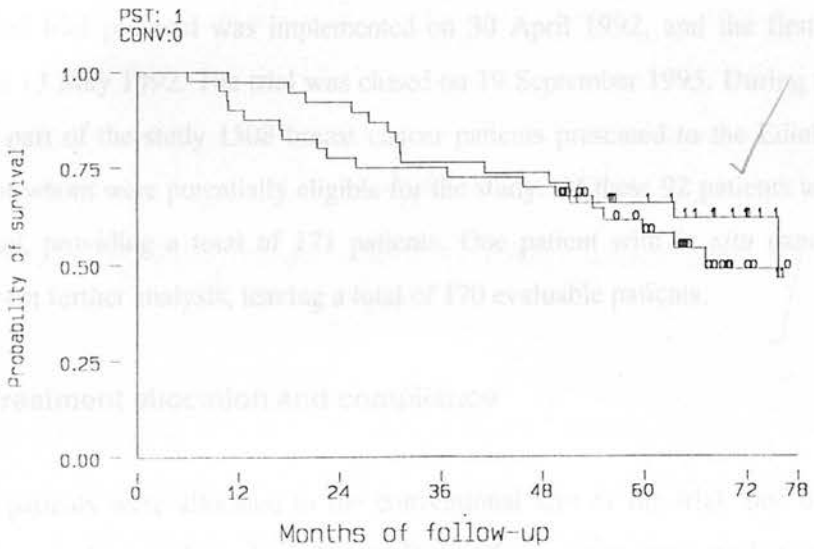

Figure 4-8: Kaplan-Meier overall survival curves by actual treatments given

4.2 RESULTS INCLUDING THE SECOND PART OF THE TRIAL

4.2.1 Recruitment and compliance

4.2.1.1 Recruitment

The modified trial protocol was implemented on 30 April 1992, and the first patient was recruited on 13 May 1992. The trial was closed on 19 September 1995. During the period of the second part of the study 1508 breast cancer patients presented to the Edinburgh Breast Unit, 257 of whom were potentially eligible for the study. Of these 92 patients were recruited into the trial, providing a total of 171 patients. One patient with *in situ* cancer only was excluded from further analysis, leaving a total of 170 evaluable patients.

4.2.1.2 Treatment allocation and compliance

Eighty six patients were allocated to the conventional arm of the trial, one of whom was excluded from further analysis (see above). Eighty five women were randomised to receive primary systemic treatment (PST).

4.2.1.2.1 Major protocol violations

There were 19 significant protocol violations. Five occurred in the first part of the trial and have been described above (4.1.1.2). The protocol violations were as follows:

4.2.1.2.1.1 Primary systemic treatment

Nine protocol violations occurred in this arm of the study six of which occurred in the second part of the trial.

Two patients requested conventional treatment after being randomised to PST. One was treated according to the conventional treatment protocol. The second patient was a postmenopausal patient who was given postoperative CMF chemotherapy.

Oophorectomy was omitted in three premenopausal patient whose tumour had responded to goserelin. Two were given postoperative chemotherapy and a third patient was given tamoxifen.

One premenopausal patient became pregnant following successful chemotherapy. She had a normal delivery and remains disease free.

4.2.1.2.1.2 Conventional treatment

Ten protocol violations occurred in this arm of the trial, 8 of which were in the second part.

One premenopausal, node-negative patient underwent oophorectomy instead of tamoxifen.

Five patients with 4 or more involved axillary lymph nodes were treated by postoperative sequential doxorubicin followed by CMF, as described by Bonadonna's group (Buzzoni *et al:* 1991). Three were postmenopausal patients who would have received tamoxifen according to the protocol. Two premenopausal patients were given this regime in place of CMF.

Two patients were given CMF in place of tamoxifen. One was postmenopausal, the second was a premenopausal women with a high grade tumour, but no involved axillary lymph nodes.

4.2.1.2.2 Minor protocol violations

Four patients in the primary systemic treatment arm who should have undergone mastectomy, were treated by breast conservation following tumour regression with PST.

4.2.1.3 Reporting of results

The results for all 170 evaluable patients are reported by intention to treat.

4.2.2 Patient and tumour characteristics

4.2.2.1 Patient characteristics

The two arms of the trial were balanced with regard to age and menopausal status as shown in Table 4-15.

	Conventional	PST	p=
Mean age (range)	52 (27-69)	52 (31-69)	0.994
Menopausal status			
Number premenopausal	39	40	
Number postmenopausal	46	45	1.000

Age: Student's t-test. Proportions compared using Fisher's exact test.

Table 4-15: Age and menopausal status distribution of patients in the entire trial

4.2.2.2 Tumour characteristics

4.2.2.2.1 Tumour diameter

The distribution of tumour sizes by intention to treat is shown in Figure 4-9. The median tumour diameter for the entire cohort of patients was 43 mm, with a range of 31 to 85 mm.

Of the 92 patients recruited into the second part of the trial, 54 had tumours between 31-40 mm in diameter. Median tumour diameters for patients treated conventionally , and for those treated by PST were 43 mm (range 31-85). There was no significant difference in tumour diameters (z=-0.51, p=0.61, Mann-Whitney U test).

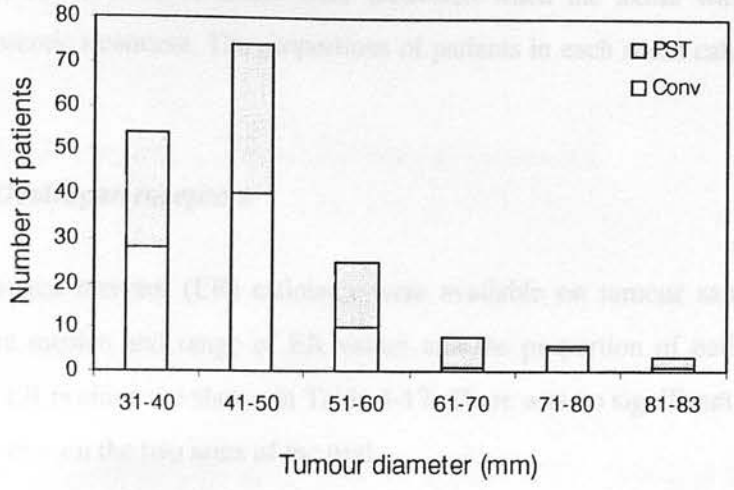

Figure 4-9: Tumour size distribution for the entire trial

4.2.2.2.2 Axillary lymph node involvement

Information about axillary nodes was available in all conventionally treated patients and 83 patients randomised to PST. The number of nodes recovered and the number of involved axillary lymph nodes are summarised in Table 4-16.

		Conventional	PST	z=	p=
Median number of nodes recovered		17 (3-33)	16 (4-34)	-0.88	0.38
Median number of nodes involved		5 (1-23)	3 (1-14)	-2.83	0.0047
Patients with involved nodes	Total	85	83		
None	76	36	40		
1-3	43	19	24	Exact	0.234
4-9	29	16	13		
•10	20	14	6		

Medians: Mann Whitney U test. Proportions: Fisher's exact test

Table 4-16: Axillary lymph node involvement by trial option

On average fewer involved nodes were recovered when the axilla was cleared following primary systemic treatment. The proportions of patients in each nodal category were however similar.

4.2.2.2.3 Oestrogen receptors

Initial oestrogen receptor (ER) estimates were available on tumour samples from all 168 patients The median and range of ER values and the proportion of patients who were ER negative or ER positive are shown in Table 4-17. There was no significant difference in initial ER values between the two arms of the trial.

	Conventional	PST	z=	p=
Median ER values	37 (1-592)	25 (0-712)	-0.53	0.596
Patients in each ER category				
ER<20	37	38	Exact	0.877
ER>19	48	45		

Medians: Mann Whitney U test. Proportions: Fisher's exact test

Table 4-17: Initial oestrogen receptor values

4.2.2.2.4 Tumour histological type and grade

The numbers of patients with different histological tumour types and grades are summarised in Table 4-18. There were no significant differences.

	Conventional	PST	p=
Histological types			
Ductal, no special type	71	73	
Ductal, special types	2	4	0.509
Lobular carcinoma	12	8	
Tumour differentiation			
Well	10	10	
Moderate	52	51	1.000
Poor	23	23	

Proportions compared using Fisher's exact test

Table 4-18: Tumour histological types and grades for the entire trial

4.2.3 Treatments and toxicity

4.2.3.1 Overall duration of hospital cancer treatment

Duration of cancer treatment is defined in section 3.5.1. At the time of analysis two patients, one in each arm of the trial were continuing to receive treatment.

Duration of treatment for each group is show in Table 4-19, according to actual treatments received. Overall, primary systemic treatment was significantly more protracted than conventional therapy. This was entirely attributable to the more prolonged treatment in patients treated by endocrine therapy.

	Conventional	PST	χ^2=	p=
All patients (n=170)	115 (21-394)	195 (80-507)	14.55	0.0001
Cytotoxic treatment only (n=81)	223 (91-394)	222.5 (80-507)	0.00	0.962
Endocrine treatment only (n=89)	42 (21-223)	147.5 (92-328)	37.16	0.0000

Treatment duration in days: median (range), compared using Log-rank test

Table 4-19: Duration of cancer treatment for all trial patients

Overall duration of cancer treatment was significantly longer for patients in the second part of the trial compared with those in the first part. Much of the difference was due to the more frequent use of radiotherapy during the second part, as well as the use of prolonged chemotherapy out with the trial protocol. When patients treated by non-trial protocols, and those given radiotherapy were excluded, duration of treatment for the remaining patients was similar (Table 4-20).

	Trial part					
	First		second		χ^2=	p=
	n	time	n	time		
All patients	78	140 (21-271)	92	199.5 (21-507)	26.00	0.000
Violations and XRT excluded	69	150 (21-271)	36	133 (21-358)	0.51	0.477
Violations and XRT only	9	39 (21-242)	56	244 (80-507)	35.03	0.000

Treatment duration in days: median (range), compared using Log-rank test. XRT: Radiotherapy

Table 4-20: Duration of cancer treatment in the first and second parts of the trial

4.2.3.2 Actual treatments received

4.2.3.2.1 Conventional treatment group

Treatment details for patients treated in the conventional arm of the study are summarised in Table 4-21. One patient with ductal carcinoma *in situ* only, was not systemically treated.

	Premenopausal	Postmenopausal	Total
Tamoxifen	11	42	53
CMF chemotherapy	24	*1*	25
A-CMF chemotherapy	*2*	*3*	*5*
Oophorectomy	*1*	*0*	*1*
Primary CAP chemotherapy	*1*	*0*	*1*
None	*1*	*0*	*1*
Total number of patients	40	46	86

Number of patients given each treatment. Italics indicate protocol violations.

Table 4-21: Details of adjuvant systemic treatment received by patients in the conventional arm of the study.

4.2.3.2.2 Primary systemic treatment

Details of primary systemic treatment are provided in Table 4-22. The table includes information on 6 patients who were treated by primary surgery.

	Premenopausal	Postmenopausal	Total
Primary tamoxifen alone	0	25	25
Primary goserelin alone	9	0	9
Primary CAP alone	22	13	35
Failed tamoxifen followed by CAP	0	4	4
Failed goserelin followed by CAP	4	0	4
Primary LHRH, postop tamoxifen	*1*	*0*	*1*
Primary LHRH, conventional CMF	*1*	*0*	*1*
Conventional A-CMF	*1*	*1*	*2*
Conventional tamoxifen	*2*	*2*	*4*
Total number of patients	40	45	85

Number of patients given each treatment. Italics indicate protocol violations.

Table 4-22: Details of primary systemic treatment for the entire trial

4.2.3.2.3 Treatment differences

Postmenopausal patients treated in the PST arm were significantly more likely to receive cytotoxic chemotherapy compared with those treated conventionally. There was no difference in the proportion of patients treated by endocrine or cytotoxic chemotherapy amongst premenopausal patients (Table 4-23).

	Conventional		PST		
	Endo	Chemo	Endo	Chemo	p=
All patients	54	31	35	50	0.006
Premenopausal patients	12	27	11	29	0.808
Postmenopausal patients	42	4	24	21	0.000

Number of patients in each category. Proportions compared using Fisher's exact test

Table 4-23: The proportion of patients treated by cytotoxic chemotherapy and by endocrine therapy

4.2.3.3 Locoregional treatment

A total of 168 patients received definitive locoregional therapy in the form of surgery. In the first part of the trial all patients received a mastectomy. In the second part breast conservation was allowed as an option. Two patients who developed evidence of metastatic disease during initial cancer treatment were treated by radiotherapy only and did not undergo surgery. The number of patients treated by different forms of locoregional therapy are summarised in Table 4-24. There were no significant differences in the proportions of patients treated by different forms of locoregional treatment.

	Conventional	PST	Total	p=
Patey mastectomy alone	54	60	114	
Patey mastectomy and XRT	11	6	17	0.280
Breast conservation (includes XRT)	20	17	37	
XRT alone	0	2	2	

Number of patients given different forms of locoregional treatment. XRT: radiotherapy. Proportions compared using Fisher's exact test.

Table 4-24: Locoregional treatment for patients in different arms of the trial

4.2.4 Follow-up and survival

4.2.4.1 Entire cohort of patients

The cohort of 170 patients have been followed up for a median of 48 months from the date of entry to the time of analysis (range: 10 to 77 months). The median follow-up until death or censoring for the entire trial has been 37 months (range 6-77 months). All patients have been seen according to protocol, and there have been no loses to follow-up.

4.2.4.1.1 Local recurrence

Four patients from the first part of the trial have been treated for locoregional recurrence (4.1.4.1.1). A fifth patient, treated by PST in the second part of the trial has been treated for local recurrence following a mastectomy.

4.2.4.1.2 Systemic recurrence

There have been 51 systemic recurrences of breast cancer amongst the 170 patients treated within the trial. The Kaplan-Meier curve for distant disease free survival for all patients is shown in Figure 4-10 (Table 14-7).

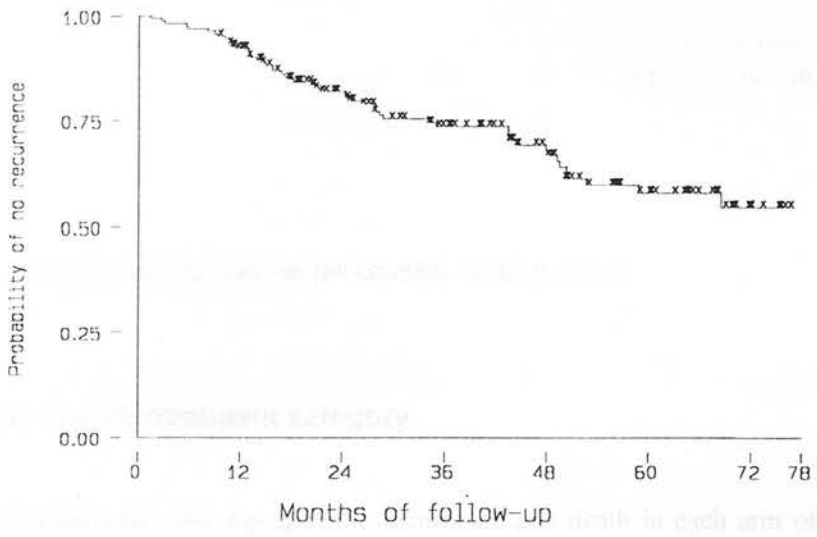

Figure 4-10: Distant disease free survival for all patients

4.2.4.1.3 Deaths

There have been 44 deaths amongst 170 patients. Forty one patients died from metastatic breast cancer. Two non-breast cancer related deaths are discussed in section 4.1.4.1.3. A third

patient died from histologically proven metastatic gastric carcinoma. She was free of breast cancer recurrence at the time of death.

The Kaplan-Meier all cause overall survival curve is shown in Figure 4-11 (Table 14-8).

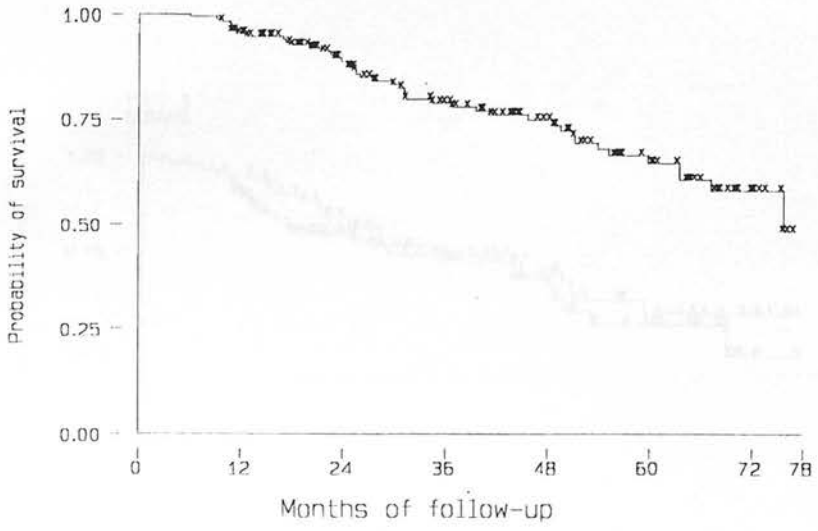

Figure 4-11: Overall survival (all causes) for all patients

4.2.4.2 Survival by treatment category

The number of patients suffering systemic recurrence and death in each arm of the trial are presented in Table 4-25. The difference in the proportion of patients is not significant.

	Conventional		PST		
	well	recurred	well	recurred	p=
Recurrence free survival	58	27	61	24	0.738
Overall survival	61	24	65	20	0.600

Proportions compared using Fisher's exact test

Table 4-25: Number of patients with systemic recurrence and death

4.2.4.2.1 Recurrence free survival

The Kaplan-Meier curves for distant disease free survival by intention to treat are presented in Figure 4-12 (Table 14-9). Median recurrence free survival for either group has not been reached yet. The difference in survival curves is not significant (hazard ratio: 0.80, 95% C.I.: 0.46-1.40, p=0.415, Cox's regression).

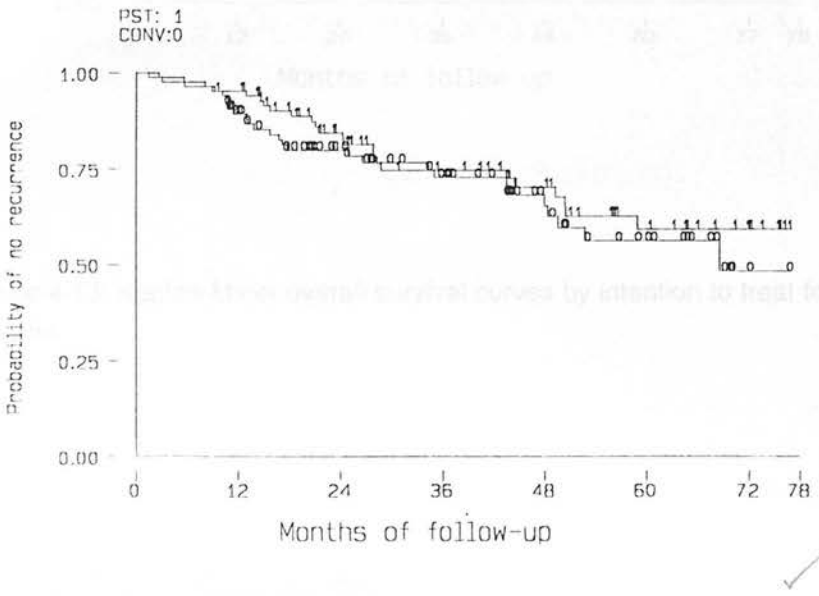

Figure 4-12: Kaplan-Meier distant disease free survival curves by intention to treat

4.2.4.2.2 Overall survival

The Kaplan-Meier curves for overall survival by intention to treat are presented in Figure 4-13 (Table 14-10). The median overall survival has not been reached for either arm of the trial. The difference in survival curves is not significant (hazard ratio: 0.73, 95% C.I.: 0.40-1.32, p=0.299, Cox's regression).

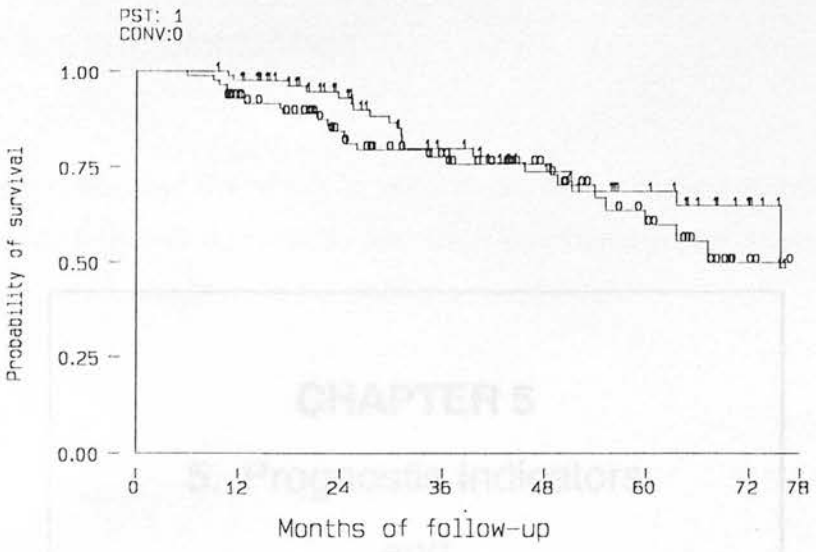

Figure 4-13: Kaplan-Meier overall survival curves by intention to treat for all patients

CHAPTER 5

5. Prognostic Indicators and Primary Systemic Treatment

5.1 PROGNOSTIC INDICATORS

The contribution of patient and tumour factors to distant disease free and overall survival was studied in patients in both parts of the trial using Cox's proportional hazard model. The factors entered into the model are summarised in section 3.5.4.3.

5.1.1 Univariate analysis

The individual contributions of each possible prognostic indicator to disease free survival are presented in Table 5-1.

	Results of univariate analysis				
	n=	Hazard ratio	95% C.I.	z=	p=
Age	170	1.00	0.97-1.03	-0.09	0.927
Tumour diameter	170	1.16	0.92-1.50	1.92	0.198
ln of initial ER	168	0.74	0.62-0.89	-3.22	0.001
Number of involved axillary nodes	168	1.12	1.07-1.16	5.45	0.000
Tumour grade	168	1.33	0.84-2.12	1.20	0.229
Mode of treatment	170	0.83	0.48-1.45	-0.65	0.514

Results calculated using Cox's proportional hazard model

Table 5-1: Univariate analysis of the contribution of various risk factors, including "actual mode of treatment" to disease free survival.

Axillary lymph node involvement and initial oestrogen receptor levels were the only significant predictors of distant disease free survival. Similar results were obtained for overall survival, as presented in Table 5-2.

	Results of univariate analysis			
	Hazard ratio	95% C.I.	z=	p=
Age	0.99	0.97-1.02	-0.35	0.725
Tumour diameter	1.19	0.91-1.55	1.30	0.195
ln of initial ER	0.71	0.58-0.88	-3.18	0.001
Number of involved axillary nodes	1.12	1.07-1.16	5.08	0.000
Tumour grade	1.18	0.70-1.98	0.63	0.529
Mode of treatment	0.77	0.41-1.43	-0.83	0.404

Results calculated using Cox's proportional hazard model

Table 5-2: Univariate analysis of the contribution of various risk factors, including "actual mode of treatment" to overall survival.

5.1.2 Multivariate models

Number of axillary lymph nodes and *ln* of initial ER were entered into a multivariate model. The results for disease free survival are presented in Table 5-3, and for overall survival in Table 5-4.

	Results of multivariate analysis			
	Hazard ratio	95% C.I.	z=	p=
ln of initial ER	0.68	0.56-0.82	-3.95	0.000
Number of involved axillary nodes	1.13	1.08-1.17	5.74	0.000
Log Likelihood = -199.78	n=166		χ^2=39.30	0.0000

Results calculated using Cox's proportional hazard model

Table 5-3: Cox's proportional hazard model to study the contribution of axillary nodes and initial ER to distant disease free survival

	Results of multivariate analysis			
	Hazard ratio	95% C.I.	z=	p=
ln of initial ER	0.63	0.50-0.79	-4.01	0.000
Number of involved axillary nodes	1.13	1.08-1.18	5.53	0.000
Log Likelihood = -155.43	n=166		χ^2=37.95	0.0000

Results calculated using Cox's proportional hazard model

Table 5-4: Cox's proportional hazard model to study the contribution of axillary nodes and initial ER to overall survival

In multivariate analysis, the number of axillary lymph nodes and initial tumour oestrogen receptor levels remain highly significant independent predictors of distant disease free and overall survival.

5.1.3 Analysis of significant risk factors

5.1.3.1 Oestrogen receptor status

Patients were categorised into oestrogen receptor positive (ER>19) and oestrogen receptor negative (ER<20) according to initial ER levels. The overall survival for ER positive and ER negative patients is presented in Figure 5-1 (Table 14-11). Oestrogen receptor status is a highly significant predictor of overall survival (hazard ratio: 0.26, 95% C.I.: 0.13-0.52, p=0.000, Cox's regression).

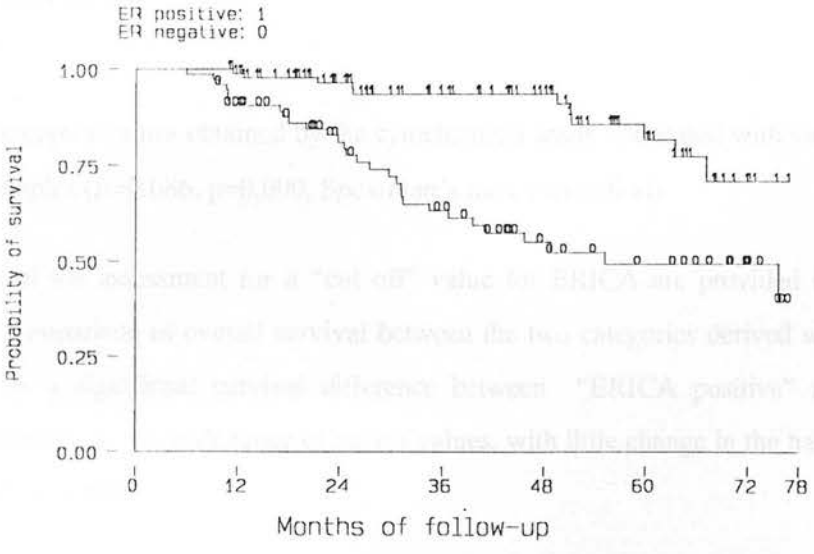

Figure 5-1: Overall survival by oestrogen receptor status

5.1.3.1.1 The significance of the ERICA assay

Information on initial oestrogen receptor values was available by the immuno-cytochemical assay in 96 patients, 47 from the first part and 49 from the second part of the trial. There was no significant difference in patient and tumour factors between those patients from whom an ERICA measurement was available and those in whom no ERICA had been performed (Table 5-5).

	ERICA done			No ERICA			Stat.	p=
Mean age (range)	52.3 (27-69)			51.5 (31-69)			t=-053	0.595
Median initial tumour diameter	44 (31-85)			43 (31-80)			z=-0.78	0.434
Median initial ER (range)	34 (2-712)			28.5 (0-623)			z=-0.11	0.915
Number of involved axillary nodes	1 (0-21)			1 (0-23)			z=-0.10	0.917
Tumour grade (well |moderate |poor)	14	59	22	6	44	24	Exact	0.232
Mode of treatment (Conv |PST)	50		46	40		34	Exact	0.877

Age compared using student's t-test. Z values by Mann-Whitney U test. Proportions compared using Fisher's exact test

Table 5-5: Patient and tumour characteristics for patients with and without ERICA values

Oestrogen receptor values obtained by the cytochemical assay correlated with values obtained on tissue samples (ρ=0.686, p=0.000, Spearman's rank correlation).

The details of the assessment for a "cut off" value for ERICA are provided in Table 5-6, along with comparison of overall survival between the two categories derived with each cut-off. There is a significant survival difference between "ERICA positive" and "ERICA negative" patients over a wide range of cut off values, with little change in the hazard ratio for different cut off levels.

The cut off level of 1-2% classifies 85% of ER positive and ER negative (see 3.5.4.3.1.2) patients correctly. At that level the difference in overall survival for "ERICA positive" (greater than 1% of tumour cells staining) and "ERICA negative" (0-1% of tumour cells staining) is highly significant (hazard ratio: 0.32, 95% C.I.: 0.14-0.83, p=0.006).

Cut off level	Test validity			Survival differences		
	EREIA+ ERICA+	EREIA- ERICA-	PPV	H.R.	95% C.I.	p=
0 vs. 1%+	31	50	0.86	0.37	0.17-0.83	0.016
0-1% vs. 2%+	31	49	0.85	0.32	0.14-0.72	0.006
0-2% vs. 3%+	31	47	0.83	0.36	0.16-0.81	0.014
0-3% vs. 4%+	31	47	0.83	0.36	0.16-0.81	0.014
0-4% vs. 5%+	32	47	0.84	0.30	0.13-0.69	0.005
0-7% vs. 8%+	33	45	0.83	0.37	0.16-0.84	0.018
0-10% vs. 11%+	33	42	0.80	0.42	0.19-0.98	0.045
0-14% vs. 15%+	33	37	0.74	0.45	0.19-1.07	0.070
0-19% vs. 20%+	35	34	0.73	0.29	0.11-0.77	0.014
0-29% vs. 30%+	35	30	0.69	0.37	0.14-0.99	0.047
0-39% vs. 40%+	37	21	0.62	0.36	0.11-1.21	0.098
0-49% vs. 50%+	38	11	0.52	-	-	1.000

ER positive by the EREIA was defined as >19. PPV: positive predictive value. Hazard ratios calculated using Cox's regression.

Table 5-6: The effects of using different cut off values for oestrogen receptor

The Kaplan-Meier survival curves for patients categorised as ER negative and ER positive at this cut off level are shown in Figure 5-2 (Table 14-12). The pattern of survival by ERICA category is similar to that found for ER determined by the EREIA assay, with survival curves converging towards the end of the follow-up period.

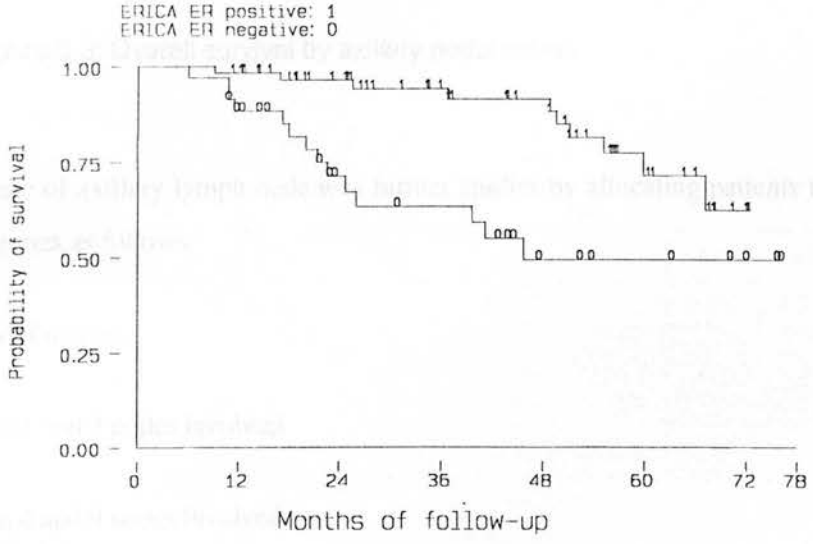

Figure 5-2: Overall survival by oestrogen receptor levels as determined by the ERICA assay

5.1.3.2 Axillary nodal involvement

The number of involved axillary lymph nodes significantly correlates with survival. The overall survival for patients with no axillary nodal involvement and those with one or more involved nodes is shown in Figure 5-3 (Table 14-13). The difference in survival is significant (hazard ratio: 3.69, 95% C.I.: 1.74-7.83, p=0.000, Cox's regression).

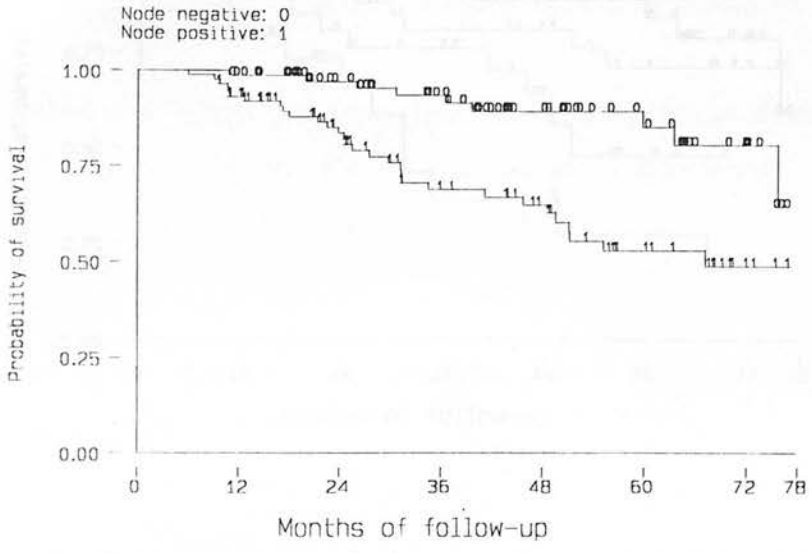

Figure 5-3: Overall survival by axillary nodal status

The influence of axillary lymph node was further studies by allocating patients to one of four nodal categories as follows:

1. No nodes involved
2. Between 1 and 3 nodes involved
3. Between 4 and 9 nodes involved
4. Ten or more nodes involved

The numbers of patients in each category are summarised in Table 4-16. The survival curves according to each of four nodal categories are presented in Figure 5-4 (Table 14-14). The relationship between nodal category and survival is highly significant (hazard ratio: 2.00, 95% C.I.: 1.51-2.65, p=0.000).

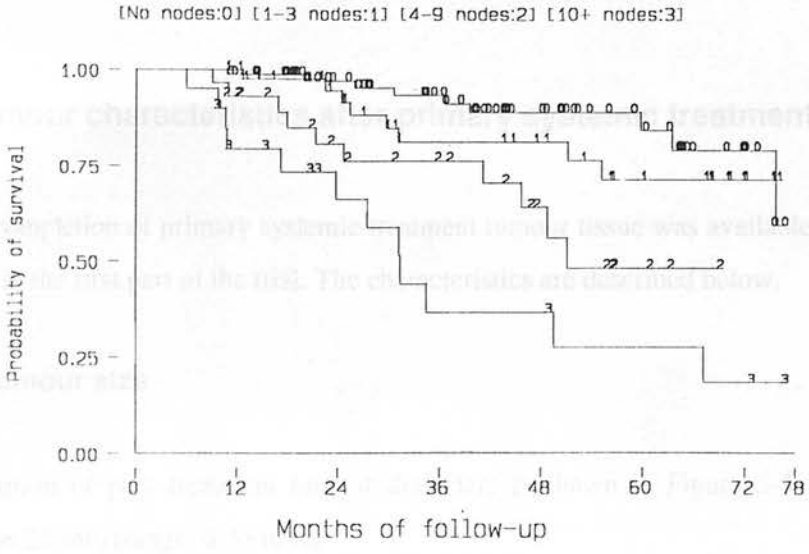

Figure 5-4: Overall survival by nodal category for all patients in the trial

Each nodal category was compared individually with other nodal categories. The results are summarised in Table 5-7.

Number of nodes	None			1-3			4-9		
	H.R.	95% C.I.	p=	H.R.	95% C.I.	p=	H.R.	95% C.I.	p=
1-3	1.66	0.6-4.3	0.302						
4-9	2.04	1.3-3.3	0.003	2.24	0.9-5.7	0.091			
>9	1.94	1.5-2.6	0.000	2.18	1.4-3.4	0.001	2.09	0.9-4.9	0.088

Table 5-7: Comparisons between different nodal categories

5.2 RESULTS SPECIFIC TO PRIMARY SYSTEMIC TREATMENT

Data are described mainly for patients in the first part of the trial. Additional data on post treatment oestrogen receptor values and tumour grade were available from patients in the second part of the trial and were used for pre- and post-treatment comparisons, and for assessment of the significance of post treatment prognostic indicators.

5.2.1 Tumour characteristics after primary systemic treatment

Following completion of primary systemic treatment tumour tissue was available in 35 of the 38 patients in the first part of the trial. The characteristics are described below.

5.2.1.1 Tumour size

The distribution of post treatment tumour diameters is shown in Figure 5-5. The median diameter was 22 mm (range: 0-55 mm).

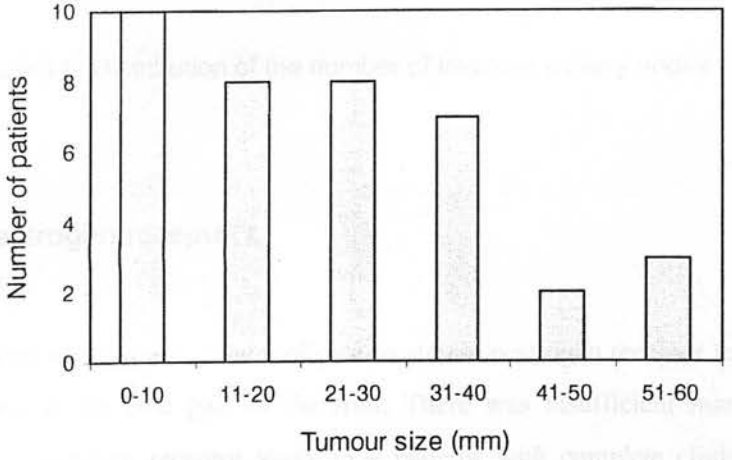

Figure 5-5: Distribution of tumour sizes following completion of primary systemic treatment

5.2.1.2 Axillary lymph node involvement

Twenty one of the 38 patients had residual axillary nodal involvement following PST. The distribution of the number of involved nodes is shown in Figure 5-6. Significantly fewer nodes were recovered following primary systemic treatment compared with conventional therapy (Table 4-5).

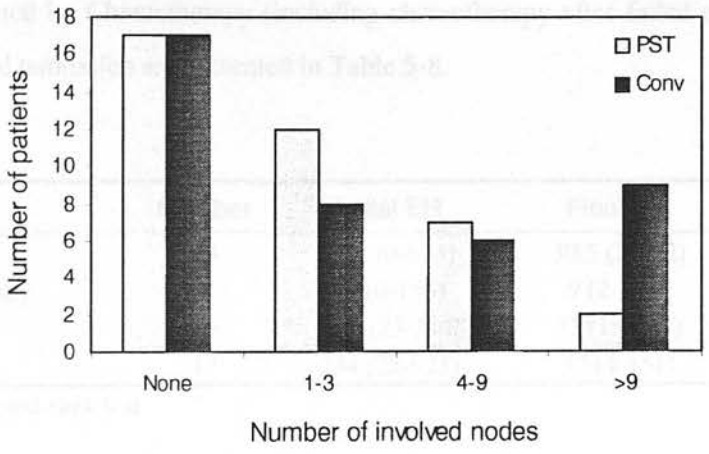

Figure 5-6: Distribution of the number of involved axillary nodes

5.2.1.3 Oestrogen receptors

Enough tumour to allow assessment of post-treatment oestrogen receptor levels was recovered in 28 patients in the first part of the trial. There was insufficient material available for postoperative oestrogen receptor assay in 9 patients with complete clinical or pathological tumour remission. Seven had been treated with chemotherapy, or had received cytotoxic chemotherapy following failed endocrine treatment. Post treatment tissue submitted for ER contained no tumour in a tenth patient who had been treated with tamoxifen alone.

The median initial ER values in the group of patients with sufficient material for a second ER assay was 40.5 *f*mol/mg (range: 0-522), significantly greater than the initial ER levels for the ten patients from whom insufficient tumour was recovered for a second assay (median 4, range: 0-108, z=-2.87, p=0.004, Mann-Whitney U test).

5.2.1.3.1 Changes in oestrogen receptor content

Data were available from 28 patients treated in the first part of the trial and from a further 20 patients treated in the second part of the trial. The results from the two parts are reported together. The median and range of pre- and post-treatment ER values for all patients, and for patients treated by Chemotherapy (including chemotherapy after failed endocrine treatment), goserelin and tamoxifen are presented in Table 5-8.

	Number	Initial ER	Final ER	z=	p=
All patients	48	40.5 (0-623)	30.5 (2-292)	2.75	0.006
Chemotherapy	21	10 (0-156)	9 (2-292)	-1.37	0.170
Goserelin	10	69.5 (23-394)	52 (15-173)	1.27	0.203
Tamoxifen	17	234 (25-623)	57 (4-151)	3.22	0.001

Wilcoxon signed-rank test

Table 5-8: Changes in ER following primary systemic treatment

Overall, post treatment values were lower than initial values, largely due to the drop in oestrogen receptor levels following primary systemic treatment with tamoxifen. (Figure 5-7).

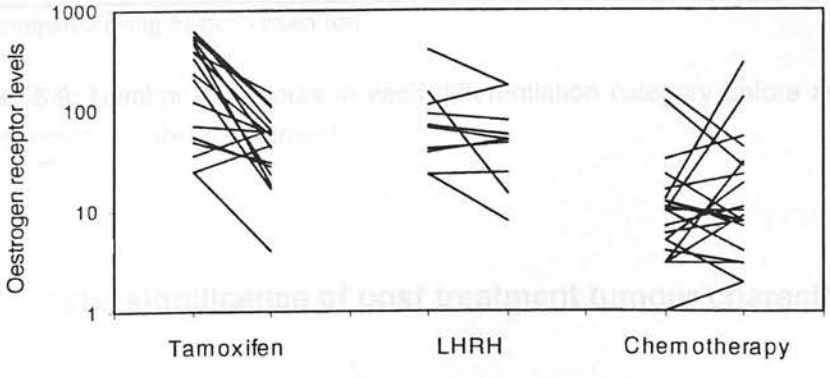

Figure 5-7: Changes in ER content following primary systemic treatment

Of the 48 patients in whom pre and post treatment ER values were available, 31 had ER>19 (ER positive) and 17 had ER<20 (ER negative). Following primary systemic treatment 5 ER positive patients became ER negative, and 4 ER negative patient became ER positive.

5.2.1.4 Tumour histological type and grade

These characteristics were assessable in 35 of the 38 patients who had completed primary systemic therapy in the first part of the trial. The histological types were identical to that found with the initial biopsy (Table 4-18). There were 11 well differentiated, 19 moderately differentiated and 5 poorly differentiated tumours following completion of primary systemic treatment.

5.2.1.4.1 changes in tumour histology

Data were available for 35 patients in the first part of the trial, and an additional 29 patients treated in the second part. The number of patients in each differentiation category before and after primary systemic treatment are shown in Table 5-9. A significantly larger proportion of tumours were classed as well differentiated following the completion of all treatment.

Initial tumour grade	Final tumour grade			Total	p=
	Well	Moderate	Poor		
Well	8	1	0	9	
Moderate	8	29	5	42	0.000
Poor	1	5	10	16	
Total	17	35	15	67	

Proportions compared using Fisher's exact test

Table 5-9: Number of tumours in each differentiation category before and after primary systemic treatment

5.2.2 Prognostic significance of post treatment tumour characteristics

The relationship between tumour factors as assessed on specimens obtained after the completion of primary systemic treatment and overall survival was studied in patients treated

by primary systemic therapy in the entire trial. Results of univariate analysis are presented in Table 5-10. Post treatment information was incomplete, and the number of cases are included in the table.

	Results of univariate analysis			
	n=	Hazard ratio	95% C.I.	z=	p=
ln of post treatment ER	49	0.42	0.24-0.74	-3.00	0.003
Number of involved axillary nodes	78	1.22	1.09-1.37	3.43	0.001
Post treatment tumour grade	66	1.80	0.86-3.80	1.55	0.120

Results calculated using Cox's proportional hazard model

Table 5-10: Contribution of post treatment tumour factors to overall survival following primary systemic treatment

Information on all three factors was available in 49 patients. The multivariate model including all three tumour factors is presented in Table 5-11.

	Results of multivariate analysis			
	Hazard ratio	95% C.I.	z=	p=
ln of post treatment ER	0.36	0.19-0.67	-3.22	0.001
Number of involved axillary nodes	1.24	1.06-1.44	2.73	0.006
Post treatment tumour grade	0.89	0.29-2.66	-0.22	0.829
Log Likelihood = -29.26	n=49		χ^2=15.57	0.0014

Results calculated using Cox's proportional hazard model

Table 5-11: The contribution of post treatment tumour factors to overall survival

Oestrogen receptor levels and number of involved lymph nodes again emerged as significant independent indicators of prognosis.

5.2.2.1 Post treatment oestrogen receptor levels

Post treatment oestrogen receptor levels were available in 49 patients. Patients were categorised into oestrogen receptor positive (ER>19) and oestrogen receptor negative (ER<20) according to post treatment ER levels. The overall survival for ER positive and ER negative patients is presented in Figure 5-8 (Table 14-15). The difference in survival is highly significant (hazard ratio: 0.17, 95% C.I.: 0.05-0.58, p=0.005).

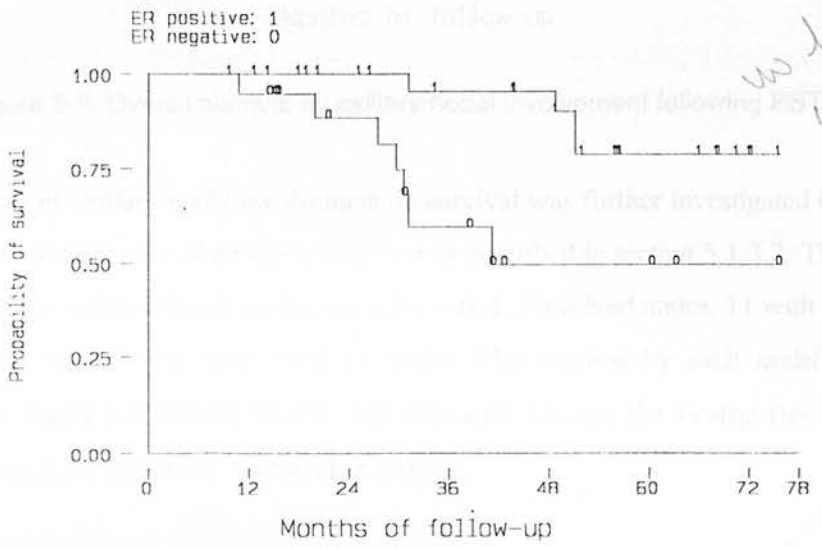

Figure 5-8: Overall survival by post treatment oestrogen receptor levels

5.2.2.2 Axillary lymph nodes

Post treatment information on axillary lymph nodes was available in 78 patients treated by PST. The overall survival for patients with no axillary nodal involvement and those with one or more involved nodes is shown in Figure 5-9 (Table 14-16). Forty one patients were node-negative and 37 patients node-positive. The difference in survival was significantly (hazard ratio 3.19, 95% C.I.: 1.01-10.02, p=0.047).

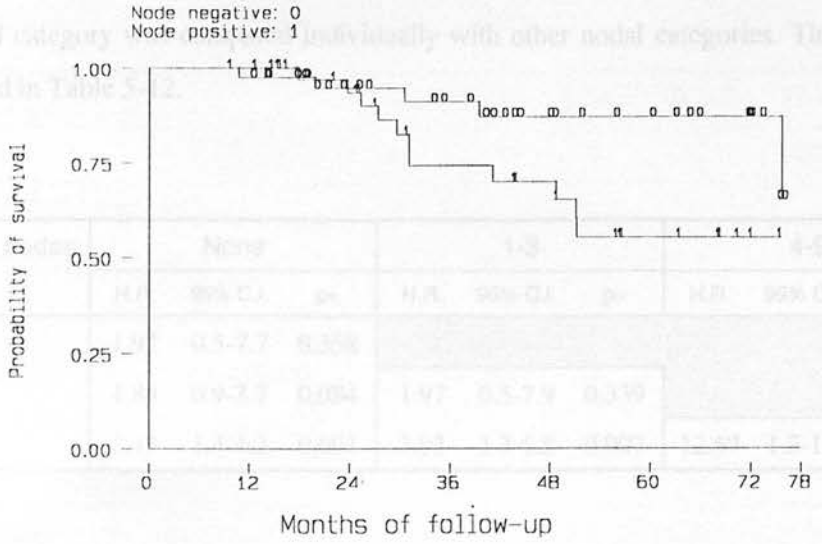

Figure 5-9: Overall survival by axillary nodal involvement following PST

The influence of axillary nodal involvement on survival was further investigated by allocating patients to four categories of nodal involvement as described in section 5.1.3.2. There were 41 patients with no axillary nodal involvement, 21 with 1-3 involved nodes, 11 with 4-9 involved nodes, and 5 with 10 or more involved nodes. The survival by each nodal category is presented in Figure 5-10 (Table 14-17). The difference between the 4 categories is significant (hazard ratio: 3.19, 95% C.I.: 1.42-4.11, p=0.001).

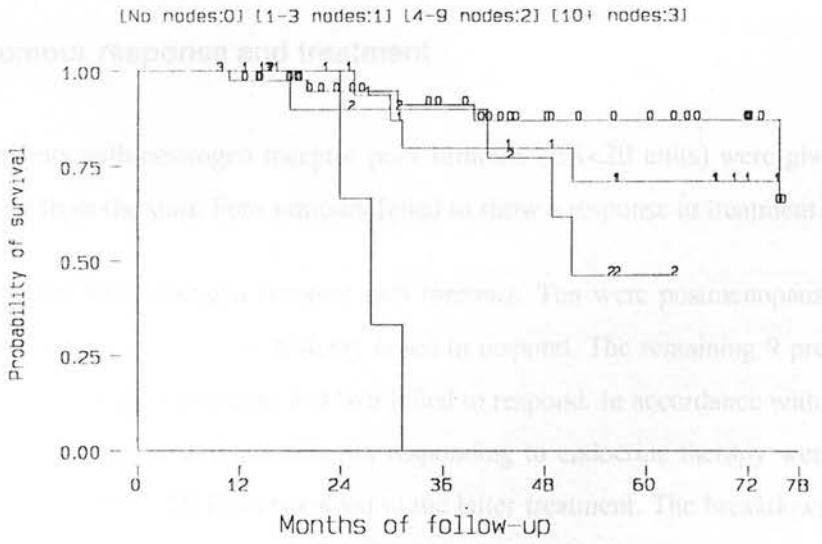

Figure 5-10: Overall survival by the number of axillary nodes involved following PST

Each nodal category was compared individually with other nodal categories. The results are summarised in Table 5-12.

Number of nodes	None			1-3			4-9		
	H.R.	95% C.I.	p=	H.R.	95% C.I.	p=	H.R.	95% C.I.	p=
1-3	1.92	0.5-7.7	0.358						
4-9	1.84	0.9-3.7	0.084	1.97	0.5-7.9	0.339			
>9	2.45	1.4-4.2	0.001	3.03	1.3-6.8	0.007	12.59	1.3-124	0.030

Table 5-12: Comparisons between different nodal categories following primary systemic treatment

The pattern of differences is similar to that found for all patients (Table 5-7), although less confidence can be placed on the results because the analysis was performed in fewer patients.

5.2.3 The significance of tumour response

Data from patients in the first part of the trial is described.

5.2.3.1 Tumour response and treatment

Nineteen patients with oestrogen receptor poor tumours (ER<20 units) were given cytotoxic chemotherapy from the start. Four tumours failed to show a response to treatment.

Nineteen patients had oestrogen receptor rich tumours. Ten were postmenopausal and were treated with tamoxifen; 3 of these patients failed to respond. The remaining 9 premenopausal patients were treated with goserelin and two failed to respond. In accordance with the primary systemic treatment protocol, 5 patients not responding to endocrine therapy were treated by cytotoxic chemotherapy. All five responded to the latter treatment. The breakdown of patients according to the six response categories defined previously (section 3.3.1.4.1) are summarised in Table 5-13.

	Total	CAP	TCAP	GCAP	TAM	GOS
Total Number	38	19	3	2	10	9
Complete Pathological remission	3	3	-	-	-	-
Complete Clinical remission	6	4	-	2	-	-
Clinical response (>75% reduction)	3	2	-	-	-	1
Partial Response (50-74% reduction)	17	5	2	-	5	5
Minimal Response (25-49% reduction)	5	1	1	-	2	1
No response (<25% reduction)	4	4	-	-	3	2

Number of patients in each category of response. CAP: Cyclophosphamide, Adriamycin and Prednisolone. TCAP: CAP following failed tamoxifen. GCAP: CAP following failed goserelin. TAM: Tamoxifen. GOS: Goserelin

Table 5-13: Response to primary systemic treatment

5.2.3.2 Treatment and speed of response

To assess differences in pattern of response, the half lives of tumours treated with any form of chemotherapy were compared with those treated with endocrine therapies alone, using the Mann Whitney U test. Four non-responding tumours had no measurable "half life" and were excluded from analysis. The median half life in response to cytotoxic chemotherapy was 25 days (range: 7-63 days), significantly shorter than the half life of 55.5 days (range: 28-116 days) achieved with endocrine therapies ($z=3.20$, $p=0.001$, Mann Whitney U test).

For a more detailed assessment of patterns of response, tumour half lives achieved with chemotherapy (CAP), tamoxifen (TAM) and goserelin (LHRH) were compared using Kruskal-Wallis one way analysis of variance. Five patients who had received chemotherapy following failed endocrine treatment (E-CAP) formed a fourth comparison group. There was a significant difference in half lives between the four treatment groups ($\chi^2=15.03$, $p=0.002$). There was however no significant difference when the goserelin, tamoxifen and E-CAP groups alone were compared ($\chi^2=3.48$, $p=0.176$). Median half life in response to CAP (25 days with non-responders excluded) was compared with that for each of the other treatment groups using the Mann-Whitney U test. Median half life following CAP was significantly shorter compared

with goserelin (43 days, p=0.008), tamoxifen (63 days, p=0.002) and E-CAP (53 days, p=0.03). The results are summarised in Figure 5-11.

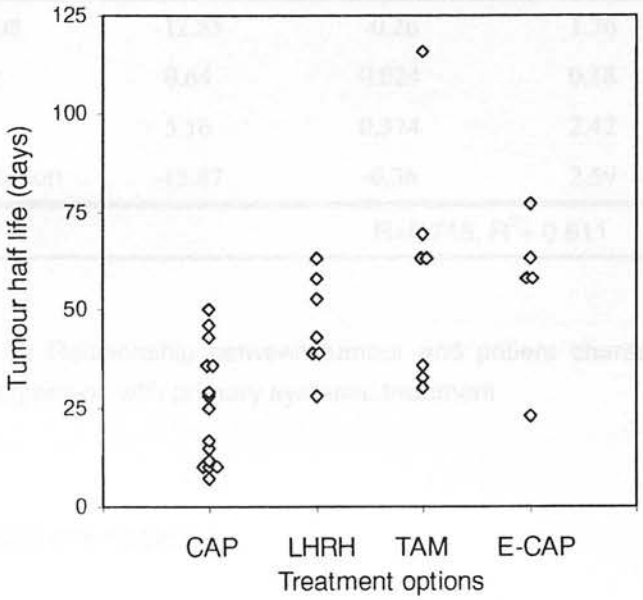

Figure 5-11: Tumour half lives in response to different regimes of treatment

5.2.3.3 Tumour characteristics and response

A multiple regression model was used to assess the contribution of patient and tumour factors to the rate of response (section 3.5.5.3). The model was tested for the entire group of patients, and separately for patients on cytotoxic and endocrine treatments.

5.2.3.3.1 All patients

The results for the entire group of 38 patients are summarised in Table 5-14. Menopausal status, tumour differentiation and tumour ER were able to explain over half of the variability seen in tumour half life (R^2=0.511, p=0.0003). Being premenopausal, having a poorly

differentiated tumour or having a low ER value were associated with faster tumour regression. Initial tumour diameter did not contribute to the model.

	Coefficient	Standardised Coefficient	t-value	Probability
Menopausal status	-12.85	-0.26	1.76	0.089
Tumour diameter	0.64	0.024	0.18	0.860
ER status	5.16	0.374	2.42	0.022
Tumour differentiation	-15.87	-0.36	2.59	0.017
Intercept = 74.58		R=0.715, R^2= 0.511		p = 0.0003

Table 5-14: Relationship between tumour and patient characteristics and tumour regression with primary systemic treatment

5.2.3.3.2 Cytotoxic chemotherapy

The results for patients given cytotoxic chemotherapy are presented in Table 5-15. Menopausal status was not a significant predictor of response rate, and did not contribute to the overall model. Poor tumour differentiation continued to predict fast response, while high initial tumour ER became a highly significant predictor of a slow response rate (Table 5-15).

	Coefficient	Standardised Coefficient	t-value	Probability
Menopausal status	-6.74	-0.15	0.79	0.439
Tumour diameter	0.96	0.05	0.23	0.823
ER ~~status~~ nab log.	9.19	0.61	3.16	0.007
Tumour differentiation	-13.12	-0.33	1.89	0.078
Intercept = 47.24		R=0.749, R^2=0.561		p = 0.0108

Table 5-15: Relationship between tumour and patient characteristics and tumour regression following primary cytotoxic therapy in 24 patients

5.2.3.3.3 Endocrine treatment

The results for patients given endocrine therapy are presented in Table 5-16. Premenopausal status and poor tumour differentiation continued to indicate a faster response rate in patients given endocrine treatment, while ER no longer contributed to the overall model.

	Coefficient	Standardised Coefficient	t-value	Probability
Menopausal status	-31.60	-0.71	2.69	0.025
Tumour diameter	-5.99	-0.21	0.93	0.379
ER status	-10.57	-0.47	1.74	0.116
Tumour differentiation	-28.00	-0.57	2.47	0.036
Intercept = 230.97		R=0.752, R^2= 0.566		p = 0.0831

Table 5-16: Relationship between tumour and patient characteristics and tumour regression following primary endocrine therapy in 14 patients

5.2.3.3.4 ER content and speed of response

The relationship between initial tumour ER content and tumour half life in response to treatment was examined for each treatment group using Spearman's rank correlation. There was no relationship between tumour half life and tumour ER content for 14 patients who had responded to endocrine treatment only (ρ=0.22, p=0.43). Fifteen patients with relatively ER poor tumours who had responded to cytotoxic chemotherapy showed a significant direct correlation between actual ER content and tumour half life (ρ=0.75, p=0.0048).

The median ER content for ER poor tumours was 4 *f*mol/mg. Responding tumours with ER content less or equal to this value had significantly shorter half lives in response to CAP compared with those tumours with ER values of 5 to 19 units (p=0.0056, Mann Whitney U test, Figure 5-12). Response to chemotherapy was significantly faster in patients with very low ER values (ER: 0-4) compared with those with moderate ER levels (ER: 5-19). (p=0.0056, Mann Whitney U test). Of the four non-responding tumours, 3 had ER values greater than 4 units.

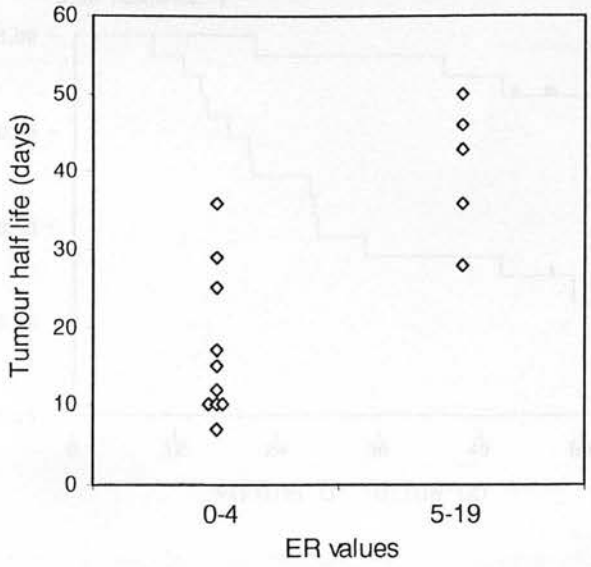

Figure 5-12: Half lives of ER negative tumours according to ER

5.2.3.4 Tumour response and survival

Patients were allocated to fast and slow response categories as described in section 3.5.5.2.2. There were 19 fast and 19 slow responding patients in each response category. Cox's proportional hazard model was used to assess the contribution of the speed of response to survival in the context of other prognostic indicators (section 3.5.4.3). Breast cancer mortality was used as the end point.

5.2.3.4.1 Recurrence free survival

On univariate analysis, response emerged as a highly significant predictor of distant disease free survival. At the time of analysis sixteen of the 19 fast responders remain recurrence free, whereas 13 of the slow responders have experienced breast cancer recurrence (hazard ratio: 6.98, 95% C.I. 1.97-24.67, p=0.003, Cox's regression). The recurrence free survival is presented in Figure 5-13 (Table 14-18).

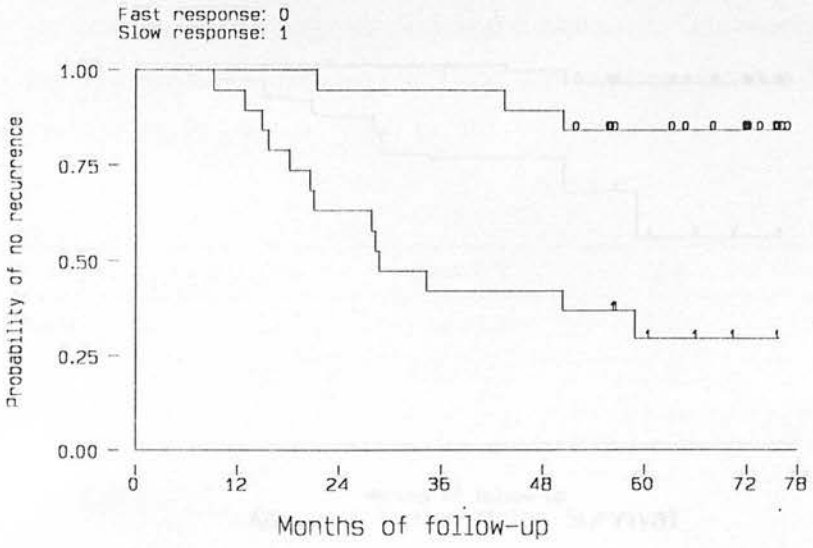

Figure 5-13: Recurrence free survival by the rate of response to primary systemic treatment

The results of multivariate analysis are presented in Table 5-17. Rate of response continues to predict disease free survival, although its influence is markedly reduced when other factors are taken into consideration.

	Hazard ratio	95% C.I.	z=	p=
Tumour response	3.83	1.00-14.65	1.96	0.050
age	1.03	0.98-1.11	1.19	0.232
Tumour diameter	1.11	0.50-2.48	0.25	0.800
Axillary nodes	7.12	1.59-31.88	2.57	0.010
ER status	0.08	0.01-0.47	-2.78	.005
Tumour differentiation	0.75	0.21-2.64	-0.45	0.651
Log Likelihood =-41.25			χ^2= 25.89	p = 0.0002

Table 5-17: Cox's proportional hazard model to assess the contribution of tumour response to distant disease free survival

Kaplan-Meier survival curves, adjusted for other prognostic indicators are presented in Figure 5-14 (Table 14-19).

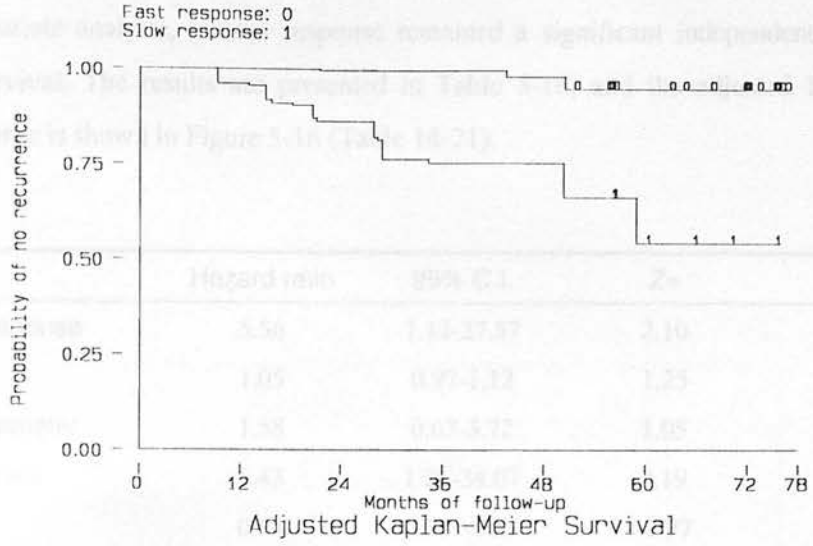

Figure 5-14: Distant disease free survival by speed of tumour response, adjusted as indicated in Table 5-17

5.2.3.4.2 Overall survival

Results for overall survival were similar to those obtained for recurrence free survival. On univariate analysis, response emerged as a highly significant predictor of overall survival. At the time of analysis 17 of the 19 fast responders remain alive, whereas 12 of the slow responders have died (hazard ratio: 9.48, 95% C.I. 2.10-42.73, p=0.003, Cox's regression). The overall survival is presented in Figure 5-15 (Table 14-20).

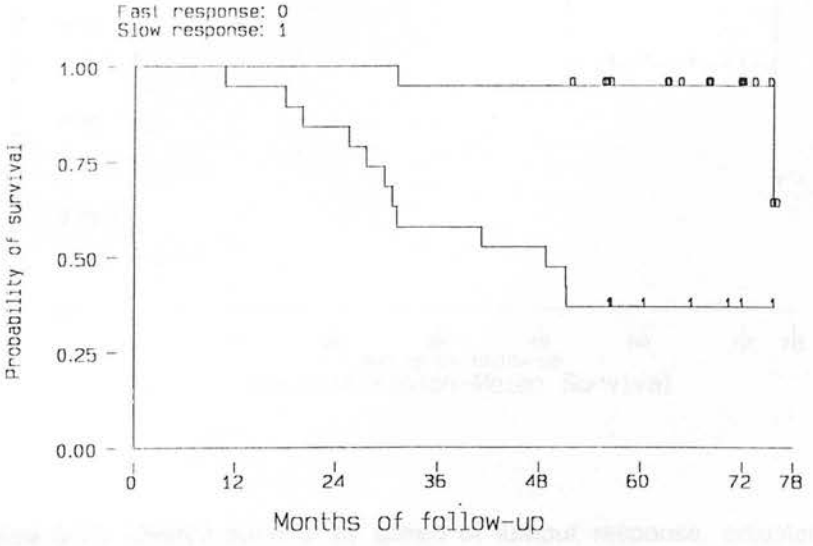

Figure 5-15: Overall survival by the rate of response to primary systemic treatment

On multivariate analysis, tumour response remained a significant independent predictor of overall survival. The results are presented in Table 5-18, and the adjusted Kaplan-Meier survival curve is shown in Figure 5-16 (Table 14-21).

	Hazard ratio	95% C.I.	Z=	P=
Tumour response	5.56	1.12-27.57	2.10	0.036
age	1.05	0.97-1.12	1.25	0.212
Tumour diameter	1.58	0.67-3.72	1.05	0.293
Axillary nodes	6.43	1.21-34.07	2.19	0.029
ER status	0.04	0.004-0.33	-2.97	0.003
Tumour differentiation	0.37	0.08-1.63	-1.31	0.189
Log Likelihood =-33.03			χ^2= 26.65	p = 0.0002

Table 5-18: Cox's proportional hazard model for the importance of speed of response to primary systemic treatment as a predictor of overall survival

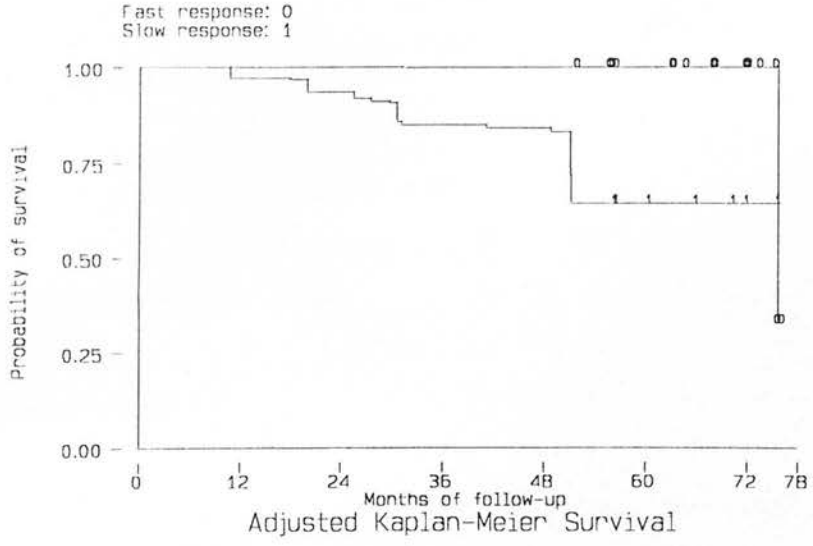

Figure 5-16: Overall survival by speed of tumour response, adjusted as indicated in Table 5-18

CHAPTER 6

6. Discussion

6.1 DETAILS OF TRIAL PROTOCOL

6.1.1 Tumour size as the main selection criterion

Tumour diameter was used as the primary entrance criterion for this study. Recruitment was confined to those patients with breast cancers greater than 4 cm in maximum diameter. The rationale for this is discussed below.

6.1.1.1 Selection of high risk patients

Patients at highest risk of recurrence are likely to derive the largest absolute reductions in the odds of recurrence and death from improvements in treatment. Confining the trial to the highest risk patients maximises the statistical power of the trial, and minimises the total number of patients who are exposed to "experimental" therapy (Pocock: 1983b). Since primary systemic therapy for operable breast cancer is experimental, it is ethically justified to confine it to those patients at the greatest risk of recurrence.

6.1.1.2 Assessment of risk

Although numerous prognostic indicators have been suggested for breast cancer (Sunderland and McGuire: 1990) the traditional measures of axillary nodal involvement and tumour size remain the most useful indicators of risk.

6.1.1.2.1 Axillary nodes

The presence of axillary lymph node involvement is the most discriminating prognostic indicator in breast cancer (Carter *et al:* 1989; Nemoto *et al:* 1980; Fisher *et al:* 1980; Valagussa *et al:* 1978; Adair *et al:* 1974). Furthermore the actual number of involved nodes has an inverse correlation with the length of recurrence free survival (Nemoto *et al:* 1980; Fisher *et al:* 1980; Fisher and Slack: 1970; Adair *et al:* 1974).

Axillary clearance is the only reliable method for obtaining accurate information about axillary nodes. Clinical staging is of no value (Borup Christensen and Lundgren: 1989; Fisher *et al:* 1981), and radiological methods remain experimental (Bruneton *et al:* 1986). Limited axillary staging using a node sample (Steele *et al:* 1985) requires a general anaesthetic, involves a significant surgical insult and does not provide information about the number of lymph nodes.

Initial axillary surgery will defeat much of the theoretical advantages of primary systemic treatment and cannot be used effectively as an entrance criterion for a trial.

6.1.1.2.2 Tumour size

Tumour size is an easily measurable parameter which can provide information on prognosis on two counts. Firstly, tumour size is an independent predictor of prognosis as indicated by multivariate analysis of risk factors, and analysis of outcome in patients with no axillary lymph node involvement (Nemoto *et al:* 1980; Koscielny *et al:* 1984; Fisher *et al:* 1980; O'Reilly *et al:* 1990; Adair *et al:* 1974). Secondly, size correlates directly with the presence and extent of axillary lymph node involvement (Carter *et al:* 1989; Paterson *et al:* 1982; Nemoto *et al:* 1980; Rosen *et al:* 1989; Fisher *et al:* 1969).

6.1.1.2.3 The choice of tumour size

Size has been found by some studies to relate to prognosis in a linear fashion throughout a range (Carter *et al:* 1989; Koscielny *et al:* 1984), while others have suggested that above a threshold value further increases in size are less significant determinants of prognosis. The threshold has most frequently been placed at 3-4 cm (Hartveit *et al:* 1984; Fisher *et al:* 1980; Duncan and Kerr: 1976; Fisher *et al:* 1969). The cut off level of 4 cm was originally chosen in order to avoid conflicts with breast conservation trials (section 2.3.5). The bulk of the evidence however suggests that there is little difference in prognosis between patients with tumours of 3-4 cm, and those who have tumours of larger than 4 cm. The protocol was later modified to allow inclusion of this additional group of patients.

6.1.2 Choice of locoregional therapy

Modified radical mastectomy is regarded as the gold standard for local control of breast cancer and was the surgical option chosen (section 1.2.2.3).

6.1.2.1 Modified radical mastectomy after response

Breast conservation after successful primary systemic treatment is the subject of a number of PST trials. These have universally shown increased local recurrence rates (Zurrida *et al:* 1994; Veronesi *et al:* 1995; Schwartz *et al:* 1994; Singletary *et al:* 1992). Since the principle aim of this trial was to compare the results of the systemic component of the treatment, locoregional therapy was standardised between the two treatment groups in order to avoid uncertainties introduced by variations in the quality of locoregional control. This standardisation has been maintained following the modification of the protocol in 1992.

6.1.3 Choice of systemic treatment

6.1.3.1 Conventional therapy

6.1.3.1.1 Postmenopausal women and node-positive premenopausal women

The choices of CMF chemotherapy as standard treatment for node-positive premenopausal women and of tamoxifen for all postmenopausal women are based on the results of large numbers of clinical trials and are well established (section 1.3.2.4).

6.1.3.1.2 Premenopausal node-negative women

The best treatment for premenopausal node-negative women is not clear. The absolute benefits derived from systemic therapy by node-negative women are relatively small because of their smaller absolute risks. The women in this trial had large cancers and were at increased risk regardless of their nodal status. It was therefore reasonable to offer them systemic therapy.

The choice of systemic therapy is more difficult. Although younger women do benefit from adjuvant tamoxifen, the size of the benefit is much smaller than that achieved with cytotoxic chemotherapy, with a proportional reduction in the odds of recurrence of 22% compared with 36% for chemotherapy (Early Breast Cancer Trialists' Collaborative Group. 1992). Since the proportional reduction in the odds of death achieved with chemotherapy is independent of nodal involvement, it may be argued that if node-negative premenopausal women require systemic therapy at all they should be offered the most effective treatment.

The choice of tamoxifen for this group of patients is a compromise between avoiding the side effects of chemotherapy and deriving smaller, but nonetheless significant benefits from tamoxifen.

6.1.3.2 Primary systemic treatment

Systemic treatment was offered as a "package" in the PST arm of the trial. Individual components of the package are nevertheless all of proven value as adjuvant treatments for breast cancer.

6.1.3.2.1 Ovarian ablation

In premenopausal women, ovarian ablation produces proportional reductions in the odds of death which are comparable in size to those achieved with cytotoxic chemotherapy (section 1.3.2.3). The treatment was confined to oestrogen receptor positive patients primarily because in the Edinburgh consecutive series, patients with ER<20U did not respond or progressed with ovarian ablation (Anderson *et al:* 1989). This decision is further supported by the findings from adjuvant trials, and studies in patients with advanced breast cancer as follows:

In the Scottish/Guys Hospital trial of chemotherapy versus ovarian ablation, patients with ER>19U derived the maximum survival advantage from oophorectomy (Scottish Cancer Trials Breast Group and ICRF Breast Unit, London: 1993). In the International Breast Cancer Study Group's (1990) trial of chemotherapy versus chemotherapy and ovarian ablation, addition of oophorectomy benefited the ER positive patients most.

In metastatic breast cancer, patients with high ER tumours experience the greatest response rates from ovarian ablation (Conte *et al:* 1989; Oriana *et al:* 1989; Chen *et al:* 1989; Kaufmann *et al:* 1989).

6.1.3.2.2 Mode of ovarian ablation

Ovarian ablation was initially achieved using the LHRH[1] analogue goserelin. The supra physiological, non-pulsatile levels of LHRH produced in the serum result in suppression of pituitary LH[2] and FSH[3] production and arrest in ovarian function (Furr: 1989; Williamson *et al:* 1988; Furr and Milsted: 1987). Administration of goserelin achieves postmenopausal oestrogen levels within 4 weeks of starting therapy (Bajetta *et al:* 1994a; Brambilla *et al:* 1991a; Kaufmann *et al:* 1989a; Nicholson *et al:* 1987a; Robertson *et al:* 1989a). In metastatic breast cancer LHRH analogues produce response rates similar to those achieved with other forms of ovarian ablation (Bajetta *et al:* 1994b; Brambilla *et al:* 1991b; Robertson *et al:* 1989b; Harvey *et al:* 1985b; Kaufmann *et al:* 1989b).

Goserelin was used as a reversible method of achieving ovarian ablation. The long term effects of medical ovarian ablation are not clear. In at least one study, direct comparison between goserelin and surgical oophorectomy suggested a survival trend in favour of the latter method (Boccardo *et al:* 1994). The trials showing a benefit in favour of adjuvant treatment with ovarian ablation are based on surgical or radiation ablation (Early Breast Cancer Trialists' Collaborative Group. 1992). It was therefore decided that once the responsiveness of the tumour to ovarian ablation had been established the patients receive conventional ovarian ablation by surgical oophorectomy.

6.1.3.2.3 Choice of chemotherapy regime

Doxorubicin is highly active against breast cancer, producing 40-50% remission rates in previously untreated metastatic breast cancer (Mouridsen: 1992; Jones *et al:* 1975; Bonadonna *et al:* 1975). Doxorubicin containing regimes produce greater overall remission

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[1]LHRH: Luteinizing Hormone Releasing Hormone (also gonadotropin releasing hormone)
[2]LH: Luteinizing Hormone
[3]FSH: Follicle Stimulating Hormone

rates and longer duration of response when compared with regimes not containing an anthracycline (Tormey *et al:* 1984; Aisner *et al:* 1987; Smalley *et al:* 1977; Muss *et al:* 1978; Bull *et al:* 1978).

Because of its high level of activity in metastatic breast cancer, doxorubicin has frequently been the first choice for the primary systemic treatment of locally advanced disease (section 2.2), and its use has been extended to the treatment of large operable breast cancers.

In the Edinburgh sequential series of primary systemic treatment the chemotherapy regime used consisted of cyclophosphamide, doxorubicin, vincristine and prednisolone. In that study a number of patients experienced significant neurotoxicity attributable to vincristine (Anderson *et al:* 1991). Since other direct comparisons have suggested equivalence between CMF and a regime of cyclophosphamide and doxorubicin (Fisher *et al:* 1989c; Fisher *et al:* 1990c), it was decided to drop vincristine from the regime.

6.1.3.2.4 Chemotherapy in postmenopausal patients

The use of chemotherapy in postmenopausal patients who fail to respond to tamoxifen is justifiable on the basis of evidence from adjuvant chemotherapy trials. Cytotoxic chemotherapy in women over the age of 50 produces reductions in the odds of recurrence and death which, although smaller than that seen for younger women, are still substantial (Early Breast Cancer Trialists' Collaborative Group: 1992).

It may be argued that high risk postmenopausal patients should receive tamoxifen and chemotherapy together as the benefits of chemotherapy appear to be in addition to the benefits of tamoxifen (Early Breast Cancer Trialists' Collaborative Group. 1992; Falkson *et al:* 1990; Fisher *et al:* 1990). Studies of the additive effects of the two modalities were however performed on patients who were at best selected for tamoxifen responsiveness by oestrogen receptor status. In the present trial patients receiving tamoxifen alone were known to be tamoxifen responsive. Combining chemotherapy with tamoxifen in known tamoxifen responsive patients is likely to be of little additional benefit. The toxicity of chemotherapy has significant adverse effects on quality of life which are particularly pronounced in older women. Any benefits are therefore likely to be outweighed by the toxicity of chemotherapy

(Gelber *et al:* 1996). It was therefore justified to use tamoxifen alone in those patients who proved responsive to it.

Postmenopausal women with oestrogen receptor poor tumours derive benefit from adjuvant tamoxifen which, in indirect comparisons, is similar in magnitude to the benefits seen with cytotoxic chemotherapy (Early Breast Cancer Trialists' Collaborative Group. 1992). It may therefore be argued that all postmenopausal patients should have received adjuvant tamoxifen.

The combination of tamoxifen with melphalan and 5-fluorouracil had an adverse effect on survival in several of the subgroups of patients in the NSABP trial (Fisher *et al:* 1983c). In cell culture systems tamoxifen reduces cytotoxicity of melphalan and 5-fluorouracil (Osborne *et al:* 1989). It was therefore argued that continuing tamoxifen could interfere with the efficacy of chemotherapy.

Tamoxifen however potentiates the actions of cyclophosphamide and doxorubicin in culture systems (Osborne *et al:* 1989). Furthermore, in a study of primary chemotherapy for operable and locally advanced breast cancers the combination of tamoxifen and chemotherapy produced the greatest rate of regression (Jacquillat *et al:* 1989a).

Even if there were persistent worries about adverse interaction between tamoxifen and chemotherapy, tamoxifen could still have been started following completion of chemotherapy. Tamoxifen treatment was not restarted however on the rationale that in non-responding postmenopausal patients further benefits from tamoxifen were unlikely.

6.2 EQUIVALENCE OF TREATMENT COMPONENTS

The hypothesis under test in this trial was that it is the timing and the selective nature of the new treatment package which has an influence on the outcome. Substantial differences in the actual treatment modalities received by the two groups would make it impossible to draw any conclusions in relation to the hypothesis under test.

There were three major differences in treatment modalities received by the patients in the two arms of the trial, as follows:

1. Choice of chemotherapy: six cycles of CAP versus six cycles of CMF

2. Greater use of chemotherapy for postmenopausal women in the PST arm

3. Oophorectomy versus tamoxifen for premenopausal women

These will be discussed in turn.

6.2.1 The choice of chemotherapy

The PST patients in this trial received a two drug regime with cyclophosphamide and doxorubicin. There were differences in the drug used and the way the treatments were administered. The equivalence of these regimes is discussed below.

6.2.1.1 Comparisons between regimes with and without an anthracycline

As discussed earlier, patients with metastatic disease given doxorubicin containing regimes have greater remission rates and longer times to progression than patients given the same regimes but with another drug (usually methotrexate) substituted for doxorubicin (Tormey *et al:* 1984; Aisner *et al:* 1987; Smalley *et al:* 1977; Muss *et al:* 1978).

In the adjuvant setting a number of trials have compared doxorubicin containing regimes with non anthracycline regimes. The largest of these were the NSABP trials B-11 and B-12. These compared a combination of melphalan and 5-fluorouracil against the same combination with

doxorubicin added. At seven years follow-up patients with oestrogen receptor poor tumours given doxorubicin had a disease free advantage, and a marginal overall survival advantage. There was however no difference when tamoxifen was added to the two treatment arms for patients with oestrogen receptor rich tumours (Fisher *et al:* 1989c).

The study by Misset and colleagues compared a CMF regime with CAF plus vincristine and found a survival advantage for the doxorubicin arm (Misset *et al:* 1992). An advantage for the anthracycline regime was also found by Beuzeboc and colleagues who compared methotrexate, mitomycin, 5-fluorouracil and cyclophosphamide with the same regime except for doxorubicin in place of fluorouracil (Beuzeboc *et al:* 1992) .

In these studies doxorubicin is either used as an extra drug or along with additional drugs. In some studies the anthracycline regimes are administered intravenously, thus guaranteeing compliance, where as at least one drug in the non-anthracycline regimes is administered by mouth. For these reasons none of these studies provide convincing evidence for the superiority of anthracycline regimes (Namer: 1993).

The most direct comparison between an anthracycline regime and an equivalent non anthracycline regime comes from the study by the International Collaborative Cancer Group (Coombes *et al:* 1996; Wils *et al:* 1993). In this study CMF (oral cyclophosphamide) was compared with a regime consisting of intravenous cyclophosphamide, the anthracycline epirubicin and 5-fluorouracil in 759 patients. Overall there was no advantage for the anthracycline containing regime, although a subset of patients given more intensive treatment seemed to benefit (Coombes *et al:* 1996).

The active components of the CAP regime used in the present study were intravenous cyclophosphamide and doxorubicin (AC). This type of regime has been directly compared with CMF in another large NSABP trial: B-15 (Fisher *et al:* 1990a). Treatment with 4 cycles of AC produced identical results to 6 cycles of CMF. The trial was interpreted as showing that AC was more acceptable to administer, although other commentators have suggested that equivalent lengths of treatment may have led to superior results for AC (Hortobagyi and Buzdar: 1993).

6.2.1.2 Differences in chemotherapy administration in this trial

The dose of cyclophosphamide was greater in the PST arm (1g/m^2 versus 600 mg/m^2). Furthermore patients given CAP experienced less marrow toxicity, which resulted in them receiving their treatment at a greater dose intensity than the CMF patients. Both the greater dose of cyclophosphamide (Hryniuk: 1988), and the greater dose intensity of treatment (Henderson *et al:* 1988) may have favoured the CAP regime.

6.2.1.3 Overall differences between chemotherapy regimes

The differences in outcome between anthracycline and non-anthracycline regimes are at best minor, and the choice of the drugs in the CAP regime is unlikely to have conferred an advantage to the PST patients as such, although the possible additional advantages of the more prolonged use of CAP are unknown. Furthermore CAP was better tolerated than CMF and was given at a greater dose intensity.

Although any advantages conferred by these factors are likely to be minor, the possibility that at least part of any observed differences in outcome are attributable to differences in chemotherapy, and not to the hypothesis under test cannot be excluded.

6.2.2 Frequency of use of chemotherapy

Compared with conventional treatment, a significantly larger number of PST patients received cytotoxic chemotherapy. The excess was entirely due to the treatment of postmenopausal patients.

The reduction in the odds of death reported by the EBCTCG (1992) in unselected women over the age of 50 was of the same order of magnitude for tamoxifen and chemotherapy. The treatment of more postmenopausal women with chemotherapy in itself therefore does not indicate more aggressive therapy for the PST patients.

It is possible that the more targeted use of chemotherapy in postmenopausal patients would produce differences in outcome which are greater than that seen in unselected patients. This possibility is consistent with the hypothesis being tested by this study.

6.2.3 Choice of endocrine therapy in premenopausal patients

Premenopausal patients with hormone responsive tumours received an oophorectomy after PST. Node-negative premenopausal patients were given tamoxifen in the conventional arm.

Ovarian ablation is a highly effective mode of adjuvant treatment for premenopausal patients, leading to proportional reduction in the odds of death in unselected premenopausal women of the order of 25%. By contrast unselected premenopausal patients derive limited benefit from tamoxifen with a reduction of 6% in the odds of death (EBCTCG: 1992).

Conventionally treated patients were selected for adjuvant tamoxifen by their negative axillary nodal status. The EBCTCG meta-analysis suggested that in premenopausal women the maximum benefits of both ovarian ablation and tamoxifen were likely to be had by node-negative patients (reductions of 42% and 19% respectively), although for both groups little statistical confidence could be placed in the actual size of the odds reduction (EBCTCG: 1992).

There are few direct comparisons between tamoxifen and ovarian ablation in premenopausal patients. In metastatic breast cancer the two modes of treatment produce similar response rates (Sunderland and Osborne: 1991; Rose and Mouridsen: 1988; Rose and Mouridsen: 1989). In the adjuvant setting ovarian ablation by radiation has been compared in 373 premenopausal women taking part in the Christie Hospital trial (Ribeiro and Swindell: 1988; Ribeiro and Swindell: 1985; Ribeiro and Palmer: 1983). In the most recent update of the trial there is no advantage for ovarian ablation, the overall trend being in favour of tamoxifen (Ribeiro and Swindell: 1992).

Overall any differences in the quality of endocrine treatment options offered to premenopausal patients in the two arms of the trial are probably minor and unlikely to influence the testing of the principal hypothesis of this trial.

6.3 DISCUSSION OF TRIAL RESULTS

6.3.1 Recruitment

Despite the complexity of the protocol, the trial was found acceptable by the majority of eligible patients, with over 90% of those approached during the first part of the trial agreeing to participate. One patient was excluded from analysis because of the presence of *in situ* disease only. This underlines the importance of histological confirmation of invasive disease before embarking on potentially toxic systemic therapy.

The recruitment rate was appreciably lower in the second part of the trial, with only 92 of 257 potential patients taking part. The main reason for this was the increasing concern that the conventional arm of the study was under-treating patients with potentially high risk cancers. Thus patients likely to have high risk tumours such as those with clinically obvious axillary lymph node involvement were frequently not approached. These patients were either treated by modifications of the primary systemic treatment regime outside the trial, or by one of the high dose conventional chemotherapy regimes under investigation within the breast unit. This concern was also reflected in the growing numbers of clinician initiated protocol violations during the later part of the study, particularly within the conventional arm.

6.3.1.1 Handling of protocol violations

6.3.1.1.1 First part of the trial

Protocol violations introduce bias into the trial, and to avoid this, analysis by intention to treat is customary (Pocock: 1983a). It was felt justifiable to exclude the patient with *in situ* disease only from survival analysis because she clearly did not have the disease the trial was designed to treat. Data from this patient were however used where questions of treatment morbidity were being addressed. The remaining four protocol violations consisted of patients swapping from one arm of the trial to the other. In order to maximise information about the efficacy and morbidity of the trial results were presented on the basis of actual treatments given. Survival

is the main outcome of the trial and data relating to it were therefore analysed by treatment intention and by actual treatments.

6.3.1.1.2 Second part of the trial

Protocol violations were more complex in the second part of the trial, and often occurred because patients were treated by regimes other than those stipulated in the trial protocol. The results of the whole study, including the second part were therefore analysed on the basis of treatment intention only.

6.3.2 Patient and tumour characteristics

The patients randomised to the two arms of the study were well balanced in terms of patient characteristics and tumour stage at diagnosis.

6.3.2.1 Axillary lymph nodes

Axillary nodal involvement is the most significant indicator of prognosis in breast cancer (Carter *et al:* 1989). There was no difference in the number of patients who were node-positive on histology between the two arms of the study. Most PST patients had their axillary lymph nodal status confirmed only after the completion of primary systemic treatment and the actual number of involved nodes was on average lower amongst the PST group of patients.

In a previous study where axillary nodal status was determined before and after systemic treatment, 14 of the 33 patients who had axillary involvement on node sampling subsequently had clear axillae (Anderson *et al:* 1991). Although the node sampling procedure is liable to remove all involved nodes in some patients (Steele *et al:* 1985) much of the discrepancy can be attributed to down staging of the tumour. These findings raise the possibility that more of the PST patients were originally node-positive and were therefore in a poorer prognostic category.

6.3.3 Length of treatment

6.3.3.1 Delay to start of treatment

Data were available for the first part of the trial. The additional surgery and tumour assessment that was required for the PST patients did not delay the start of definitive treatment. This was largely achieved through the use of day case surgery under local anaesthesia.

6.3.3.2 Duration of treatment

Data were available for all patients. The initial cancer treatment was on average significantly more protracted in PST patients. Three factors contributed to this:

1. Need for regular tumour monitoring during primary endocrine therapy.

2. Greatly prolonged treatment for patients in whom endocrine therapy failed.

3. The significantly larger number of patients who received cytotoxic chemotherapy.

The implications of the length of treatment on quality of life are discussed in chapter 7.

6.3.4 Treatment toxicity

Toxicity data were analysed for patients in the first part of the study only.

There was little toxicity amongst endocrine treated patients, the most significant being menopausal symptoms.

The CAP regime was better tolerated as regards myelotoxicity, but caused significantly greater minor toxicity in terms of nausea and mucositis.

Total alopecia in patients given CAP was expected, and patients were warned about it during the pre-recruitment counselling sessions. Alopecia was not a significant problem in the CMF treated patients.

6.3.5 Survival results

6.3.5.1 Differences in survival

All patients have been fully followed up, and there have been a large number of events, particularly amongst the patients in the first part of the study. At the present stage of follow-up no significant differences in disease free and overall survival have emerged. A trend in favour of the primary systemic treatment group became apparent early on during follow-up, and has been maintained.

6.3.5.2 The power of the study

The trial had a target of 326 patients, to be recruited at a rate of 60 per year. The trial was closed after 5 years and 9 months, having recruited 171 patients. The original survival estimate for the patients treated conventionally was 50% at 5 years. This projection appears to have been accurate for patients treated in the first part of the trial. This group have had a median recurrence free survival of 53 months by intention to treat, and it is likely that median overall survival will be around 5 years. The proportion of patients surviving within the PST arm at the present stage of follow-up are also consistent with the projected survival figures. The assumptions on which the trial's initial power calculations were based have therefore not been contradicted.

An absolute survival difference of 15% between 65% and 50% at 5 years represents a 30% reduction in the odds of death. This is comparable in size to the best results of the trials of adjuvant versus no adjuvant therapy (EBCTCG: 1992), and it will be unrealistic to expect a difference which is much larger than this.

If the projected survival of 65% at five years for primary systemic treatment is actually true, the first part of the trial on its own will have a 20% power of being able to detect this difference at the 5% level of statistical significance, and the power for the entire trial will be 45%.

The odds of death for those who have survived up to five years are reduced over the subsequent years (survival curves become less steep), and even if the postulated 30%

reduction in the odds of death is maintained, the absolute survival difference will not change a great deal, thus the power is unlikely to improve appreciably with longer follow-up.

The present report of the entire trial refers to a median follow-up of 37 months. A follow-up of at least five years is required before any conclusions can be drawn in relation to survival outcome.

6.3.5.3 The problem of inadequate recruitment

The recruitment target for the study was 60 patients per year. Despite the fact that more than 90% of eligible patients were recruited, the study had accrued only 70 patients by the end of the second year, well short of its projected target.

In an attempt to increase the recruitment rate, a number of other centres were approached regarding participation in the trial, and the trial was widely publicised amongst other surgeons treating breast cancer within the Lothian Region and surrounding areas. Mainly because of the complexity of the protocol, no other centres joined the trial, and only one patient was recruited from outside the Edinburgh Breast Unit.

The modification of the protocol in order to allow recruitment of patients with tumours over 30 mm, was also partly designed to improve recruitment rate. It was expected that this modification would have increased the number of patients potentially eligible for the trial to 80 per year. During the subsequent 41 months 257 potentially eligible patients did present, and had the previous recruitment rate of 90% been maintained, the trial would have achieved adequate power. Unfortunately the overall recruitment rate during the second part of the trial was only 35% for reasons which were explained in section 6.3.1. In retrospect the projected recruitment period of 5 years may have been too long for a trial treating patients within the very rapidly moving field of high risk breast cancer, leading to a loss of interest in the trial, particularly in its later stages. Recruitment to the trial was closed after the completion of its projected accrual period.

6.3.6 Indicators of prognosis

6.3.6.1 All patients

Axillary lymph node involvement and oestrogen receptor status were found to be highly significant indicators of prognosis, while tumour size and tumour histological grade were found not to be important.

6.3.6.1.1 Oestrogen receptor status

High oestrogen receptor content has previously been reported to correlate with improved prognosis in breast cancer (Paterson *et al:* 1982; Kinne *et al:* 1981; Knight, III *et al:* 1977) although not all studies have found a significant independent relationship (Fisher *et al:* 1983c; Singh *et al:* 1988c). In the present study a very strong relationship was found between oestrogen receptor status and survival. The relationship was found to be independent of other prognostic indicators.

6.3.6.1.1.1 The significance of the immuno-cytochemical assay

Previous reports examining the relationship between ER and prognosis have examined ER in homogenised tissue. The immuno-cytochemical assay has the advantage of being able to be performed on samples obtained by fine needle aspiration.

The characteristics of the subgroup of patients in whom ER was determined by the immuno-cytochemical assay were similar to those for the entire cohort of patients. ER determined on fine needle aspirates provides information about prognosis which is similar to that provided by examining homogenised tissues.

A number of different cut off values were examined for ER as measured by ERICA. The difference in prognosis was not sensitive to the cut off level. The presence of even very small amounts of ER staining correlated with a more favourable prognosis.

6.3.6.1.2 Axillary lymph nodes

The relationship between involvement of axillary lymph nodes, as assessed by primary surgery, and survival in breast cancer is well described (Carter *et al:* 1989; Fisher *et al:* 1981; Adair *et al:* 1974; Fisher and Slack: 1970). In the present study the relationship between nodal involvement and prognosis was confirmed. As in other studies the prognosis was related to the number of involved axillary lymph nodes (Fisher *et al:* 1983a) with patients with 10 or more tumours having the worst outlook.

6.3.6.1.3 Tumour size

Previous studies have indicated that while tumour size is an independent indicator of prognosis, the relationship is mainly true for smaller tumours. Once larger than 3-4 cm, further increases in size have little further adverse effects on prognosis (Hartveit *et al:* 1984; Fisher *et al:* 1980; Fisher *et al:* 1969; Carter *et al:* 1989). In the present study all patients were selected to have tumours larger than 30 mm, and tumour size was not found to relate to prognosis.

6.3.6.1.4 Tumour histological grade

While grade has been related to prognosis in other studies (Sunderland and McGuire: 1990; Meakin *et al:* 1979; Singh *et al:* 1988), its assessment can be difficult and its value as a prognostic indicator is highly dependant on consistent observers (Gilchrist *et al:* 1985). Histological grade was not found to relate to prognosis, either in the entire group of patients or in those treated with primary systemic therapy.

6.3.6.2 Patients given primary systemic treatment

As with the entire group, axillary lymph nodes and oestrogen receptor status were found to be independent indicators of prognosis in PST patients. In addition the speed of tumour response emerged as an additional indicator of prognosis.

6.3.6.2.1 Oestrogen receptor status

The relationship between ER and survival was strong amongst PST patients particularly when lymph node status was taken into account.

Measurement of preoperative ER levels was necessary in order to decide treatment. Prognosis was determined according to initial ER values. Post treatment oestrogen receptor levels, when available, had shown significant change from their starting values. Furthermore 9 patients changed their ER status with treatment.

Despite these changes, post treatment ER values retain their prognostic significance, with those patients with ER positive patients (ER>19) surviving significantly longer.

6.3.6.2.2 Axillary lymph nodes

Response to primary systemic treatment can potentially down stage the tumour such that some patients with originally involved axillae appear to become node-negative. There were strong indications of this down staging effect in the present study (section 5.2). There is little known about the relationship between axillary nodal involvement in axillae down staged following primary systemic treatment. In a study of 56 patients with large operable breast cancers treated by primary high dose chemotherapy, Botti and colleagues (1995), reported that the number of involved nodes following chemotherapy does correlate with survival at three years. A surprising finding in that study was that amongst node-positive patients those who had failed to respond to chemotherapy had a better prognosis. Response was defined according to UICC criteria and oestrogen receptor status was not considered.

In the present study patients who had uninvolved axillae following completion of primary systemic therapy had a better prognosis than those who had any residual involved lymph nodes. The size of the relationship was particularly strong when other prognostic indicators were taken into account, and was independent of tumour response.

The number of involved axillary lymph nodes recovered following primary systemic treatment correlated with survival. Because of the small numbers in each nodal category, little confidence can be placed on the results of comparisons between nodal subgroups,

nevertheless, the pattern is similar to that seen for all the patients, and patients with 4 or more residual nodes following systemic therapy have a grave prognosis.

6.3.6.2.3 Speed of tumour response

The relationship between overall tumour response to primary systemic therapy and long term survival has been observed previously by the Edinburgh group (Anderson *et al:* 1991), and has also been reported extensively by other investigators (Scholl *et al:* 1995; Sataloff *et al:* 1995; Hortobagyi *et al:* 1988; Jacquillat *et al:* 1991). In these studies the patients were divided on the basis of clinical regression according to the UICC criteria (Hayward *et al:* 1977). Clinical response defined in this way was reported not to relate to survival, whereas response determined by the histological examination of the tumour did (Scholl *et al:* 1995). Since detailed information about response was available in this study, it was possible to relate the pattern of response, and not simply the extent of final response to outcome.

The actions of cytotoxic chemotherapy and endocrine therapy are essentially different in that chemotherapy produces regression by inducing cell death, whereas endocrine treatment reduces cell proliferation and relies on the natural process of cell loss for tumour regression (Knabbe *et al:* 1987; Cullen *et al:* 1989). The relatively slow rate of regression by endocrine therapy has been well described (Gazet *et al:* 1991; Anderson *et al:* 1991; Anderson *et al:* 1989), and was again observed in the present study. In order to be able to relate tumour response to outcome it was necessary to define fast and slow response for each type of treatment separately. The dividing point between fast and slow responses was simply chosen to be the median response time, and the data were not explored for the "best" cut off point.

Patients with the fastest responses in their own category had a significantly better prognosis compared with those with slower responding tumours. Once corrected for other important prognostic indicators such as axillary nodal involvement and ER status, the size of the difference between the two groups was greatly reduced, but remained significant.

The present use of rate of response for determining prognosis is particularly important in attempting to quantify the prognosis of patients on endocrine therapy whose tumours respond relatively slowly and who may therefore have considerable residual tumour burden at the time of locoregional therapy.

6.3.6.2.4 Interactions between axillary lymph node status, ER and response

Tumours with high oestrogen receptor content are known to respond relatively poorly to chemotherapy (Livingston and Mortimer: 1987; Rosner *et al:* 1989; Anderson *et al:* 1989). In the present study only patients with ER<20U were given cytotoxic chemotherapy. The cut off level of "20U" is much higher than used in many previous studies (Oriana et al*:* 1989; Cocconi *et al:* 1990; Fisher *et al:* 1983), and patients given chemotherapy had a wide range of ER values. The speed of response to cytotoxic chemotherapy in patients with tumour ER levels of <20U depended on the actual level of tumour ER. Thus patients with the lowest ER values had the fastest responses to cytotoxic chemotherapy and were more likely to have few residual involved axillary nodes.

6.3.7 Assessment of prognosis following primary systemic treatment

One of the potential disadvantages of using primary systemic treatment is the loss of potential prognostic indicators. The results presented here indicate that tumour characteristics determined after primary systemic treatment retain their value as prognostic indicators. Furthermore, supplementary prognostic information is provided by observations regarding tumour response.

The tumour oestrogen receptor levels provide valuable information about the patient's prognosis, and may be used in making decisions regarding future systemic therapy. This information was available from the incisional biopsy taken prior to the start of primary systemic treatment. The current results indicate that oestrogen receptor values determined by the immuno-cytochemical assay, and oestrogen receptor levels determined from specimens obtained after systemic therapy, can provide similar information to the initial ER values, without the need for incisional biopsy.

The current results have also confirmed that residual axillary lymph node involvement is an important indicator of prognosis following primary systemic treatment, particularly when the confounding effect of oestrogen receptor content is accounted for. The grouping of the number of nodes into different prognostic categories (Fisher *et al:* 1983a), appears to apply after primary systemic therapy.

CHAPTER 7

7. Psychological Morbidity and Primary Systemic Treatment

7.1 INTRODUCTION

7.1.1 Psychological morbidity and cancer

7.1.1.1 Prevalence of psychiatric disorders

The experience of having cancer is a major stressful life event. The association between the diagnosis of malignancy and the presence of psychological disturbance was observed early in the history of the study of neoplasia (Goldfarb *et al:* 1967; Guy: 1759). It was however only recently that attempts have been made to formally observe and describe the psychological disturbances caused by cancer, and to distinguish them from simple "unhappiness" (Derogatis *et al:* 1983; Greer: 1985; Vachon and Lyall: 1976; Craig and Abeloff: 1974; Holland: 1977; Peck: 1972). Derogatis and his colleagues used structured interviews and applied strict diagnostic criteria to assess the state of mind of a sample of 215 randomly selected patients with a variety of malignancies. Nearly half the patients had formally identifiable psychiatric disease. The main symptoms were anxiety or depression in 85% of the patients, and the psychiatric problem was classed as an adjustment disorder in 68% (Derogatis *et al:* 1983).

7.1.1.2 The influence of treatment

The psychological blow of a cancer diagnosis is usually followed by the stress of having to cope with unpleasant treatment, be it major or mutilating surgery, cytotoxic chemotherapy or radiotherapy. Such treatment is in itself often accompanied by significant levels of anxiety and mood disturbance.

Cytotoxic chemotherapy has been associated with significant psychological morbidity. This is often directly related to the toxicity experienced with the treatment (Cooper *et al:* 1980; Maguire *et al:* 1980). Patients undergoing cytotoxic chemotherapy express significant anxiety in anticipation for each cycle of treatment (Nerenz *et al:* 1982). The anxiety has been linked to the severity of the expected acute side effects such as nausea , and may follow the classic patterns of a conditioned response (Jacobsen *et al:* 1993). Duration of treatment in itself

influences the severity of the psychological disturbances experienced by the patients, thus regimes lasting for a year are significantly more morbid compared with six month chemotherapy regimes (Hughson *et al:* 1986). Depression is another association with cytotoxic chemotherapy (Foltz *et al:* 1984), resulting more from chronic side effects such as generalised malaise or chronic fatigue. Depressive symptoms have also been observed in cancer patients undergoing radiotherapy (Berglund *et al:* 1991; Lasry *et al:* 1987). The prevalence of radiotherapy associated symptoms also appears to relate to the experience of physical side effects (Graydon: 1994). Studies which have examined the long term psychological sequelae of treatment suggest that the problems are most apparent at the time of treatment with most patients returning to normal after the completion of treatment (Berglund *et al:* 1991).

7.1.2 Psychiatric morbidity in breast cancer

Anxiety, depression and impairment of daily function particularly in relation to body image and sexual function, have been well documented following a diagnosis of breast cancer (Maguire *et al:* 1978; Renneker and Cutler: 1952; Bard and Sutherland: 1955; Morris *et al:* 1977). Much emphasis has been placed on the influence of breast loss on subsequent levels of psychological morbidity (Bartelink *et al:* 1985; Fallowfield *et al:* 1986; Maunsell *et al:* 1989; Fallowfield and Hall: 1991; Lasry *et al:* 1987; Roberts *et al:* 1972; Morris *et al:* 1977). Comparisons between mastectomy and breast conserving treatments have however made it clear that the type of surgery has little influence on the more serious psychological problems following breast cancer (Goldberg *et al:* 1992; Fallowfield *et al:* 1990; Fallowfield and Hall: 1991; van Heeringen *et al:* 1989; Wilson *et al:* 1988), and that these problems can largely be explained in terms of the diagnosis of malignancy and the effects of subsequent treatment (Senescue: 1963; Maunsell *et al:* 1992; Alagaratnam and Kung: 1986; Deadman *et al:* 1989).

7.1.3 Primary systemic treatment and psychiatric morbidity

Patients undergoing primary systemic therapy for cancer are likely to share the experience of all cancer sufferers in relation to the diagnosis of malignancy and subsequent treatment. There

is however little known about any additional psychological morbidity which may be associated with delaying the removal of the primary tumour.

7.1.3.1 Primary systemic treatment and breast cancer

Historically, removal of the breast tumour has been seen as the most important component of treatment for breast cancer (see section 1.2). It may be speculated that patients also perceive ablative surgery as the most important part of the treatment for their cancer. This contention is supported by the fact that many women continue to choose mastectomy over breast conservation when the choice is offered them (Wilson *et al:* 1988; Morris and Royle: 1987). If this is the case, surgical delay introduced by primary systemic treatment may be seen as a potential additional source of psychological stress.

There is little actual information available about patients' perceptions of what treatment is most appropriate for their cancer. It is however apparent that patients often overestimate their chances of survival with conventional therapy, and that they are much more receptive to new treatments when given accurate information about their prognosis (Siminoff *et al:* 1989; Fetting *et al:* 1990).

The present randomised trial has provided an opportunity for the study of psychiatric morbidity in relation to primary systemic treatment.

7.1.4 Measurement of psychological morbidity

7.1.4.1 The structured interview

The structured interview is the gold standard for assessment of psychological morbidity. Such interviews have the advantage of being able to address issues specific to a particular treatment, and to explore and identify new areas of concern. An interview is however a time consuming process, requiring trained staff, and may be open to different interpretations, depending on the diagnostic criteria in use (Spitzer *et al:* 1978; Wing *et al:* 1978).

7.1.4.2 Self rating questionnaires

Specific aspects of psychological morbidity can be explored in similar groups of patients using questionnaires which are completed by patients. The items in the questionnaires are usually derived from the detailed assessment of large numbers of structured interviews, but once validated, questionnaires provide a relatively simple way of assessing morbidity.

A number of such validated questionnaires have been developed which allow assessment of mood, psychological adjustment and general well-being of patients receiving hospital treatment, and in particular treatment for cancer.

Anxiety, depression and adjustment disorders are the most frequently observed psychological problems experienced by cancer patients (Derogatis *et al:* 1983). Two well validated questionnaires were selected to address these specific problems.

7.1.4.2.1 The Hospital Anxiety and Depression (HAD) scale

The HAD scale, developed in 1983 by Zigmond and Snaith (Zigmond and Snaith: 1983), has been designed specifically for the assessment of mood disorders in non-psychiatric hospital patients. It takes into account the effects of physical illness on mood and is designed to assess the states of anxiety and depression separately. The scale has been used extensively for the assessment of psychological morbidity in cancer patients (Morris and Royle: 1987; Fallowfield *et al:* 1990; Rosenqvist *et al:* 1993; Bulman: 1992; Hopwood *et al:* 1991; Hopwood *et al:* 1991). The results compare well with other methods of measuring anxiety and depression (Miller *et al:* 1995; Fallowfield *et al:* 1990).

7.1.4.2.2 The Mental Adjustment to Cancer (MAC) scale

The MAC scale described by Watson and her colleagues (Watson *et al:* 1988), was developed from analysing the outcome of structured interviews with breast cancer patients (Greer *et al:* 1979) and was later extended to include responses from patients with other forms of cancer. The five sub scales of the MAC scale are specifically designed to assess the various facets of the patients' style of adjustment to a cancer diagnosis. The MAC scale is of particular interest

in that the response to its different items have been linked to survival outcome from breast cancer (Greer *et al:* 1990; Greer *et al:* 1979).

The MAC and the HAD scales were used to assess psychological morbidity in patients entering this trial of selective primary systemic treatment in breast cancer.

7.1.5 Overall quality of life

Quality of life issues are assuming increasing importance in the assessment of the results of clinical trials, particularly where new treatments result in modest gains (Gelber and Gelber: 1995; Schipper: 1990). The present study of psychological morbidity addresses only one of the measures of quality of life. Some of the other aspects are covered by findings regarding length of treatment, treatment related toxicity and surgical morbidity.

7.1.5.1 Quality adjusted survival analysis

Quality adjusted survival analysis provides a way in which the impact of adverse effects of treatment on the patient's overall quality of life can be taken into consideration when interpreting the significance of small survival gains from treatment (Gelber and Gelber: 1995).

7.1.5.1.1 The TWiST method

In 1986 Gelber and colleagues described a method of dividing the patients survival following the diagnosis of cancer into three separate phases. The first is the diagnosis and treatment phase. The final phase is the time following the diagnosis of recurrence until death. The phase between these is termed "time without symptoms of disease and subjective toxic effects of treatment" and abbreviated as TWiST. Gelber and colleagues showed that the chemotherapy for node-positive premenopausal women, not only resulted in prolonged survival, but also produced gains in TWiST (Gelber and Goldhirsch: 1986).

7.1.5.1.2 The Q-TWiST method

7.1.5.1.2.1 Inadequacies of the TWiST technique

There are two problems with the TWiST method. The first problem is that it assigns no value to life during treatment, or after recurrence. The second problem is related to the treatment of censored data. The most common reason for censoring is that the patient is alive and recurrence free at the time of assessment. In the traditional TWiST methodology, the results assessed at a time point before the death of all patients are biased in favour of the treatment with the shortest duration since patients who may have undergone prolonged treatment, and are censored at the time of assessment may not have had enough time to derive the maximum benefit from their treatment (Gelber *et al:* 1989).

7.1.5.1.2.2 The Q-TWiST methodology

The problems inherent in the TWiST methodology have been overcome by using Quality adjusted TWiST or Q-TWiST (Gelber *et al:* 1995; Glasziou *et al:* 1990; Goldhirsch *et al:* 1989).

In this method the average time spent by the group of patients in each of the three health phases following diagnosis of cancer is calculated as the area under the survival curve for that health phase. The relative worth of each health phase is then assigned a numerical value between 'zero', representing a state comparable to being dead, and 'one' representing a state of "perfect health". This value is termed the "utility coefficient". The utility coefficient applicable to each health phase is multiplied by the area under the survival curve to calculated the quality adjusted mean time spent in that phase. The Q-TWiST is the sum of the quality of adjusted values for each of the three survival phases as follows:

$$\textbf{Q-TWiST}=(u_{TOX} \times TOX)+TWiST+(u_{REL} \times REL)$$

Where TOX= mean time in treatment phase, REL= mean time in recurrence phase, u= utility coefficient, TWiST= time without symptoms of disease and toxicity of treatment.

The utility coefficients are the components of the equation which can be assigned using quality of life data.

7.1.5.1.2.3 Comparing Q-TWiST for different treatments

The most practical way to compare the Q-TWiST for two treatment groups is to estimate the variance using a "bootstrap" technique (Efron: 1980). In this technique the data are sampled with replacement from the original data to derive a new sample equal in size to the original. The analysis is then repeated on the new data set a large number of times to generate a set of results. The standard deviation of this "bootstrap sample" can then be used as the variance for the Q-TWiST.

The basic techniques have been developed to allow inclusion of covariates using proportional hazard models (Cole *et al:* 1993), and quality adjusted meta-analysis (Gelber *et al:* 1996; Cole *et al:* 1995).

7.1.5.1.2.4 The application of Q-TWiST

The technique has been used to show that chemotherapy increases quality adjusted survival in premenopausal women (Cole *et al:* 1995; Hurny *et al:* 1996), but has little impact in postmenopausal women (Gelber *et al:* 1996). It has also been used in assessing the impact of Zidovudine treatment for acquired immunodeficiency syndrome (Gelber *et al:* 1992), and the outcome of clinical intervention on the quality of life with epilepsy (Schwartz *et al:* 1995).

The method was used in this trial to assess the quality adjusted survival difference between patients treated by primary systemic treatment and those treated conventionally.

7.2 PATIENTS AND METHODS

7.2.1 Patients

All patients were those taking part in the main trial of primary systemic treatment. The psychological study was confined to the first 69 patients recruited to the trial. Patients were independently asked to participate in the psychological study. Patients with known previous psychiatric illness and those who required psychiatric intervention during the study were excluded. Patients who developed recurrence within 8 weeks of completing treatment as defined in section 3.5.1.1 were also excluded.

7.2.1.1 Psychological support

All patients were seen by a specialist breast care nurse at the time of first presentation, at the time of confirmation of diagnosis and prior to making any final decisions regarding any subsequent treatment. Furthermore, the patients had unrestricted access to the breast care nursing team at all other times, and were seen at regular intervals during prolonged treatments. Before entry into the trial each patient had two full consultations on consecutive days with the surgeon in charge of conducting the trial. The patient was seen along with a close friend or a relative, and a breast care nurse was also present. During these consultations the rationale for the trial and all possible treatments were fully discussed with the patient. Written information was provided following the first consultation, and patients were asked to choose a treatment option following the second consultation. Following completion of all treatment, patients were given further verbal information regarding their specific type of tumour, lymph node status and oestrogen receptor status. Specific information in relation to prognosis was only given if directly asked for by the patient.

Patients who displayed significant difficulty in coping with their diagnosis or treatment were referred for a formal psychiatric consultation.

7.2.1.2 Baseline patient data

Data were available for patients' general characteristics and tumour characteristics, as described in section 4.1.2. Baseline social parameters were established by obtaining data regarding patients social class, marital status and employment status as follows:

7.2.1.2.1 Social class

Occupational social class, according to the Registrar General's Classification of occupations (O.P.C.S.: 1980), was recorded. Patients were classified according to their own occupation if single and according to husband's occupation if married.

The following categories of social class were recorded:

1. I. Professional
2. II. Managerial
3. III non manual
4. III. manual
5. IV. Skilled manual
6. V. Unskilled manual

For the purposes of statistical analysis social classes I, II and III non manual were categorised as "NON-MANUAL", while social classes III manual, IV and V were classed as "Manual".

7.2.1.2.2 Marital status

This was recorded as follows:

1. Married or living with partner
2. Single, widowed or divorced living with another adult
3. Single, widowed or divorced living with children
4. Single, widowed or divorced living alone

For the purposes of analysis, patients in category 1 were designated "WITH PARTNER" while those in categories 2, 3 and 4 were classed as "WITHOUT PARTNER"

7.2.1.2.3 Employment status

The patients' own employment status was recorded as described by the patient, and classed as follows:

1. Currently in work
2. Previously in work, retired
3. Previously in work, Unemployed
4. Housewife

For the purposes of analysis patients in category 1 were classed as "IN PAID WORK" while those in categories 2, 3 and 4 were allocated to the single category of "NOT IN PAID WORK".

7.2.2 Psychological questionnaires

7.2.2.1 The questionnaires

The Hospital Anxiety and Depression Scale (HAD scale) and the Mental Adjustment to Cancer Scale were used. The questionnaires are presented and described in detail in the appendix (section 14.2.).

Patients were given the questionnaires and asked to complete and return them on their next visit or to post them back. Those who failed to return their questionnaires were reminded once. If patients still failed to return a questionnaire after being reminded, they were categorised as having declined to take part in the study of psychological morbidity.

7.2.2.1.1 The HAD scale

This is a general questionnaire designed for assessment of reaction to illness. It assess 2 factors: anxiety and depression. Each factor is assessed by seven questions.

In addition to assessing the degree with which the patient's mood is affected by anxiety or depression, the HAD scale is designed to detect pathological levels of either trait. The cut off can be set anywhere between 8 and 10, depending on the desired level of sensitivity and specificity (Zigmond and Snaith: 1983). For this study a score of 1 to 9 was regarded as within normal limits. Scores of 10 and over were regarded as pathological.

7.2.2.1.2 The MAC scale

This questionnaire is specifically designed to assess the patient's attitude to a diagnosis of cancer. It has 40 items which address 5 factors. The factors and their possible range of scores are as follows:

1. Fighting spirit	16-64
2. Hopelessness and helplessness	6-24
3. Anxious preoccupation	9-36
4. Fatalism	8-32
5. Avoidance	1-4

7.2.2.2 Timing

Patients undergoing primary systemic treatment were requested to complete questionnaires early and late during the period of systemic therapy, but before undergoing mastectomy. All patients were requested to complete the same questionnaires after the completion of their hospital based treatment, as defined in section 3.5.1.1.

7.2.3 Quality adjusted survival analysis

The Q-TWiST method, as introduced in section 7.1.5.1.2 was used for quality adjusted survival analysis.

7.2.3.1 Phases of survival

The three phases of survival were defined as follows:

7.2.3.1.1 The treatment phase

This phase lasted from the time of entry into the trial until the date of discharge to long term follow-up. Hospital visits for breast reconstruction were not regarded as cancer treatment. Time of discharge to long term follow-up was defined as follows:

7.2.3.1.1.1 Cytotoxic chemotherapy

Three weeks after the final cycle of chemotherapy, or the date the patient had fully recovered from any immediate side effects of their final cycle of chemotherapy, whichever was later.

7.2.3.1.1.2 Endocrine treatment

The time when the patient was first started on long term tamoxifen, or when the patient had fully recovered from any complications of surgery, whichever was later.

7.2.3.1.1.3 Radiotherapy

If radiotherapy was the last adjuvant treatment given, the patient was discharged to long term follow-up three weeks after the final dose of radiotherapy, or the date the patient had fully recovered from any immediate side effects of radiotherapy, whichever was later.

7.2.3.1.2 The recurrence phase

7.2.3.1.2.1 Local recurrence

Local recurrence, without systemic recurrence, can be regarded as a condition which can be treated within a definable period of time, leaving the patient to continue to enjoy good health thereafter. For the purpose of calculating Q-TWiST, The duration of treatment for local recurrence was measured and added to the total time with systemic recurrence.

Treatment for local recurrence was defined as starting on the day of diagnosis, and continued until the patient had again been discharged to long term follow-up. The criteria for discharge were as defined for the treatment of primary disease.

7.2.3.1.2.2 Systemic recurrence

The recurrence phase was defined as starting on the day when diagnosis of systemic recurrence was confirmed, and continued until the time of death.

For patients with local recurrence prior to systemic recurrence, the date of diagnosis of systemic recurrence was brought forward by the duration of treatment for local recurrence.

Patients with treated local recurrence who at the time of diagnosis had not developed systemic recurrence, were defined as having had a date of recurrence equal to the date of analysis minus the duration of treatment for local recurrence.

7.2.3.1.3 TWiST phase

Survival time which was not allocated to treatment or recurrence was defined as TWiST.

7.2.3.2 Utility coefficients

The utility coefficient for TWiST was designated as "one" (7.1.5.1.2.2). Analyses were then performed to cover all possible extreme situations. No further analysis was performed once it was established that no difference in quality adjusted survival could be detected even in the extreme situations.

7.2.3.2.1 Comparison of overall survival

Treatment and recurrence phase are designated as having a utility of one. This represents the extreme situation where treatment and recurrence are assumed to have no impact on quality of life. The analysis simply compares overall survival between the two groups.

7.2.3.2.2 Comparison of disease free survival

Life after recurrence is given a utility of zero. and life with treatment a utility of one. The analysis compares recurrence free survival.

7.2.3.2.3 Comparison of treatment free survival

Treatment phase was given a utility coefficient of zero. The results represent overall survival after completion of all treatments.

7.2.3.2.4 Comparison of TWiST survival

Treatment and recurrence phase are designated as having no utility. This represents the extreme, where the quality of life during treatment and recurrence is comparable to being dead. The analysis compares only the TWiST.

7.2.4 Analytical methods

All statistical analyses were performed using the statistical software package Stata 4.0 for Windows, Stata Corporation, 702 University Drive East, College Station, Texas 77840 USA.

The results were analysed on the basis of actual treatments received.

7.2.4.1 Direct comparisons

Actual scores were treated as ordered categorical data and compared using non parametric techniques. Paired data were compared using Wilcoxon signed-rank test and unpaired data using the Mann-Whitney U test. Proportions were compared using Fisher's exact test. Where

a "mean" value is reported (e.g.: mean age) comparisons were made using Student's t-test. Other tests are specified within the results section.

7.2.4.2 Patient and tumour factors and psychological outcomes

The relationships between patient and tumour characteristics (explanatory variables) and psychological outcomes (outcome variables) were assessed using univariate and multivariate techniques.

7.2.4.2.1 Univariate techniques

Where the explanatory variables were dichotomous the differences in the outcomes for each category were compared using the Mann-Whitney U test. The relationships between continuous explanatory variables and the outcome variables were examined using the Spearman Rank correlation coefficient.

The following categorical explanatory variables were examined:

1. Treatment option: Conventional or primary systemic treatment
2. Adjuvant treatment: Cytotoxic chemotherapy or endocrine treatment
3. Axillary lymph node status: Nodes involved or not involved
4. Oestrogen receptor status: Negative (<20U) or positive (>19U)
5. Breast reconstruction: Performed and not performed
6. Social class: Manual or Non-manual
7. Partnership: With partner or not with partner
8. Employment: Working or Not in work

The following continuous explanatory variables were examined:

1. Age
2. Tumour diameter at diagnosis

Tumour response was examined in relation to psychological scores late during primary systemic treatment.

7.2.4.2.2 Multivariate techniques

Because of the relatively small number of cases involved, clinically important degrees of confounding may have gone unnoticed in univariate analysis. The relationship between explanatory and outcome variables was therefore further examined using multivariate techniques.

Since psychological outcome variables are categorical, an ordered logistic regression model (McCullagh: 1977) was used. The frequency distributions of scores for each outcome variable were examined and an appropriate number of ordered categories, each including approximately equal number of cases were derived. The number of categories were as follows: Anxiety: 8, Depression: 6, Fighting spirit: 9, Hopelessness/ helplessness: 4, Anxious preoccupation: 7, Fatalism: 8 and Avoidance: 3. The re-coded outcome variables were used to build multiple regression models.

All 10 explanatory variables were tested starting with variables with the greatest degree of significance on univariate analysis. Those variables which contributed to the model with $p<0.15$ were retained in the model.

7.2.4.3 Analysis of survival

To assess the relationship between each psychological outcome variable and distant disease free survival and overall survival, each outcome variable was re-coded into a dichotomous variable by coding values lower than the median score to zero and those greater than the median to one. The outcomes for the categories were compared using a log-rank test. Where a difference was found, the relationship was further examined in a multivariate model using Cox's proportional hazard model (Cox: 1972). Axillary lymph node status and the natural logarithm of the actual oestrogen receptor measurements were entered into the model as well as any other patient or tumour factors which were found to relate to psychological outcome.

7.2.4.4 Quality adjusted survival analysis

The principles of Q-TWiST analysis are summarised in section 7.1.5.1.2.

The area under the survival curves was calculated from life tables. This is equal to the sum of the product of the probability of survival at the beginning of each time band and the length of that time band, and represents "mean" survival. The standard error of mean survival was estimated using the "bootstrap" procedure, by re-sampling the data 2500 times. The standard deviation of the bootstrap sample by definition represents the standard error of the mean.

Q-TWiST analysis was performed using a computer programme module specially written to work with the statistical analysis package "Stata 4". The details of the programme are provided in the appendix (14.3).

7.3 RESULTS

7.3.1 Patients

7.3.1.1 Recruitment

Of the 69 patients recruited for the psychiatric study, 34 (including 2 originally randomised to primary systemic treatment arm) received conventional therapy and 35 (including one patient originally randomised to conventional therapy) received primary systemic treatment. Thirty patients given primary systemic treatment and 27 patients treated conventionally returned completed psychological questionnaires.

7.3.1.2 Reasons for not entering the study

7.3.1.2.1 Primary systemic treatment arm

Thirty of the 35 eligible patients participated in the psychological study. Four patients declined to take part. One patient who required treatment for an overt anxiety state was excluded.

All patients completed two sets of questionnaires, one at the start and one following completion of treatment. Twenty-eight patients also completed a third questionnaire late during primary systemic treatment.

7.3.1.2.2 Conventional arm

Of the 34 patients treated by conventional therapy, 27 patients took part in this study. Three patients declined to take part. Two patients developed recurrence during or immediately after the completion of treatment and were excluded. Two further patients who required psychiatric intervention, one for an overt anxiety state and the second for depression, were also excluded.

7.3.1.3 Patient characteristics

Distribution of various patient and tumour characteristics for patients taking part in the study and those patients remaining outside the study are summarised in Table 7-1. The general characteristics of participants and non-participants were similar, although a greater proportion of the non-participants (7/ 12 vs. 13/ 57), also chose not to undergo breast reconstruction. Five of the 7 patients declining to take part had also declined breast reconstruction.

	In the study	Not in the study		
Number of patients	57	12	Stat	p=
Age (mean±SEM)	50.0±1.3	54.6±3.2	t=1.41	0.16
Treatment (PST / CONV)	30 / 27	5 / 7	Exact	0.540
Social Class (man/nonman)	20 / 37	6 / 6	Exact	0.347
Partner (with/without)	31 / 26	7 / 5	Exact	1.000
Employment (working/not)	31 / 26	4 / 8	Exact	0.218
Tumour size (median, range)	45 (41-80)	45 (41-85)	z=0.06	0.956
ER (median, range)	19 (0-472)	17.5 (0-552)	z=-1.01	0.331
Axillary nodes (pN1 / pN0)	33 / 24	7 / 5	Exact	1.000
Adjuvant therapy (endo/chemo)	26 / 31	7 / 5	Exact	0.540
Breast reconstruction (yes/no)	44 / 13	5 / 7	Exact	0.031

Unless otherwise specified, number of patients in each category are reported. MAN: manual , NON MAN: non manual, ER: Oestrogen receptor levels, pN1: involved nodes, pN0: uninvolved nodes, ENDO: endocrine therapy, CHEMO: cytotoxic chemotherapy.

Table 7-1: Characteristics of patients in the study of psychological morbidity

The distributions of basic social profiles of the patients in the primary systemic treatment arm and those in the conventional arm of the study are presented in Table 7-2. The profiles are confined to those patients taking part in the study of psychological morbidity. There were no differences between the two groups.

	PST	CONV		
Number of patients	30	27	Stat	P=
Age (mean±SEM)	49.7±1.9	50.2±2.0	t=0.22	0.827
Breast reconstruction (yes/no)	25 / 5	19 / 8	Exact	0.345
Social Class (man/nonman)	19 / 11	18 / 9	Exact	1.000
Partner (with/without)	17 / 13	14 / 13	Exact	0.793
Employment (working/not)	17 / 13	14 / 13	Exact	0.793

Number of patients in each category are reported.

Table 7-2: Social characteristics of patients in the study of psychological morbidity

7.3.1.4 Timing of questionnaires

Of the 30 patients in the primary systemic treatment arm of the study all returned questionnaires in the initial stages and 28 in the late stages of preoperative systemic treatment.

Following completion of treatment, 30 further questionnaires were completed by patients undergoing primary systemic treatment and 27 by patients in the conventional arm of the study.

7.3.1.5 Relationship between questionnaire items

A total of 115 questionnaires were completed. The HAD and the MAC scale together covered 7 items. To assess whether the items were related to each other all 115 questionnaires were considered together. The correlation coefficients between each of the seven items were calculated using linear regression. The correlation matrix is presented in Table 7-3. Although significant relationships were detected between a number of the items, these were generally weak with the values for the correlation coefficients ranging between 0.05 and 0.55. The largest relationship was between the two items of the HAD scale (ρ=0.66, p=0.0001).

	ANX.											
DEP	0.66	0.001	DEP.									
F.S.	-0.40	0.001	-0.46	0.001	F.S.							
H.H.	0.51	0.001	0.42	0.001	-0.55	0.001	H.H.					
A.P.	0.42	0.001	0.33	0.001	-0.05	0.628	0.28	0.003	A.P.			
FAT.	0.18	0.060	0.05	0.629	-0.1	0.268	0.26	0.007	0.15	0.101	FAT.	
AVO	0.28	0.002	0.31	0.001	-0.15	0.100	0.19	0.040	0.53	0.001	0.17	0.066
	ρ=	p<	ρ=	p<	ρ=	p<	ρ=	p<	ρ=	p<	ρ=	p<

ANX.: anxiety, DEP. Depression, F.S.: Fighting spirit, H.H.: Hopelessness/ helplessness, A.P.: Anxious preoccupation, FAT.: Fatalism, AVO.: Avoidance. Adjusted Spearman Rank correlation coefficient and the significance of the correlation are presented.

Table 7-3: Correlation matrix, demonstrating the relationship between the seven items covered by the HAD and the MAC scales

In the studies leading to the design of the MAC scale, "fighting spirit" and "avoidance" behaved as desirable mechanisms of psychological adjustment, while other factors indicated poor adjustment (Watson *et al:* 1988; Watson *et al:* 1984). In the present study avoidance scores directly correlated with all other scores except for fighting spirit where the relationship was an inverse one. It therefore appears that in this group of patients avoidance behaved as a negative psychological trait.

Each of the seven items were analysed independently.

7.3.2 Psychological score and primary systemic treatment

7.3.2.1 Early versus late during primary systemic treatment

Twenty-eight patients completed questionnaires during early and the later stages of primary systemic treatment.

7.3.2.1.1 Abnormal levels of anxiety and depression

Anxiety and depression scores of 10 and over using the HAD scale were classed as pathological. The number of patients with a pathological score during the early and late parts of treatment are presented in Table 7-4. Abnormal levels of anxiety were common, affecting

one in five patients. Depression was rare. There were no significant differences in the number of patients with pathological anxiety and depression scores at different stages of preoperative treatment.

	Early during PST	Late during PST	Stat	p=
Total	30	28		
Anxiety score •10	6 (20.0%)	6 (21.4%)	Exact	1.000
Depression score •10	0	1 (3.6%)	Exact	0.483

Numbers of patients in each category are reported

Table 7-4: Patients with pathological levels of anxiety and depression early and late during primary systemic treatment

7.3.2.1.2 Changes in scores with treatment

The actual scores for the early and late stages of treatment for the 2 items of the HAD scale and the 5 items of the MAC scale were compared using the Wilcoxon signed-rank test. The median and range of scores for each item are presented in Table 7-5. Overall, there was no significant change in the scores for any of the questionnaire items. There was however a tendency for patients to have increased levels of depression (p=0.068) and to be more anxiously pre-occupied with their cancer (p=0.052).

Factor (range)	Early during PST	Late during PST	Change			z=	p=
Total	28	28	inc	dec	nc		
ANX. (0-21)	7.5 (2-15)	7 (0-18)	8	14	*6*	-1.22	0.224
DEP. (0-21)	**2 (0-9)**	**2.5 (0-10)**	**13**	**5**	***10***	**-1.82**	**0.068**
F.S. (16-64)	53 (46-62)	51.5 (42-63)	12	14	*2*	-0.63	0.532
H.H. (6-24)	8 (6-18)	8 (5-18)	11	8	*9*	-1.11	0.267
A.P. (9-36)	**21 (9-28)**	**22.5 (12-28)**	**15**	**10**	***3***	**-1.94**	**0.052**
FAT. (8-32)	19 (9-24)	19 (8-27)	11	8	*9*	-1.07	0.283
AVO. (1-4)	2 (1-4)	2 (1-4)	1	3	*24*	-1.00	0.317

ANX: anxiety, DEP: Depression, F.S.: fighting spirit, H.H.: Hopelessness/ Helplessness, A.P.: anxious preoccupation, FAT.: Fatalism, AVO.: Avoidance. The possible range of scores for each item are presented. The "change" column refers to the number of patients whose scores increased (inc), decreased (dec) or did not change (nc). Scores were compared using Wilcoxon signed-rank test

Table 7-5: Responses to the elements of the HAD and MAC scales during the early and late part of primary systemic treatment

7.3.2.2 Change in score before start and following completion of treatment

Thirty patients completed questionnaires at the start of primary systemic treatment and following the completion of all treatments.

7.3.2.2.1 Abnormal levels of anxiety and depression

Following completion of treatment none of the patients maintained a pathological level of anxiety or depression, significantly fewer than the 6 patients who had abnormal anxiety levels during treatment (p=0.012, Fisher's exact test).

7.3.2.2.2 Changes in scores for individual questionnaire items

The points scored for the 2 items of the HAD scale and the 5 items of the MAC scale during primary systemic treatment and following completion of treatment were compared using the Wilcoxon signed-rank test. The median and range of scores for each item are presented in Table 7-6.

Factor (range)	During treatment	After treatment	Change			z=	p²
Number of patients	30	30	inc	dec	nc		
ANX. (0-21)	7.5 (2-15)	3.5 (0-9)	3	26	*1*	-4.42	0.001
DEP. (0-21)	2 (0-9)	2 (0-9)	8	14	*8*	-1.47	0.142
F.S. (16-64)	53 (46-62)	53 (42-62)	14	12	*4*	-0.17	0.868
H.H. (6-24)	8 (6-18)	7.5 (6-15)	7	18	*5*	-1.89	0.059
A.P. (9-36)	21 (9-28)	20 (10-26)	10	18	*2*	-2.24	0.025
FAT. (8-32)	19 (9-24)	17.5 (8-23)	12	12	*6*	-0.80	0.425
AVO. (1-4)	2 (1-4)	1.5 (1-4)	2	13	*15*	-2.84	0.005

The possible range of scores for each item are presented. The "change" column refers to the number of patients whose scores increased (inc), decreased (dec) or did not change (nc). Scores were compared using the Wilcoxon signed-rank test. ANX: anxiety, DEP: Depression, F.S.: fighting spirit, H.H.: Hopelessness/ Helplessness, A.P.: anxious preoccupation, FAT.: Fatalism, AVO.: Avoidance

Table 7-6: Responses to the HAD and MAC scales during primary systemic treatment and following completion of all treatment.

There was a highly significant decrease in anxiety levels following completion of treatment, 26 patients showing a reduction in their score (median score of 3.5 vs. 7.5, p=0.0001, Wilcoxon signed-rank test, Figure 7-1). There were also significant reductions in the levels of anxious preoccupation (median of 20 vs. 21, p=0.025, Wilcoxon signed-rank test) and avoidance (median of 1.5 vs. 2, p=0.005, Wilcoxon signed-rank test). Furthermore, there was a reduction in the levels of hopelessness/ helplessness which approached significance (median 7.5 vs. 8, p=0.059, Wilcoxon signed-rank test).

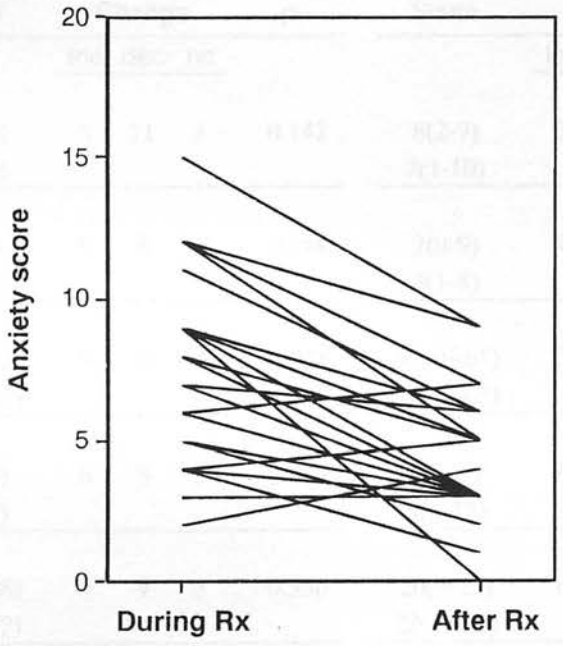


Figure 7-1: Change in the anxiety score as assessed by the HAD scale with completion of primary systemic treatment

7.3.2.3 Response to primary systemic therapy and psychological scores

Three of the 28 patients who returned a second questionnaire had failed to respond to primary systemic treatment. Four further patients who eventually responded to cytotoxic chemotherapy had failed to respond to initial endocrine therapy. The psychological scores in this group of

seven patients were analysed separately from the scores for the 21 patients who responded to treatment. Median and range of scores and the number of patients who showed a change in their score and the direction of the change are presented in Table 7-7. There was no significant change in any of the scores for responding patients. The scores for hopelessness/ helplessness, anxious preoccupation and fatalism all showed a tendency to increase for non-responding patients although an increase in anxious preoccupation was the only score to achieve statistical significance.

	Responding patients (n=21)					Non responding patients (n=7)				
Factor	Score	Change			p=	Score	Change			p=
		inc	dec	nc			inc	dec	nc	
ANX.										
Early	7(3-15)	5	11	*5*	0.142	8(2-9)	3	3	*1*	0.916
Late	7(0-18)					7(1-10)				
DEP.										
Early	2(0-7)	9	4	*8*	0.244	2(0-9)	4	1	*2*	0.129
Late	2(0-10)					3(1-8)				
F.S.										
Early	53(46-62)	9	10	*2*	0.935	56(46-61)	3	4	*0*	0.397
Late	52(42-63)					51(47-63)				
H.H.										
Early	9(6-18)	6	8	*7*	0.580	8(6-9)	**5**	**0**	*2*	**0.042**
Late	8(5-18)					9(6-13)				
A.P.										
Early	22(15-28)	9	9	*3*	0.350	20(9-23)	6	1	*0*	0.203
Late	23(16-27)					22(12-28)				
FAT.										
Early	19(9-24)	6	7	*8*	0.887	19(16-24)	5	1	*1*	0.139
Late	19(8-23)					21(18-27)				
AVO.										
Early	2(1-4)	0	2	*19*	0.157	2(1-4)	1	1	*5*	1.000
Late	2(1-4)					2(1-4)				

Median (range) of scores and the number of patients whose scores increased (inc), decreased (dec) or did not change (nc) are presented. Early and late values were compared using the Wilcoxon signed-rank test

Table 7-7: Median and range of psychological scores during primary systemic treatment according to response

To further assess the effects of response on psychological well-being the scores for responders and non responders were compared using the Mann-Whitney U test. The median and range of scores are presented in Table 7-8.

	Early during PST			Late during PST		
Factor	R. (n=23)	N.R. (n=7)	p=	R. (n=21)	N.R. (n=7)	p=
ANX.	7 (3-15)	8 (2-9)	0.621	7 (0-18)	7 (1-10)	0.632
DEP.	2 (0-7)	2 (0-9)	0.766	2 (0-10)	3 (1-8)	0.727
F.S.	53 (46-62)	56 (46-61)	0.538	52 (42-63)	51 (47-63)	0.811
H.H.	9 (6-18)	8 (6-9)	0.158	8 (5-18)	9 (6-13)	0.627
A.P.	22 (15-28)	20 (9-23)	0.094	23 (16-27)	22 (12-28)	0.540
FAT.	19 (9-24)	19 (16-24)	0.225	**19 (8-23)**	**21(18-27)**	**0.029**
AVO.	2 (1-4)	2 (1-4)	0.578	2 (1-4)	2 (1-4)	0.328

Median and range of scores for each category are reported. R: response to primary systemic treatment from the start. NR: No response. Scores were compared using the Mann-Whitney U test.

Table 7-8: Difference in psychological scores between responding and non responding patients

On univariate analysis patients who had failed to respond to treatment appeared to be significantly more fatalistic in their attitude compared with those patients who did respond (z=2.18 p=0.029, Mann-Whitney U test). However when adjusted for the effects of age using multivariate analysis, response no longer appeared to be of any significance (Table 7-9).

y= Fatalistic attitude	Coefficient	95% C.I.	z=	p=
Age	0.08	0.01 to 0.16	2.13	0.033
Tumour size	0.90	-0.20 to 2.00	1.60	0.110
Response	-1.13	-2.89 to 0.63	1.26	0.209
Log likelihood: -48.3			χ^2=11.79	0.0081

Ordered logistic regression model

Table 7-9: Contribution of "response" to the level of "Fatalistic attitude" late during primary systemic therapy.

7.3.2.4 Mode of primary systemic therapy and psychological scores

Of the 28 patients who returned a second questionnaire 8 were given endocrine treatment only, and 20 had received cytotoxic chemotherapy. Psychological scores for the two groups were analysed separately. Median and range of scores and the number of patients who showed a change in their score and the direction of the change are presented in Table 7-10.

	Cytotoxic chemotherapy (n=20)					Endocrine treatment (n=8)				
Factor	Score	Change			p=	Score	Change			p=
		inc	dec	nc			inc	dec	nc	
ANX.										
Early	7.5(2-15)	8	9	*3*	0.756	8 (4-12)	**0**	**5**	***3***	**0.041**
Late	7(0-18)					6 (2-12)				
DEP.										
Early	3(0-9)	**12**	**3**	***5***	**0.014**	2(0-7)	1	2	*5*	0.414
Late	3(1-10)					2 (0-8)				
F.S.										
Early	54(46-62)	7	11	*2*	0.126	52(46-58)	5	3	*0*	0.181
Late	52(42-63)					51(47-63)				
H.H.										
Early	8(6-17)	9	4	*7*	0.060	11(6-12)	2	4	*2*	0.234
Late	8(5-18)					9(6-12)				
A.P.										
Early	22(9-28)	**13**	**6**	***1***	**0.022**	21(15-26)	2	4	*2*	0.453
Late	23(12-28)					21(16-24)				
FAT.										
Early	19(9-24)	8	8	*4*	0.405	19(12-21)	5	1	*1*	0.139
Late	19(8-27)					20(12-21)				
AVO.										
Early	2(1-4)	1	3	*16*	0.317	1.5 (1-3)	0	0	*8*	1.000
Late	2(1-4)					1.5 (1-3)				

Median and range of scores. The number of patients whose scores increased (inc), decreased (dec) or did not change (nc) are presented. Early and late values were compared using the Wilcoxon signed-rank test.

Table 7-10: Psychological scores during primary systemic treatment according to the mode of adjuvant therapy

Patients given cytotoxic chemotherapy became significantly more depressed and anxiously preoccupied towards the end of primary systemic treatment. They also had a tendency to feel more hopeless. Psychological score for patients given endocrine therapy did not significantly change except in the case of anxiety, where patients were less anxious towards the completion of primary systemic therapy.

The effects of the mode of primary systemic treatment on psychological well-being was further studied by comparing the late scores of patients on endocrine and cytotoxic therapy using the Mann-Whitney U test. The median and range of scores are presented in Table 7-11. There were no significant differences in psychological scores between the two groups.

	Early during PST			Late during PST		
Factor	CY. (n=20)	EN. (n=10)	p=	CY. (n=20)	EN. (n=8)	p=
ANX.	7.5 (2-15)	7.5 (4-12)	0.740	7 (0-18)	6 (2-12)	0.878
DEP.	3 (0-9)	2 (0-7)	0.476	2 (1-10)	2 (0-8)	0.237
F.S.	54 (46-62)	52 (46-68)	0.353	52 (42-63)	51 (47-63)	0.818
H.H.	8 (6-17)	10.5 (6-12)	0.411	8 (5-18)	9 (6-12)	0.756
A.P.	22 (9-28)	21 (15-27)	0.808	23 (12-28)	21 (16-24)	0.092
FAT.	19 (9-24)	19.5 (12-21)	0.706	19 (8-27)	20(12-21)	0.878
AVO.	2 (1-4)	2 (1-3)	0.405	2 (1-4)	1.5 (1-3)	0.321

Median and range of scores. CY: primary cytotoxic therapy. EN: primary endocrine therapy. Scores were compared using the Mann-Whitney U test.

Table 7-11: Psychological scores for patients treated by primary cytotoxic and primary endocrine therapy

7.3.3 Differences in psychological scores by treatment option

Following the completion of all treatment, 30 patients given primary systemic treatment and 27 patients treated conventionally returned completed questionnaires. To assess whether there were differences in psychological adjustment between the two groups, the scores for each of the seven psychological factors were compared.

7.3.3.1 Abnormal levels of anxiety and depression

There was a single patient in the conventional arm of the study who had a pathologically raised level of anxiety. The same patient also had a depression score that was pathological. No patient given primary systemic treatment had a pathological level of depression or anxiety following the completion of all treatment. The difference between the two groups was not significant (p=1.000, Fisher's exact test).

7.3.3.2 Differences in scores between the two groups

The mean, median and range of scores for each of the seven factors are presented in Table 7-12. Patients treated conventionally had a greater score for fighting spirit compared with those treated by primary systemic therapy (z=2.06, p=0.038, Mann-Whitney U test), but they also had a tendency to be more anxiously preoccupied with cancer (z=1.91, p=0.055, Mann-Whitney U test). Overall there were no differences between the two groups.

	CONV			PST				
Factor (range)	mean	med	range	mean	med	range	z=	p=
ANX. (0-21)	5.0	4	0-16	4.2	3	0-9	-0.66	0.511
DEP. (0-21)	2.5	2	0-11	2.1	2	0-9	-0.65	0.516
F.S. (16-64)	**55.7**	**56**	**47-64**	**52.9**	**53**	**42-62**	**-2.07**	**0.038**
H.H. (6-24)	7.6	7	6-12	8.3	7.5	6-15	-0.49	0.626
A.P. (9-36)	22.0	23	14-28	20.0	20	10-26	-1.92	0.055
FAT. (8-32)	17.7	17	10-30	17.4	17.5	8-23	-0.05	0.962
AVO. (1-4)	2.0	2	1-4	1.7	1.5	1-4	-1.29	0.199

Scores were compared using the Mann-Whitney U test. ANX: anxiety, DEP: Depression, F.S.: fighting spirit, H.H.: Hopelessness/ Helplessness, A.P.: anxious preoccupation, FAT.: Fatalism, AVO.: Avoidance

Table 7-12: Psychological scores after the completion of all treatment for patients treated conventionally and by PST

7.3.4 Patient and tumour characteristics and psychological outcomes

Ten patient and tumour characteristics (explanatory variables, section 7.2.4.2) were tested for their contribution to psychological outcome following the completion of all treatments. The results of univariate analysis are presented in Table 7-13.

	ANX	DEP	F.S.	H.H.	A.P.	FAT.	AVO.
Age							
ρ=	-0.16	-0.05	-0.13	0.08	0.01	**0.54**	0.09
p=	0.183	0.612	0.322	0.731	0.970	**0.0001**	0.793
Tumour size							
ρ=	0.09	0.03	-0.09	0.20	0.10	0.22	0.22
p=	0.572	0.950	0.471	0.210	0.474	0.112	0.205
Treatment option							
PST (n=30)	3 (0-9)	2 (0-9)	53(42-46)	7.5(6-15)	20(10-26)	17(8-23)	1.5 (1-4)
CONV (n=27)	4 (0-16)	2 (0-11)	56(47-64)	7 (6-12)	23(14-28)	17(10-30)	2 (1-4)
p=	0.511	0.516	**0.038**	0.626	0.055	0.962	0.199
Mode of adjuvant treatment							
Chemo (n=30)	3.5 (0-9)	2 (0-9)	55(42-62)	7.5(6-15)	22(10-26)	17 (8-23)	2 (1-4)
Endo (n=27)	4 (0-16)	1 (0-11)	55(47-64)	7 (6-12)	21(14-28)	20(11-24)	2 (1-4)
p=	0.703	0.942	0.736	0.626	0.879	0.118	0.658
Axillary lymph node status							
Pos (n=33)	3 (0-9)	2 (0-5)	56(47-64)	7 (6-12)	22(14-28)	17(10-30)	2 (1-4)
Neg (n=24)	5 (2-16)	2 (0-11)	53(42-63)	7.5(6-15)	21(10-28)	17(8-24)	2 (1-3)
p=	0.372	0.657	0.194	0.321	0.697	0.576	0.547
Oestrogen receptor status							
Neg (n=29)	5 (0-16)	2 (0-11)	53(42-62)	8(6-15)	22(10-28)	17(8-30)	2 (1-4)
Pos (n=28)	3 (0-9)	1 (0-5)	56(47-64)	7(6-10)	20(14-28)	18(11-24)	1.5 (1-4)
p=	0.071	0.342	**0.051**	0.284	0.532	0.516	**0.035**
Breast reconstruction							
Done (n=13)	4 (0-9)	1 (0-4)	53(47-64)	8(6-12)	22(10-26)	18(14-24)	2 (1-3)
None (n=44)	4 (1-16)	2 (0-11)	56(42-63)	7(6-15)	21(14-28)	17(8-30)	2 (1-4)
p=	0.817	0.250	0.276	0.623	0.647	**0.032**	0.960
Social class							
Non-man (n=37)	5 (0-16)	2 (0-11)	53(47-64)	7.5(6-15)	22(10-28)	18(8-24)	2 (1-4)
Manual (n=20)	3 (1-9)	2 (0-9)	56(42-63)	7 (6-14)	21(14-28)	17(10-30)	1 (1-4)
p=	0.519	0.683	0.239	0.523	0.687	0.250	**0.063**
Partnership							
With (n=31)	3(0-9)	1 (0-5)	56(42-64)	6 (6-13)	22(10-28)	16(10-24)	1 (1-4)
Not with (n=26)	5 (1-16)	2 (0-11)	52(47-60)	8 (6-15)	21(14-28)	19(8-30)	2 (1-4)
p=	0.283	0.316	0.101	**0.009**	0.879	0.162	0.118
Employment							
In work (n=26)	3 (0-9)	2 (0-9)	56(48-62)	7 (6-14)	21(15-28)	17(10-30)	2 (1-4)
Not (n=31)	4 (0-16)	2 (0-11)	53(42-64)	7 (6-15)	22(10-28)	19(8-24)	1.5 (1-3)
p=	0.858	0794	0.221	0.503	0.541	**0.096**	0.448

Age and tumour size were compared using Spearman Rank correlation coefficient. The remaining factors were compared using the Mann-Whitney U test.

Table 7-13: Relationship between patient and tumour factors and psychological outcomes

These findings and the results of multivariate analysis for each outcome are detailed below.

7.3.4.1 The HAD scale: Anxiety

Patients with oestrogen receptor rich tumours had a tendency to report lower levels of anxiety compared with patients with oestrogen receptor poor tumours (z=-1.81, p=0.071, Mann-Whitney U test), but there was no significant relationship between any of the explanatory variables and anxiety. No further significant contributors to anxiety were identified on multivariate analysis.

7.3.4.2 The HAD scale: Depression

There was no relationship between any of the explanatory variables considered and depression.

7.3.4.3 The MAC scale: Fighting Spirit

Patients treated conventionally reported significantly higher levels of fighting spirit compared with patients given primary systemic treatment (z=-2.07, p=0.038, Mann-Whitney U test). There was also a greater degree of fighting spirit amongst oestrogen receptor positive patients (z=-1.95, p=0.051, Mann-Whitney U test).

Multivariate analysis confirmed that treatment option and oestrogen receptor status were highly significant independent predictors for the level of fighting spirit. In addition the choice to undergo breast reconstruction appeared to relate to higher levels of fighting spirit (p=0.051). The best model was derived by including "partnership" as one of the explanatory variables. The details of the model are presented in Table 7-14.

y= Fighting spirit	Coefficient	95% C.I.	z=	p=
Treatment option	-1.32	-2.31 to -0.33	-2.61	0.009
ER status	1.07	0.11 to 2.02	2.19	0.028
Reconstruction	1.25	0.00 to 2.50	1.95	0.051
Partnership	0.71	-0.22 to 1.65	1.50	0.134
Log likelihood = -115.9			χ^2=14.71	0.005

Ordered logistic multivariate regression model

Table 7-14: Contribution of patient and tumour factors to the level of "Fighting spirit".

7.3.4.4 The MAC scale: Hopelessness/ Helplessness

Patients who were living with a partner displayed a significantly smaller level of hopelessness/ helplessness compared with patients not living with another adult (z=-2.61, p=0.009, Mann-Whitney U test). On multivariate analysis, not having a partner remained the only significant independent factor associated with hopelessness/ helplessness.

7.3.4.5 The MAC scale: Anxious Preoccupation

There was a suggestion that conventionally treated patients may be more anxiously pre-occupied with their cancer compared with those patients treated by primary systemic therapy (z=-1.92, p=0.055, Mann-Whitney U test). On multivariate analysis this relationship was maintained, but no new factors emerged as significant.

7.3.4.6 The MAC scale: Fatalistic attitude

There was a highly significant relationship between increasing age and increasingly fatalistic attitude (ρ=0.54, p=0.0001, Spearman Rank correlation coefficient). Patients with the lowest levels of fatalism (less than the median), had a mean±SEM age of 45.5±1.64, ten years younger than patients with the highest levels: 54.9±1.72 (t=-3.92 d.f.=55, p=0.0002, Student's t-test). Furthermore, not opting for breast reconstruction appeared to be associated with

greater fatalism (z=-2.15, p=0.032, Mann-Whitney U test). There was also a suggestion that patients who were not working had a more fatalistic outlook.

On multivariate analysis it became clear that breast reconstruction and employment were confounded by age, neither remaining significantly related to a fatalistic attitude. It however also emerged that once controlled for the effect of age, increasing tumour size was associated with an increasingly fatalistic attitude. The regression model is presented in Table 7-15.

y= Fatalistic attitude	Coefficient	95% C.I.	z=	p=
Age	0.12	0.07 to 0.18	4.37	<0.0001
Tumour size	0.64	0.08 to 1.20	2.23	0.026
Log likelihood = -105.6			χ^2= 24.57	<0.0001

Ordered logistic multivariate regression model

Table 7-15: Contribution of patient and tumour factors to the level of "Fatalistic attitude"

7.3.4.7 The MAC scale: Avoidance

Oestrogen receptor positive patients were significantly less likely to respond by avoidance than were oestrogen receptor negative patients (z=-2.11, p=0.035, Mann-Whitney U test). There was also a tendency for patients in the non-manual social class to show less avoidance behaviour.

On multivariate analysis, oestrogen receptor status remained significantly associated with avoidance, and social class remained in the model. The best model in addition contained treatment option. The final model is presented in Table 7-16.

y= Avoidance	Coefficient	95% C.I.	z=	p=
ER status	-1.13	-2.16 to -0.09	-2.13	0.034
Social class	-0.918	-1.97 to 0.13	-1.72	0.086
Treatment option	-0.823	-1.84 to 0.20	-1.58	0.144
Log likelihood = -56.1			χ^2=10.32	0.016

Ordered logistic multivariate regression model

Table 7-16: Contribution of patient and tumour factors to the degree of "Avoidance"

7.3.5 Relationship between psychological outcome and survival

Each psychological outcome was dichotomised as described in section 7.2.4.3. Cox's regression was used to assess the contribution of each outcome measure to event free survival, distant disease free survival and overall survival. The results for event free survival are presented in Table 7-17. High levels of anxious preoccupation were associated with poorer event free survival.

	Univariate analysis of recurrence free survival			
	Hazard ratio	95% C.I.	z=	p=
ANX.	1.23	0.55-2.73	0.50	0.616
DEP.	1.24	0.55-2.80	0.53	0.597
F.S.	0.95	0.43-2.12	-0.13	0.901
H.H.	1.39	0.62-3.10	0.80	0.424
A.P.	**2.38**	**1.02-5.57**	**2.00**	**0.039**
FAT.	0.86	0.39-1.92	-0.37	0.714
AVO.	1.14	0.50-2.56	0.31	0.757

Table 7-17: Event free survival by psychological scores

The results for distant disease free survival and overall breast cancer survival are presented in tables Table 7-18 and Table 7-19 respectively.

	Univariate analysis of distant disease free survival			
	Hazard ratio	95% C.I.	z=	p=
ANX.	1.35	0.60-3.06	0.72	0.471
DEP.	1.40	0.60-3.23	0.78	0.431
F.S.	1.04	0.46-2.37	0.10	0.917
H.H.	1.26	0.56-2.87	0.56	0.574
A.P.	**2.19**	**0.92-5.17**	**1.79**	**0.066**
FAT.	0.94	0.42-2.14	-0.14	0.888
AVO.	1.29	0.56-2.98	0.60	0.548

Table 7-18: Distant disease free survival by psychological scores

	Univariate analysis of overall survival			
	Hazard ratio	95% C.I.	z=	p=
ANX.	1.10	0.47-2.60	0.22	0.828
DEP.	1.13	0.48-2.70	0.28	0.776
F.S.	1.22	0.52-2.87	0.45	0.653
H.H.	1.05	0.45-2.48	0.91	0.911
A.P.	**2.23**	**0.90-5.54**	**1.74**	**0.073**
FAT.	0.77	0.32-1.84	-0.59	0.557
AVO.	1.13	0.47-2.69	0.27	0.789

Table 7-19: Overall survival by psychological scores

Patients with high levels of anxious preoccupation were diagnosed with a breast cancer event (either local or distant recurrence) significantly earlier than patients with low levels of anxious preoccupation. The difference persisted for distant disease free and overall survival, although it did not reach significance at the 95% level. The Kaplan-Meier event free survival curves are shown in Figure 7-2 (Table 14-22). Overall survival curves are shown in and Figure 7-3 (Table 14-23).

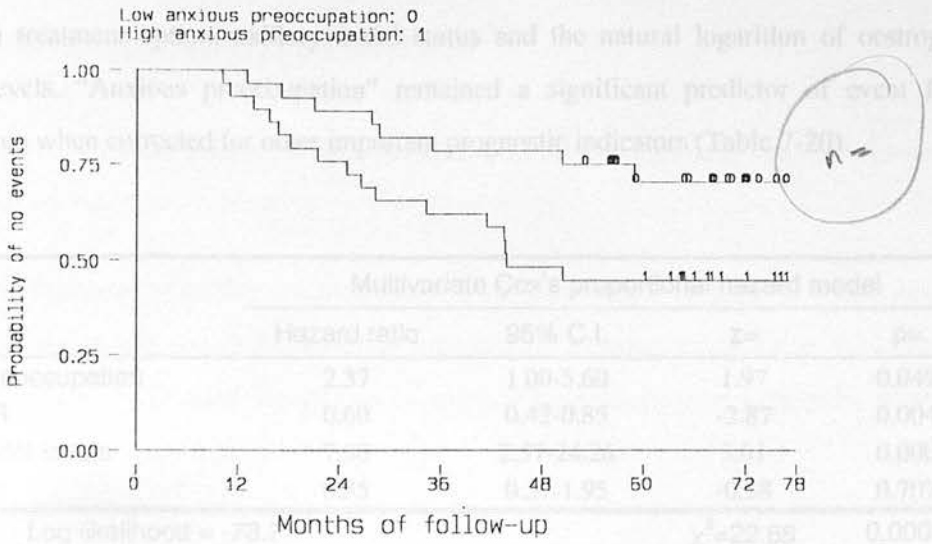


Figure 7-2: Event free survival by the level of anxious preoccupation.

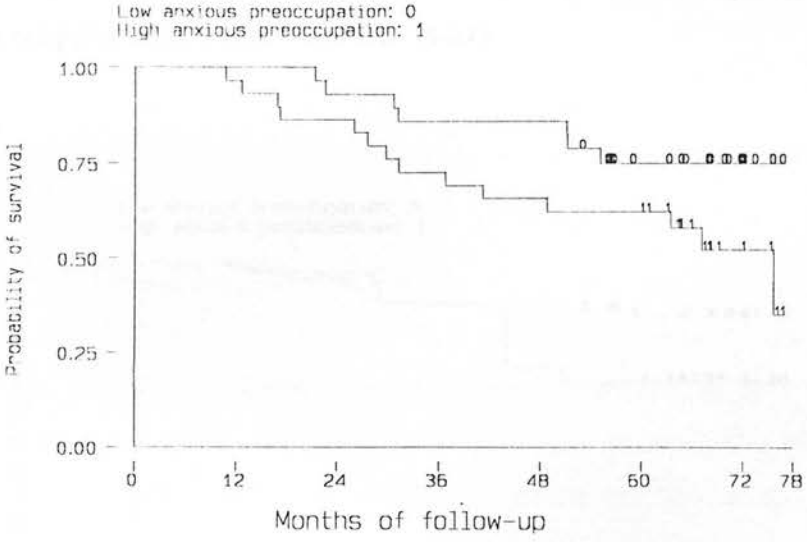


Figure 7-3: Overall survival by the level of anxious preoccupation

Treatment option was the only factor which related to the level of anxious preoccupation. Anxious preoccupation was entered into a multivariate Cox's proportional hazard model,

along with treatment option, axillary nodal status and the natural logarithm of oestrogen receptor levels. "Anxious preoccupation" remained a significant predictor of event free survival even when corrected for other important prognostic indicators (Table 7-20).

	Multivariate Cox's proportional hazard model			
	Hazard ratio	95% C.I.	z=	p=
Anxious preoccupation	2.37	1.00-5.60	1.97	0.049
ln initial ER	0.60	0.42-0.85	-2.87	0.004
Axillary nodal status	7.90	2.57-24.26	3.61	0.000
Trial option	0.85	0.37-1.95	-0.38	0.707
Log likelihood = -78.7			χ^2=22.68	0.0001

Table 7-20: Contribution of the level of anxious preoccupation in conjunction with relevant patient and tumour factors to event free survival

The event free survival advantage of low anxious preoccupation when adjusted for other prognostic indicators was marginal. The Kaplan-Meier survival curves, adjusted as appears in Table 7-20, are provided in Figure 7-4 (Table 14-24).

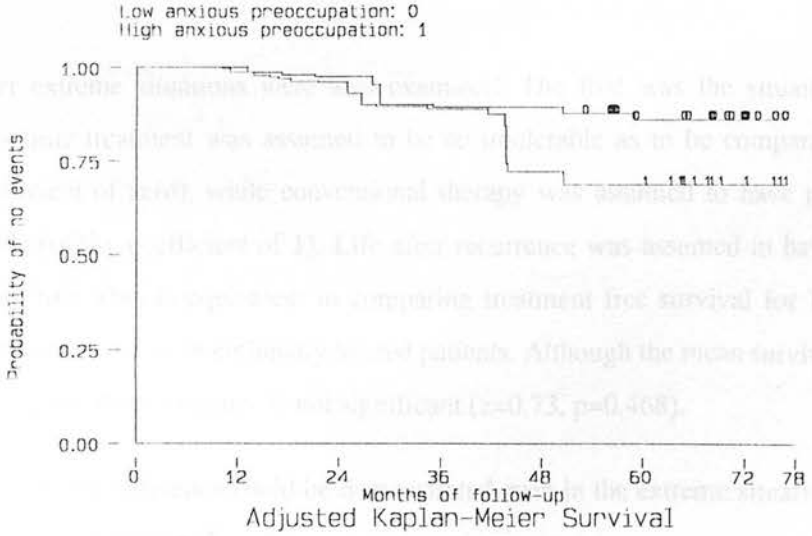


Figure 7-4: Adjusted event free survival by level of anxious preoccupation

7.3.6 Quality adjusted survival analysis

The duration of treatment for each arm of the study and details of disease free and recurrence free survival are reported in chapter 4.

The extreme measures of quality adjusted survival are reported for all patients taking part in the trial. Mean survival and 95% confidence intervals are summarised in Table 7-21. There were no significant differences for phases of survival between patients treated by primary systemic and conventional therapy.

	All patients		Conventional		PST			
	n=171		n=86		n=85		z=	p=
	mean	95% C.I.	mean	95% C.I.	mean	95% C.I.		
Overall survival	60	56-64	58	52-64	62	56-68	-0.84	0.402
Disease free survival	56	52-60	55	48-61	57	50-63	-0.45	0.651
Treatment free survival	55	51-59	54	48-60	55	50-61	-0.22	0.823
TWiST	51	46-55	51	44-57	50	44-57	0.12	0.907

Means compared using the "normal" test

Table 7-21: Quality adjusted survival analysis for all patients within the trial

Two further extreme situations were also examined. The first was the situation in which primary systemic treatment was assumed to be so intolerable as to be comparable to death (utility coefficient of zero), while conventional therapy was assumed to have no impact on quality of life (utility coefficient of 1). Life after recurrence was assumed to have no impact on quality of life. This is equivalent to comparing treatment free survival for PST patients with overall survival for conventionally treated patients. Although the mean survival is smaller (55 vs. 60 months) this difference is not significant (z=0.73, p=0.468).

Since no significant difference could be demonstrated even in the extreme situations, no other utility coefficients were tested.

7.4 CONCLUSIONS AND DISCUSSION

7.4.1 The conduct of the study

This study employed two validated questionnaires for the semi-quantitative measurement of a limited number of factors relevant to overall psychological adjustment to cancer. Little is known about patients' perceptions of primary systemic treatment as well as how such treatment influences the patients' daily activities, and these may form the basis for further study. The main area of concern for this study was major psychological morbidity and psychological adjustment; it did not aim to provide a comprehensive assessment of the patients' psychological well-being. Within these constraints, the study was able to uncover a number of findings which will be discussed below.

7.4.1.1 The effects of patient non-participation

Twelve of the 69 patients potentially eligible for the study did not participate. Five were excluded by design, but seven patients (10%), declined to take part. It is possible that this group of seven patients may have psychological reactions which were different from the cohort as a whole, as suggested by the fact they were also less likely to have opted for breast reconstruction. However their relatively small number, and the fact that they were equally distributed between the two treatment groups makes it unlikely that their exclusion would have introduced significant bias into the overall findings of the study.

7.4.1.2 The significance of an "avoidance" response

In the present study, an "avoidance" response directly correlated with other indicators of poor psychological adjustment. During the development of the MAC scale, denial was seen as a positive coping strategy (Watson *et al:* 1988; Nerenz *et al:* 1982) and, along with "fighting spirit", was found to predict a positive survival outcome for patients with breast cancer (Greer *et al:* 1990; Greer *et al:* 1979). Avoidance has in the past been regarded as one of the most common reactions to cancer (Shands *et al:* 1951; Peck: 1972), but there are conflicting

opinions on its role in psychological adjustment (Klein: 1971; Watson *et al:* 1984) . During its construction, the MAC scale retained only one item addressing the "avoidance" response. The reasons and possible significance of this were discussed in the original description of the scale (Watson *et al:* 1988). It was suggested then that the relative importance of "avoidance" as a response may be changing with changes in medical practice.

Patients taking part in the present study were repeatedly reminded of their diagnosis and its implications. It is therefore possible that an avoidance response reflects general lack of psychological adjustment. Alternatively, this anomalous result may simply be the result of the inherent instability of using a single item to assess the avoidance response.

7.4.2 Primary systemic treatment and psychological response

7.4.2.1 Adjustment during and after primary systemic treatment

Patients undergoing primary systemic treatment reported high levels of anxiety during therapy. High levels of anxiety have been reported for patients about to undergo surgery or awaiting other treatment (Miller *et al:* 1995). It was noteworthy that these levels appeared to remain relatively high throughout what was frequently a lengthy period of primary systemic therapy. Other psychological scores also remained at best unchanged. Indeed there was a suggestion that patients may become more anxiously preoccupied and more depressed as primary systemic treatment progressed. Levels of anxiety, anxious preoccupation, hopelessness and avoidance decreased following the completion of all treatment. The biggest reduction was in anxiety levels. This supports the contention that patients experienced poor psychological adjustment during primary systemic therapy. It is however likely that much of this is related to the fact that a significant proportion of these patients were actively receiving cytotoxic chemotherapy at the time of the second psychological assessment. Cytotoxic chemotherapy has been found to independently influence psychological adjustment (Hughson *et al:* 1986; Cooper *et al:* 1980; McArdle *et al:* 1981; Maguire *et al:* 1980; Nerenz *et al:* 1982). In the present study, patients receiving primary cytotoxic chemotherapy became psychologically less well adjusted during primary systemic therapy as evidenced by increasing levels of depression,

anxious preoccupation and hopelessness/ helplessness. No such deterioration was observed amongst endocrine treated patients.

Psychological adjustment for conventionally treated patients during adjuvant cytotoxic chemotherapy was not assessed in this study. It is therefore not possible to separate the contribution of the timing of treatment and the mode of treatment to the psychological maladjustment experienced by patients undergoing primary systemic therapy.

7.4.2.2 The psychological effects of failure to respond

The number of patients who failed to respond to primary systemic therapy was small, making it difficult to draw any firm conclusions about the influence of response on psychological well-being. There were however strong indications that lack of response was associated with worsening psychological scores. Most of the non-responding patients had increases in hopelessness, anxious preoccupation and fatalism, and had a significantly more fatalistic outlook compared with responding patients.

7.4.2.3 Residual psychological morbidity following completion of all treatment

Following the completion of all treatment, the relationship between treatment option and psychological outcome was examined using multivariate techniques. Even when corrected for other factors, patients given primary systemic treatment displayed less fighting spirit compared with conventionally treated patients although they were also less anxiously preoccupied. There were no other differences in psychological adjustment according to the treatment given.

Although the main purpose of this part of the study was to assess differences in psychological morbidity between patients treated conventionally and those treated by primary systemic treatment, the multivariate techniques used revealed other factors which can influence psychological outcome. These are discussed below.

7.4.3 Factors influencing psychological outcome

Psychological outcome was found to be influenced by a number of patient and tumour factors.

7.4.3.1 Patient factors

From amongst the patient factors, having a partner was associated with less hopelessness/ helplessness and greater fighting spirit, while increasing patient age strongly related to a fatalistic attitude.

7.4.3.2 The influence of oestrogen receptor status

Patients with oestrogen receptor positive tumours were found to be psychologically better adjusted compared with patients who had oestrogen receptor poor tumours. Thus they were less anxious, had greater fighting spirit and less avoidance.

While it is possible to explain the relationship between patient factors and psychological outcome on an intuitive basis, it is more difficult to find reasons for the connection between tumour oestrogen receptor level and psychological well-being. Such a relationship has been observed in one other study (Razavi *et al:* 1990), however other groups have failed to show any correlation between oestrogen receptor levels and psychological adjustment (Rosenqvist *et al:* 1993; Hislop and Kan: 1990; Maunsell *et al:* 1990).

In the present study the information given to patients regarding the trial and its various options placed a great deal of emphasis on oestrogen receptor levels as a prognostic indicator, and as an important factor in deciding final treatment. During the post-mastectomy consultation, there was a tendency to present indicators of a good prognosis such as lack of axillary nodal involvement or higher oestrogen receptor levels enthusiastically as a piece of good news, while indicators of a poorer prognosis such as lack of oestrogen receptors were generally put forward as neutral news (neither good nor bad). The combination of preoperative emphasis on oestrogen receptors and postoperative presentation of results could have disproportionately influenced the patients' perception of their prognosis, and hence their overall degree of psychological adjustment.

7.4.4 Psychological adjustment and survival

Disease free survival was longest for patients with the lowest levels of anxious preoccupation. This effect was independent of other important prognostic indicators such as oestrogen receptor status, tumour size or axillary nodes. Relationships between high levels of fighting spirit and avoidance and longer survival in early breast cancer have previously been reported (Greer *et al:* 1990; Greer *et al:* 1979). The levels of fighting spirit and avoidance had been determined using interviews which eventually formed the basis for the development of the MAC scale (Watson *et al:* 1988). Longer survival has also been reported for better adjusted patients with good social support in metastatic breast (Derogatis *et al:* 1979) and lung cancer (Ganz *et al:* 1991). While it is possible that psychological adjustment may have a direct effect on outcome through various psychosomatic routes (Levy *et al:* 1987; Southam: 1969), the present result may be explained in at least two further possible ways:

Firstly, psychological adjustment may be influenced by the information the patient has been given regarding prognosis. Thus poor psychological adjustment may simply reflect patients' awareness of their poor prognosis.

Secondly, anxiously preoccupied patients may report symptoms of recurrence earlier than others, creating the impression of shorter disease free survival, without influencing the overall survival.

Although the relationship between psychological adjustment, oestrogen receptors and survival is not directly relevant to the study of psychological morbidity in primary systemic treatment, it illustrates the importance of the way information exchange with the patient may influence final psychological outcome. This factor should be more directly taken into account in any future studies.

7.4.5 Overall quality of life issues

The present trial was aimed at comparing two treatment packages which are very different in terms of the demands they palace on patients' time, requirements for attending hospital and the

types of treatment related toxicity expected. It is therefore essential that small differences in treatment outcome are carefully balanced against the possibility of poorer quality of life.

The appraisal of quality of life comprises many issues of which psychiatric and emotional well-being are only one aspect. Quality of life assessment should also include measures of the patients level of physical capacity, the ability to maintain social and sexual functioning, and overall measures of well-being (Moinpour *et al:* 1989). Other measures relate to specific ways in which treatment interferes with quality of life such as treatment related toxicity, and the impact of treatment on patients' daily living (Cella and Tulsky: 1993; Love *et al:* 1989).

A number of instruments have been developed specifically aimed at addressing overall quality of life issues in cancer patients (Ganz *et al:* 1992; Cella *et al:* 1993; Moinpour: 1994; Cella and Tulsky: 1990), and in particular in patients with breast cancer (Winer: 1994; Levine *et al:* 1988). The proper application of these measures can often be difficult, and results depend very much on the participation of clinicians involved in all aspects of assessment, treatment and follow-up (Cella and Tulsky: 1990; Schipper: 1990; Hayden *et al:* 1993). It is nevertheless important that an integrated approach to measurement of quality of life is adopted in future trials of different forms of systemic therapy.

7.4.6 Quality adjusted survival analysis

Throughout the quality adjusted analysis, it was assumed that the time after completion of treatment and before development of recurrence has a utility value of "1". Significant psychological morbidity related to the diagnosis of malignancy may become apparent during this "TWiST" phase. This study did not find a difference in psychological adjustment following completion of all treatment. and the assumption that TWiST time can be assigned a relative utility of "1" for both arms of the trial can be upheld.

There was no difference in quality adjusted measures of survival between the two arms of the study, even when the most extreme situations were examined. A difference against PST may have been expected because of the more prolonged treatment phase when primary systemic treatment was used. It is however possible that losses from more prolonged treatment are offset by minor gains in survival.

7.4.7 Overall conclusion

Primary systemic treatment is acceptable as a mode of systemic therapy, and is not associated with lasting excess psychological morbidity. The greater length of the treatment phase does not adversely effect quality adjusted survival.

CHAPTER 8

8. Surgical Morbidity and Primary Systemic Treatment

8.1 INTRODUCTION

Surgery forms an important part of many of the protocols for primary systemic treatment of breast cancer (Mauriac *et al:* 1991; Jacquillat *et al:* 1990; Forouhi and Chetty: 1991; Fisher and Wickerham: 1991; DeVita, Jr. 1990). The outcome of surgery following systemic therapy is examined in this chapter.

8.1.1 Surgical morbidity associated with mastectomy

8.1.1.1 Frequency of complications

Modified radical mastectomy (Patey and Dyson: 1948) is the operation of choice for local treatment of larger breast cancers (Osborne and Borgen: 1990). Mastectomy is associated with significant surgical morbidity. While complications ranging from nerve injuries to air embolism are well recognised following mastectomy (Aitken and Minton: 1983), it is the local complications which are most frequent and result in the greatest morbidity (Feigenberg *et al:* 1977; Say and Donegan: 1974; Hayes and Bryan: 1984; Budd *et al:* 1978). The late complications of lymphoedema and shoulder dysfunction (Pollard *et al:* 1976; Dawson *et al:* 1989; Petrek *et al:* 1990; Aitken and Minton: 1983) can often follow problems in the early postoperative period. Persistent seroma formation is the most frequently reported complication of the axillary component of the operation, being reported in 10-50% of patients (Hayes and Bryan: 1984; Budd *et al:* 1978; Bryant and Baum: 1987; Tadych and Donegan: 1987). Although not a serious complication as such, seroma formation predisposes to infection (Hayes and Bryan: 1984), other flap complications (Aitken and Minton: 1983), and late lymphoedema (Tadych and Donegan: 1987). The more serious complication of wound infection is reported in 8-18% of patients (Aitken and Minton: 1983; Say and Donegan: 1974; Chen *et al:* 1991; Beatty *et al:* 1983; Budd *et al:* 1978), while flap necrosis happens in 3-10% of cases (Feigenberg *et al:* 1977; Say and Donegan: 1974; Hayes and Bryan: 1984; Budd *et al:* 1978).

8.1.1.2 Known risk factors for complications

A number of patient factors can influence the rate of complications following surgery. Age is an important risk factor for seroma formation and wound infection (Tejler and Aspegren: 1985; Say and Donegan: 1974; Vinton *et al:* 1990; Borup Christensen and Lundgren: 1989; Chen *et al:* 1991; Miller and Falcone: 1991). Obesity also predisposes to infections and skin necrosis (Tejler and Aspegren: 1985; Say and Donegan: 1974; Vinton *et al:* 1991; Hoefer, Jr. *et al:* 1990; Miller and Falcone: 1991), and the risks of skin necrosis is significantly increased in smokers (Miller *et al:* 1980; Craig and Rees: 1985; Rees *et al:* 1984). Number of involved lymph nodes appears to be the most important tumour factor in predisposing to complications (Say and Donegan: 1974; Hoefer, Jr. *et al:* 1990; Bryant and Baum: 1987; Petrek *et al:* 1990).

8.1.1.3 The effects of breast reconstruction

Primary breast reconstruction following mastectomy helps with postoperative psychological adjustment and may be offered as an option to patients undergoing mastectomy (Dean *et al:* 1983; Bostwick, III: 1990). Complications following primary reconstruction using implants, either with the tissue expansion technique (Radovan: 1984; Argenta: 1984; De Mey *et al:* 1991) or with the latissimus dorsi myocutaneous flap reconstruction technique (Biggs and Cronin: 1981; Schneider *et al:* 1977), appear to be related to the mastectomy rather than to the reconstructive procedure as such (Vinton *et al:* 1990; Miller and Falcone: 1991). Risk factors for complications following mastectomy with primary breast reconstruction appear to be the same as for mastectomy alone (Vinton *et al:* 1991; Miller and Falcone: 1991). Prosthetic breast reconstruction however may be associated with a small excess of cases of complication, particularly in the 3-6% of cases which result in implant loss (Miller and Falcone: 1991), and may therefore act as an additional risk factor for complications following mastectomy (Vinton *et al:* 1991).

8.1.2 Systemic treatment and surgery

8.1.2.1 Theoretical background

During normal wound healing, the wound passes through the three phases of inflammation, proliferation and maturation (Thomas *et al:* 1995; Springfield: 1993; Hunt: 1990; Waldorf and Fewkes: 1995). Systemic treatment particularly with cytotoxic agents can cause neutropenia (Dionigi *et al:* 1980), interfere with cell proliferation and impair collagen synthesis (Ferguson: 1982) and can therefore potentially interfere with all three phases of wound healing (Springfield: 1993; Ehrlichman *et al:* 1991; Drake and Oishi: 1995). Experimental studies in animal models suggest that cytotoxic agents, given before or after surgery, have their maximum effect on the proliferative and the maturation phase of the healing process (Lawrence *et al:* 1986; Ferguson: 1982; Devereux *et al:* 1979), although increased susceptibility to infection is also an important factor (Dionigi *et al:* 1980; Drake and Oishi: 1995; Waldorf and Fewkes: 1995).

8.1.2.2 Clinical effects in non-breast malignancy

A number of studies have reported increased surgical complication rates in relation to cancer chemotherapy. Postoperative complications such as wound dehiscence and wound infections amongst a group of children receiving cytotoxic chemotherapy for a variety of cancers were three times more common if the children had been given initial systemic treatment (Angerpointner *et al:* 1989). In patients undergoing prosthetic reconstruction following limb salvage surgery for malignant or benign bone tumours, the risk of prosthetic infection and limb loss was greatest if surgery followed systemic therapy. Postoperative chemotherapy also increased the risk of surgical complications, although it did so to a much smaller extent (McDonald *et al:* 1990). Pneumonectomy following aggressive preoperative chemotherapy and radiotherapy is associated with very high levels of morbidity and mortality in lung cancer patients (Fowler *et al:* 1993).

Not all studies have found primary systemic therapy to be detrimental. Early postoperative chemotherapy had no adverse effects on the surgical outcome following surgery for epithelial ovarian cancer. The down staging achieved with preoperative treatment improves the outcome

of operations for such tumours as oesophageal cancer (Le Prise *et al:* 1994; Girvin *et al:* 1995; Schlag: 1991), hepatocellular cancer (Lygidakis *et al:* 1995) and pancreatic carcinoma (Weese *et al:* 1990). In a series of patients with a variety of advanced malignancies, including breast cancer, major surgery within three weeks of cytotoxic chemotherapy was associated with relatively low rates of morbidity and mortality (Finn *et al:* 1980).

8.1.2.3 Effects on operations for breast cancer

Mastectomy in combination with peri-operative chemotherapy for operable breast cancer has been associated with increased surgical morbidity, and unexpected mortality in one study (Ludwig Breast Cancer Study Group: 1983), although most other studies addressing this question have not found any such increase. In a retrospective analysis of patients treated by mastectomy, pre or postoperative radiotherapy was found to be associated with a greatly increased incidence of wound complications, but no increase was detected with the use of perioperative thiotepa (Say and Donegan: 1974). In another randomised trial of perioperative versus postoperative chemotherapy, surgical morbidity was similar in the two arms (Sertoli *et al:* 1995).

High rates of surgical complications have been reported with mastectomy following intensive primary chemotherapy for locally advanced breast cancer (Sauter *et al:* 1993), although wound infection or flap necrosis rates have been reported to be comparable with rates found in historical controls (Luboinski *et al:* 1991; Broadwater *et al:* 1991; Danforth, Jr. *et al:* 1990). Surgery following primary chemotherapy in these series was often less extensive than that performed in the historical control groups, and should therefore have been expected to be associated with lower rates of morbidity (Frank: 1992).

8.1.3 Study objectives

The objectives of this study were to investigate in a prospective randomised trial whether primary systemic treatment increased the morbidity associated with modified radical mastectomy, and to identify patient and tumour factors other than the mode of systemic therapy which may contribute to mastectomy related morbidity.

8.2 PATIENTS AND METHODS

8.2.1 Patients

All patients taking part in the main trial of primary systemic treatment versus conventional therapy were included in the study. Briefly these were women aged under 70 with operable, localised breast cancers more than 4 cm in maximum diameter. The criteria for inclusion in the study and randomisation procedures are detailed in section 3.2.

8.2.2 Study design

Patients were randomly allocated to one of the study options by the Scottish Cancer Trials Office and data were recorded prospectively, with prior knowledge of treatment options.

8.2.2.1 Systemic treatment

All patients were treated in accordance with the protocol detailed in section 3.3.1.2 and 3.3.2.2.

8.2.3 Surgical details

8.2.3.1 The operation

All patients underwent surgery in accordance with the trial protocol (sections 3.3.1.5 and 3.3.2.1). General anaesthesia was used in all cases. Mastectomy with level III axillary clearance, with the division of the pectoralis minor muscle was carried out removing a 3 cm skin margin around the tumour. Where a tumour had regressed with therapy, its pre-treatment size was used to plan skin margins. For larger tumours skin closure was achieved using a latissimus dorsi myocutaneous flap (LD flap). Skin flaps where raised with the minimum use of diathermy. All wounds were irrigated with Ticept® (Seton Healthcare, Oldham, U.K.)

solution for 2 minutes prior to closure. Two closed suction drains were used for mastectomies and 4 for LD flaps. Skin closure was achieved using a continuous subcuticular technique, with an absorbable suture material.

8.2.3.2 Breast reconstruction

8.2.3.2.1 Latissimus dorsi myocutaneous flaps

This procedure was selected if it was required for adequate skin closure. Where additional bulk was required to match the other breast, a silicone gel filled prosthesis (Nagor Ltd., P.O. Box 21, Douglas, Isle of Man, U.K.) was placed under the flap, superficial to the pectoralis major muscle. In practice all patients required a prosthesis and the majority of prosthesis were of the smooth type.

8.2.3.2.2 Subpectoral tissue expansion technique

This technique was used for all other patients who requested immediate breast reconstruction. A subpectoral pocket was created and a silicone tissue expansion device (Dow Corning Wright, 5677 Airline Road, Arlington, TN 38002) was placed in position. The injection port was located in an accessible position in the axillary space.

8.2.3.3 Peri-operative precautions and postoperative care

8.2.3.3.1 Antibiotic prophylaxis

No antibiotics were used in patients undergoing mastectomy alone. Patients with breast implants were given prophylactic flucloxacillin and benzylpenicillin. Penicillin allergic patients were given erythromycin. Antibiotics were started at induction of anaesthesia and given intravenously for 48 hours postoperatively. Oral antibiotics were continued thereafter for a further 5 days, or until removal of all surgical drains, whichever was later.

8.2.3.3.2 Prophylaxis against deep venous thrombosis

All patients wore anti-embolism stockings throughout the perioperative period. Subcutaneous heparin was started an hour before surgery and continued at a dose of 5000 units twice daily until the patient was fully mobile.

8.2.3.4 Postoperative care

Each suction drainage tube was removed when it drained less than 30 mls of fluid in a 24 hour period. Patients were mobilised on the first postoperative day. Shoulder physiotherapy was started on the second postoperative day and maintained until discharge. Patients who made an uncomplicated recovery were discharged one day after the removal of their last surgical drain. The timing of discharge in other patients was dictated by the severity of their complications.

8.2.3.5 Surgical follow-up

Inpatients were examined daily and were reviewed one week after discharge. Patients with complications requiring outpatient treatment were seen weekly until recovery. Thereafter patients were discharged to long term follow-up, where they were seen within six weeks.

8.2.4 The recording of surgical complications

8.2.4.1 Wound complications

Wound complications were divided into *minor* and *major* categories. A further category of *any complication* was created by combining the minor and major categories. Each complication was recorded as either "absent" or "present'. Complications were defined as follows:

8.2.4.1.1 Minor complications

8.2.4.1.1.1 Minor seroma

Any wound collection requiring drainage to relieve discomfort.

8.2.4.1.1.2 Minor infection

Wound erythema in the absence of an implant, associated with pyrexia less than 38°C and treated by oral antibiotics only, whether or not positive on culture.

8.2.4.1.1.3 Minor wound edge necrosis

Superficial sloughing of edges of the mastectomy or LD flaps, or full thickness necrosis involving an area no greater than 1 cm in diameter, and requiring outpatient dressings only.

8.2.4.1.2 Major complications

8.2.4.1.2.1 Major wound collection

Any wound collection requiring open drainage.

8.2.4.1.2.2 Major infection

Any wound infection with positive bacteriology on culture and requiring intravenous antibiotics, or open surgical drainage or removal of an implant.

8.2.4.1.2.3 Major flap necrosis

Any area of full thickness necrosis of mastectomy or LD flap requiring surgical excision or removal of an implant.

8.2.4.2 Systemic complications

Any deep venous thrombosis or pulmonary embolism proven radiologically, and any chest infection proven on positive sputum culture were recorded.

8.2.4.3 Delayed complications

Since the aim of the study was to assess immediate operative complications, the late complications of mastectomy including lymphoedema and shoulder immobility were not included in the assessment. Any late complications relating to a tissue expander device or its subsequent replacement with a permanent prosthesis were also omitted.

8.2.5 Analytical methods

All statistical analyses were performed using the statistical software package Stata 4.0 for Windows, Stata Corporation, 702 University Drive East, College Station, Texas 77840 USA.

The results were analysed on the basis of actual treatments received. Primary systemic treatment was treated as the "treatment" group and conventional therapy as the "control" group.

8.2.5.1 Direct comparisons

The odds ratio, 95% confidence intervals, and the significance for the difference in the proportion of patients in each treatment category with or without a complication were calculated for each complication category using exact statistical methods.

8.2.5.2 Relationship between patient and tumour factors and complications

The relationships between patient and tumour characteristics (explanatory variables) and complications (outcome variables) were assessed using univariate and multivariate techniques. For the first analysis all patients were considered together and "mode of treatment" was regarded as an explanatory variable. An additional analysis was performed only on the "study" patients when the variable "adjuvant therapy: cytotoxic or endocrine" was substituted for the variable "mode of treatment".

8.2.5.2.1 Variables examined

8.2.5.2.1.1 Explanatory variables

The following categorical explanatory variables were examined:

1a.	Mode of treatment:	conventional or primary systemic treatment
1b.	Adjuvant therapy:	Cytotoxic or endocrine (study patients only)
2.	Breast reconstruction:	Performed and not performed
3.	Smoking habit:	Smoker or non-smoker

Patients were defined as non-smokers if they had not smoked for 3 months or more before entering the study.

The following continuous explanatory variables were examined:

1. Age
2. Tumour diameter at diagnosis
3. The number of involved lymph nodes
4. Body mass index (weight in kilos / the square of height in meters)

8.2.5.2.1.2 Outcome variables

Three outcome variables were independently examined as follows:

1. Any seroma
2. Any infection
3. Any necrosis

8.2.5.2.2 Statistical methods

8.2.5.2.2.1 Univariate techniques

Where the explanatory variables were dichotomous the proportions of patients with or without complications were compared using exact statistical methods. Where the explanatory variable

was continuous (e.g.: age), the difference between the explanatory variable for the group with or without complications was examined using the Mann-Whitney U test.

8.2.5.2.2.2 Multivariate techniques

Because of the relatively small number of cases involved, clinically important degrees of confounding may have gone unnoticed in univariate analysis. The relationship between explanatory and outcome variables was therefore further examined using logistic regression.

All 8 explanatory variables were tested starting with variables with the greatest degree of significance on univariate analysis. Those variables which contributed to the regression model with a probability of <0.15 were retained.

8.2.5.3 Hospital stay and outpatient treatment

The date of admission, discharge and final discharge from outpatient follow-up were recorded for all patients. Total inpatient stay was calculated from the dates of admission and discharge. Total duration of surgical treatment was calculated from the date of first admission to hospital to the date of final surgical discharge.

Inpatient hospital stay and the duration of treatment were compared between the primary systemic treatment group and the conventionally treated group using the log-rank test.

8.3 RESULTS

8.3.1 Patients

8.3.1.1 Recruitment

Seventy nine eligible patients were randomised into the study. The details of the patients are presented in section 4.1.2.1. Thirty nine patients were randomised to conventional therapy and 40 to primary systemic treatment. There were four protocol violations. One patient from the conventional arm was treated by primary systemic therapy, and 3 patients randomised to the study arm received conventional therapy. None of these four patients suffered any surgical complications. Thirty eight patients were treated by primary systemic treatment and 41 patients by conventional therapy.

	Conventional	P.S.T.	Statistic	p value
Number of patients	41	38		
Adjuvant Treatment				
Cytotoxic therapy	-	24		
Endocrine therapy	-	14		
Breast reconstruction				
Tissue expander	11	16		
LD Flap	15	11	Exact	0.485
None	15	11		
Smoking habit				
Smokers	16	12		
Non-smokers	25	26	Exact	0.638
Age [mean (range)]	52 (31-69)	51 (33-69)	t=0.48	0.633
Tumour diameter [Median (range)]	4.6 (3.9-8.5)	4.5 (4.1-7.9)	z=-0.77	0.444
Nodes involved [median (range)]	1 (0-23)	1 (0-13)	z=-1.2	0.231
Body mass index [median (range)]	25.0 (19.6-42.5)	26.1 (19.6-41.4)	z=1.05	0.294

Unless otherwise stated, number of patients in each category are reported

Table 8-1: Patient and tumour characteristics.

8.3.1.2 Patient characteristics

The full details of the patients and their treatments are summarised in sections 4.1.2.1 and 4.1.3.4.

The distribution of patient and tumour characteristics relevant to this part of the study are summarised in Table 8-1. There were no significant differences between the two groups.

8.3.2 Complications and mode of treatment

8.3.2.1 Wound complications

Seventeen conventionally treated patients developed a total of 14 minor and 6 major complications. Fourteen patients given primary systemic treatment developed 11 minor and 6 major complications (Table 8-2). There were no significant differences between the number of complications in patients treated by primary systemic treatment and those treated conventionally. Seroma was the most frequent minor complication, affecting 11 patients treated conventionally and 7 patients treated by primary systemic treatment. The most frequent major complication was wound infection, affecting 3 conventional and 4 primary systemic therapy patients.

Complication	Conventional	P.S.T.	Odds ratio	95% CI	Exact p=
Total number	41	38			
Seroma					
minor	11	7	0.62	0.21-1.80	0.429
major	2	1	0.53	0.05-6.06	1.000
all	13	8	0.57	0.21-1.59	0.318
Infection					
minor	1	4	4.71	0.50-44.1	0.19
major	3	4	1.49	0.31-7.14	0.705
all	4	8	2.47	0.68-8.90	0.215
Necrosis					
minor	3	1	0.34	0.03-3.44	0.616
major	2	2	1.08	0.14-8.10	1.000
all	5	3	0.62	014-2.78	0.713
All minors	14	11	0.79	0.30-2.04	0.638
All majors	6	6	1.09	0.32-3.74	1.000
All complications	17	14	0.82	0.33-2.04	0.818

Numbers of patients in each category are reported

Table 8-2: Number of complications according to the mode of treatment

8.3.2.2 Hospital stay and outpatient treatment

The duration of hospital stay and the total length of surgical treatments are summarised in Table 8-3. There were no significant differences between conventionally treated patients and those given primary systemic treatment.

Median (range)	Conventional	P.S.T.	χ^2	p value
Days of hospital stay	8 (3-127)	8 (3-23)	0.13	0.719
Days of surgical treatment	11 (3-127)	10 (4-106)	0.69	0.406

Table 8-3: Hospital stay and duration of surgical treatment

8.3.3 Patient and tumour factors and complications

8.3.3.1 All patients

The relationship between the patient and tumour factors and each of the outcome variables is presented in Table 8-4. These are further discussed below.

	Total number	Number given PST	Number of smoker	Number with recon	Mean Age	Median tumour diam	Median involved Nodes	Median BMI
Statistic		Exact	Exact	Exact	t-test	M-W U	M-W U	M-W U
Seroma								
present	21	8	7	**10**	**55**	4.5	1	25.5
Absent	58	30	21	**43**	**48**	4.5	0.5	25.8
p value		0.32	1.00	**0.03**	**0.05**	0.79	0.64	0.71
Infection								
present	12	8	3	7	52.5	4.9	1.5	**27.8**
Absent	67	30	25	46	50	4.5	1	**25.4**
p value		0.22	0.52	0.52	0.71	0.37	0.45	**0.03**
Necrosis								
present	8	3	2	4	50	4.9	0	**32.8**
Absent	71	35	26	49	50	4.5	1	**25.4**
p value		0.71	0.71	0.43	0.87	0.28	0.24	**0.0003**

Number in each category are reported. recon: reconstruction. BMI: Body Mass Index. Exact: Fisher's exact test. M-W U: Mann-Whitney U test.

Table 8-4: The association between patient and tumour factors and development of complications for the entire group of patients

8.3.3.1.1 Seroma

On univariate analysis, seroma formation appeared to be more common with older age (odds ratio 1.05, 95% CI: 1.00-1.10) and in the absence of a breast reconstruction (odds ratio 0.32, 95% CI: 0.11-0.90).

A logistic regression model containing these two variables was of borderline significance, with neither variable achieving statistical significance on their own (Table 8-5).

y= Seroma	Odds ratio	95% CI	z=	p value
Age	1.02	0.96 to 1.08	0.70	0.583
Reconstruction	0.42	0.12 to 1.51	-1.33	0.183
Log likelihood= -43.1			χ^2=5.23	0.073

Multivariate logistic regression model

Table 8-5: The relationship between seroma formation and age and breast reconstruction.

8.3.3.1.2 Infection

On univariate analysis, patients with larger body mass indices were at greater risk of developing wound infection (odds ratio: 1.15, 95% C.I.: 1.03 to 1.30). The association with body mass index was maintained on multivariate analysis, and no other significant factors emerged.

8.3.3.1.3 Necrosis

On univariate analysis, patients with larger body mass indices were at greater risk of developing skin edge necrosis. This association was highly significant (odds ratio: 1.32, 95% C.I.: 1.13 to 1.55). The strong association with body mass index was maintained on multivariate analysis, and no other significant factors emerged.

8.3.3.2 Primary systemic treatment only

The relationship between the patient and tumour factors and each of the outcome variables is presented in Table 8-6. The mode of adjuvant treatment was not significantly associated with

any of the complications. The pattern of association between complications and patient and tumour factors for this subset of patients was similar to that seen for the entire group of patients.

	Total number	Number given chemo	Number of smoker	Number with recon	Mean Age	Median tumour diam	Median involved Nodes	Median BMI
Statistic		Exact	Exact	Exact	t-test	M-W U	M-W U	M-W U
Seroma								
present	8	4	2	4	**57.5**	4.5	1.5	26.3
Absent	30	10	10	23	**47**	4.5	0	26.1
p value		0.43	1.00	0.20	**0.01**	0.87	0.57	0.28
Infection								
present	8	4	2	4	54	4.7	1	**30.6**
Absent	30	10	10	23	48	4.5	0.5	**25.6**
p value		0.43	1.00	0.20	0.51	0.82	0.84	**0.003**
Necrosis								
present	3	2	1	1	50	5.1	0	**37.1**
Absent	35	12	11	26	48	4.4	1	**25.9**
p value		0.54	1.00	0.20	0.45	0.18	0.67	**0.017**

Number in each category are reported. recon: reconstruction, BMI: Body Mass Index. Exact: Fisher's exact test. M-W U: Mann-Whitney U test.

Table 8-6: The association between patient and tumour factors and development of complications for patients given primary systemic treatment

8.3.3.2.1 Seroma

Older age was associated with seroma formation in the PST group (odds ratio: 1.12, 95% C.I.: 1.02 to 1.24). In this subset the effect of age was independent of breast reconstruction, and age remained the only significant predictor of seroma formation on multivariate analysis.

8.3.3.2.2 Infection

Larger BMI was the only significant risk factor for wound infections (odds ratio: 1.30, 95% C.I.: 1.07 to 1.56).

8.3.3.2.3 Necrosis

Large BMI was a risk factor for wound age necrosis (odds ratio: 1.31, 95% C.I.: 1.04 to 1.65). There were no other significant associations on uni- or multivariate analysis.

8.4 CONCLUSIONS AND DISCUSSION

8.4.1 Complication rates

The overall incidence of surgical complications in this group of patients was 39%. Most complications were minor and self limiting. Clinically important complications occurred in 15% of patients, a finding similar to other observations (Feigenberg *et al:* 1977; Vinton *et al:* 1991; Say and Donegan: 1974; Hoefer, Jr. *et al:* 1990; Budd *et al:* 1978).

8.4.2 Differences between study and control arms

This randomised trial found no difference in the rate of complications following mastectomy whether this was performed as initial treatment or followed a period of systemic therapy.

These results are consistent with those from previous uncontrolled series. No excess complications were found in 54 patients undergoing mastectomy following aggressive chemotherapy for locally advanced breast cancer (Danforth, Jr. *et al:* 1990). Complication rates following chemotherapy for large operable breast tumours in a further 106 patients were similar to those for a group of 95 matched controls (Broadwater *et al:* 1991). Wound healing following biopsy in the irradiated breast was not found to be adversely influenced by cytotoxic chemotherapy prior to surgery (Pezner *et al:* 1992). Primary chemotherapy did not influence prosthetic infection rates in 17 patients following breast reconstruction (Hoffman *et al:* 1991), nor did it influence complication rates or cosmetic outcome in 207 patients being treated by breast conservation (Engel *et al:* 1991).

8.4.3 The influence of patient and tumour factors

Whether patients treated by primary systemic therapy had received cytotoxic treatment or endocrine treatment only did not influence their surgical outcome.

Older patients had a greater risk of forming a seroma, particularly following primary systemic therapy. The influence of breast reconstruction on seroma formation rates is not clear. Younger patients more frequently had breast reconstruction (section 8.3.1.2), and this may partly be responsible for the apparent fewer seromas seen in the presence of reconstruction.

The most striking finding was the strong influence of obesity on the risk of post-mastectomy wound complications, and in particular wound infection and wound necrosis. This is consistent with the findings from other studies (Aitken and Minton: 1983; Vinton *et al:* 1991; Vinton *et al:* 1990) and may be related to larger breast size (Pezner *et al:* 1992).

8.4.4 Overall conclusion

This study adds to the overall weight of evidence that primary systemic therapy does not adversely influence the outcome of surgery for breast cancer.

PART: 3:

OPTIMISING THE MONITORING TECHNIQUE

CHAPTER 9

9. Tumour Markers and Tumour Monitoring

9.1 INTRODUCTION

Cancer cells, by reason of their abnormal differentiation can produce and secrete molecules normally not found in significant quantities in the body. When these molecules are detectable in the circulation they have the potential to be used as serological tumour markers (Jacobs and Haskell: 1991). Monitoring serum levels of such markers can potentially complement tumour size measurement in monitoring response to primary systemic treatment.

9.1.1 Tumour markers in breast cancer

Onco-foetal proteins, cytokeratins and acute phase proteins are released in a number of malignancies, and have all been used as markers of breast cancer (Rustin and Bagshawe: 1987; Tjandra and McKenzie: 1988). By their nature however they are non-specific , and have the added disadvantage of being expressed in a relatively small proportion of cancers (van Dalen: 1989).

Monoclonal antibodies raised against normal and neoplastic tissue components have been extensively investigated as the basis for various assays for breast cancer specific tumour markers (Tjandra and McKenzie: 1988). While marker assays aimed at oncogene products and other cancer specific molecules are in the early stages of development (Hayes: 1993), one antigen, the Polymorphic Epithelial Mucin (PEM) antigen (Gendler *et al:* 1990) or Episialin (Ligtenberg *et al:* 1990), has formed the basis for some of the most extensively studied marker assays in breast cancer.

9.1.2 The Polymorphic Epithelial Mucin antigen

9.1.2.1 Suitability as a tumour marker

Normal and malignant breast epithelial cells express a high molecular weight glycoprotein on the luminal side of their apical surface, which is also released on human milk fat globule membranes (Taylor-Papadimitriou *et al:* 1981; Arklie *et al:* 1981; Ceriani *et al:* 1977;

Hilkens *et al:* 1981; Ceriani *et al:* 1982; Peterson *et al:* 1978). Although the molecule can also be detected on non-mammary epithelium, transplanted breast tumours release high quantities of this molecule into the circulation (Ceriani *et al:* 1977), much more than other epithelial malignancies investigated in the same way (Sasaki *et al:* 1981).

The glycoprotein is a differentiation antigen (Lundy *et al:* 1985), present on both normal and malignant cells. The protein core of the molecule contains a region coded for by a tandem repeated DNA sequence. (Swallow *et al:* 1987; Siddiqui *et al:* 1988). This sequence codes for a 20 amino acid region, and the molecule's polymorphism is attributable to the different number of repeats of this sequence which can range anywhere between 21 and 125 times (Gendler *et al:* 1990). The glycoprotein produced by cancer cells shows an aberrant pattern of glycosylation (Burchell *et al:* 1987). The carbohydrate side chains in the aberrantly glycosylated molecule are shorter than normal, allowing the highly immunogenic core protein chain to become available for antibody action (Burchell *et al:* 1989). This combination of factors has made this molecule a target for the development of monoclonal antibody based tumour marker assays.

Human milk fat globulins, and membrane preparations from cultured human breast carcinoma cells or human metastatic carcinoma deposits have been used by different groups to produce a number of monoclonal antibodies against different epitopes of the glycoprotein antigen, (Ashall *et al:* 1982; Cordell *et al:* 1985; Kenemans *et al:* 1988; Burchell *et al:* 1984; Taylor-Papadimitriou *et al:* 1981; Kufe *et al:* 1984; Hilkens *et al:* 1984; Hilkens *et al:* 1981; Xing *et al:* 1989; Tjandra *et al:* 1988; Stacker *et al:* 1985). The cloning of the DNA sequence for the core protein by different groups (Gendler *et al:* 1990; Ligtenberg *et al:* 1990), has now confirmed that these antibodies do indeed act on different epitopes of the same antigen. Nevertheless many of the assays developed to detect the antigen have been traditionally investigated as though they detect distinct molecules, and depending on the antibody they use, have been designated as distinct "tumour markers".

Two tumour marker, CA 15-3, and an $HMFG_2$ (Human Milk Fat Globule antigen) were selected for use in this study.

9.1.3 The CA 15-3 tumour marker

9.1.3.1 Characteristics

CA 15-3 is recognised in a sandwich type immunoradiometric assay, using two different monoclonal antibodies,DF3 and 115D8, for its primary and tracer molecules. The DF3 antibody was generated against the membrane enriched fraction of a human metastatic carcinoma (Scholm *et al:* 1984; Kufe *et al:* 1984), and the 115D8 antibody was raised against human milk fat globules (Hilkens *et al:* 1984a; Hilkens *et al:* 1981a). Both antibodies can be used to independently demonstrate their target antigen in the sera of breast cancer patients (Hilkens *et al:* 1984b; Hayes *et al:* 1985b). The combined assay (Tobias *et al:* 1985) has been commercially available in kit form (CIS International, Paris) since the mid 1980's and has been extensively investigated in the diagnosis and follow-up of breast cancer patients.

9.1.3.1.1 Expression in the normal population and patients with benign disease

As with any biochemical assay, the baseline expression of CA 15-3 is likely to vary between different populations, and ideally each laboratory will establish its own reference values. In practice however, the baseline values obtained in European populations are fairly similar.

A number of groups have reported CA 15-3 value for healthy blood donors, and patients with benign disease. Although the distribution of CA 15-3 is skewed (Colomer *et al:* 1989a), most reports present the data as mean and standard deviation (S.D.) for the population studied. The normal values from different reports are summarised in Table 9-1. The largest study of normal values was a Spanish study (Colomer *et al:* 1989a), which reported normal values for 275 healthy blood donors and 1220 patients with a variety of non-malignant, non-breast related conditions. Based on this study 95% of normal individuals or patients with benign disease will have a CA 15-3 value less than 37 U/ml (mean + 2S.D.). The next largest study, a Japanese study of 462 normal individuals found a much lower 95% cut-off level of 19 U/ml (Fujino *et al:* 1986). Because of the difference in patterns of breast disease amongst the Japanese, this cut-off may not however be applicable to European populations. Three further major studies from Italy, France and Ireland, looking at healthy individuals, reported 95% cut-off levels of 25 (Gion *et al:* 1991), 24, (Pons-Anicet *et al:* 1987) and 27 U/ml (O'Hanlon *et*

al: 1995a) respectively, while a variety of other values ranging from 15 to 44 U/ml were reported by other smaller studies in Caucasian women (Table 9-1). A number of other studies have reported normal values based on median CA 15-3 levels (Kallioniemi *et al:* 1988; Hayes *et al:* 1986; Safi *et al:* 1991). The largest of these contained 1050 patients and recommended a cut off of 30 U/ml (Hayes *et al:* 1986).

Reference	Country of origin	Sample type	n=	mean	S.D.	Mean +2S.D.
(Colomer *et al:* 1989a)	Spain	Benign disease	1220	16	10.5	37
		Normal	275	16.5	9.4	35
(Fujino *et al:* 1986)	Japan	Normal	462	10.3	4.3	19
(Gion *et al:* 1991)	Italy	Normal	193	14.0	5.6	25
(Pons-Anicet *et al:* 1987)	France	Normal	100	13.7	5.2	24
(O'Hanlon *et al:* 1995a)	Ireland	Benign disease	73	16.8	5.1	27
(Eskelinen *et al:* 1988)	Finland	Benign disease	52	13.7	7.2	28
(Sacks *et al:* 1987)	Australia	Normal	30	18.0	4.9	28
		Benign disease	13	12.0	1.4	15
(Barak *et al:* 1988)	Israel	Normal	22	16.6	6.5	40
(van Dalen: 1989)	Netherlands	Benign disease	10	21.0	11.5	44

Table 9-1: Studies stating mean and standard deviations (S.D.) for CA 15-3 levels measured in normal individuals, or patients with non-malignant conditions.

9.1.3.2 CA 15-3 in patients with breast cancer

9.1.3.2.1 Metastatic disease

The levels of CA 15-3 generally appear to reflect tumour burden in breast cancer. The highest values are reported amongst patient with distant metastatic disease (Colomer *et al:* 1986;

Colomer *et al:* 1989; Fujino *et al:* 1986; Barak *et al:* 1988; Kerin *et al:* 1989; Zanco *et al:* 1989; Steger *et al:* 1989). In one study total body tumour burden was estimated by defining the sites of tumour metastases, and CA 15-3 values were shown to correlate with the estimated tumour burden (Colomer *et al:* 1989b). CA 15-3 has been used, often in conjunction with other markers, for follow-up of disease free breast cancer patients and has been shown to be successful in the detection of metastatic disease before it is clinically apparent (Geraghty *et al:* 1992; Viscera *et al:* 1994; Colomer *et al:* 1989; Martoni *et al:* 1988; Zanco *et al:* 1989).

9.1.3.2.2 Localised breast cancer

Elevated marker levels have been reported for all stages of disease in patients with non-metastatic breast cancer. In these patients CA 15-3 values correlate with tumour diameter (Gion *et al:* 1991; Pons-Anicet *et al:* 1987; O'Hanlon *et al:* 1995) and extent of nodal involvement (O'Hanlon *et al:* 1995a; Pons-Anicet *et al:* 1987a; Gion *et al:* 1991a) and average marker levels increase with increasing stage of the disease (O'Hanlon *et al:* 1995b; O'Hanlon *et al:* 1995b; Horobin *et al:* 1991b; Gion *et al:* 1991b).

Most patients with early cancers [stage I and II (Beahrs *et al:* 1988)], have CA 15-3 levels which are comparable to the normal population, but even in earliest stages of the disease 10-20% of patients show marker levels above the normal range (O'Hanlon *et al:* 1995a; Horobin *et al:* 1991a; Kallioniemi *et al:* 1988a; Gion *et al:* 1991a). Furthermore, even when marker levels are within the normal range, drops in marker levels can be detected following removal of the primary cancer (O'Hanlon *et al:* 1995a; Omar *et al:* 1989a; Eskelinen *et al:* 1989a).

9.1.3.2.3 Response assessment

Several studies have evaluated the role of CA 15-3 in the assessment of response following systemic therapy for metastatic cancer. It is clear that the changes in marker levels correlate with tumour response (Colomer *et al:* 1986; Barak *et al:* 1988). Paradoxical responses however can be seen in individual patients with rises in marker level following successful initial induction, and rapid initial falls in patients who fail to respond (Kiang *et al:* 1990). CA 15-3 has not been previously evaluated for the assessment of response to primary systemic treatment in either locally advanced, or operable breast cancer.

superior, although in some cases the combined assay enhances the overall sensitivity (Bieglmayer *et al:* 1988; Rasoul-Rockenschaub *et al:* 1989).

In the present study CA 15-3 and $HMFG_2$ were studied simultaneously.

9.2 PATIENTS AND METHODS

9.2.1 Patients

9.2.1.1 Samples during primary systemic treatment

Sequential samples were obtained from two groups of patients. The first group were a subset of patients from those undergoing primary systemic therapy. Serum samples were obtained before the start of treatment, at three weekly intervals during the period of primary systemic treatment, immediately prior to mastectomy and at least 4 weeks after the date of the mastectomy. Tumour volume was measured clinically and by ultrasound (section 10.2.1.2.3) each time a serum samples were obtained.

The second group included patients undergoing primary cytotoxic chemotherapy for locally advanced non-metastatic breast cancer (T_4, N_{0-2}, M_0). Samples were obtained before the start of chemotherapy and at completion of chemotherapy prior to start of locoregional treatment.

9.2.1.2 Pre and postoperative samples

These were available for patients undergoing primary systemic treatment within the trial, and additionally in a subgroup of patients treated in the conventional treatment arm of the trial. Further pre and postoperative samples were obtained from patients who were suitable for entry to the trial, but had declined to be randomised.

9.2.2 Assay techniques

Serum samples were separated from 10 mls of clotted blood and stored at -70°C until analysis. All samples were analysed simultaneously.

9.2.2.1 The CA 15-3 Assay

9.2.2.1.1 Description

The CA 15-3 antigen was measured using the commercially available kit by CIS bio international, France (ref: ELSA-CA 15-3).

The assay is a solid phase two site immunoradiometric assay. The CA 15-3 antigen is "sandwiched" between two monoclonal antibodies raised against sterically remote sites on the antigen molecule.

The monoclonal antibody 115 D8, raised against human milk fat globule membranes (Hilkens *et al:* 1981) is used as the primary antibody. The tracer antibody is the monoclonal antibody DF3 (Kufe *et al:* 1984), labelled with ^{125}I.

9.2.2.1.2 Kit components

1. Plastic assay tubes pre-coated on their base with an excess amount of 115 D8 monoclonal antibody.

2. Tracer reagent containing ^{125}I labelled DF3 monoclonal antibody in buffer with protein and preservative.

3. Standard solutions of cell culture derived CA 15-3 in buffer, protein and preservative provided in ready-to-use dilutions of zero, 15, 40, 80, 140 and 240 arbitrary units per millilitre (U/ml).

4. Control solution at a concentration of 30 U/ml in protein matrix with preservative.

5. Diluent containing buffer, protein and preservative for use with patient sera.

9.2.2.1.3 Assay procedure

All materials were handled using no-touch techniques and standard rules of radiation safety were observed throughout.

Standard sample and control were assayed in triplicate, while patient samples were assayed in duplicates. All patient samples were assayed at the same time.

20μl of patient sera or control serum were added to 1 ml of diluent in a disposable polystyrene tube (Falcon U.K.) and mixed over a vortex mixer. 300μl of diluted samples, and 300μl of pre-diluted standard sera were added to appropriately labelled assay tubes coated with the primary antibody and mixed over a vortex mixer. Tubes were incubated for 1 hour at room temperature in a shaking incubator (Dynatech). At the end of the incubation period, the contents of the tube were aspirated to dryness and the tubes washed three times by adding 3 mls of distilled water to the tube on each occasion mixing and then discarding the water.

300μl of the solution containing tracer antibody was next added to each tube and the tubes incubated for a further hour at room temperature in a shaking incubator. On completion of the second incubation period, the tubes were again aspirated to dryness and washed 3 times with distilled water.

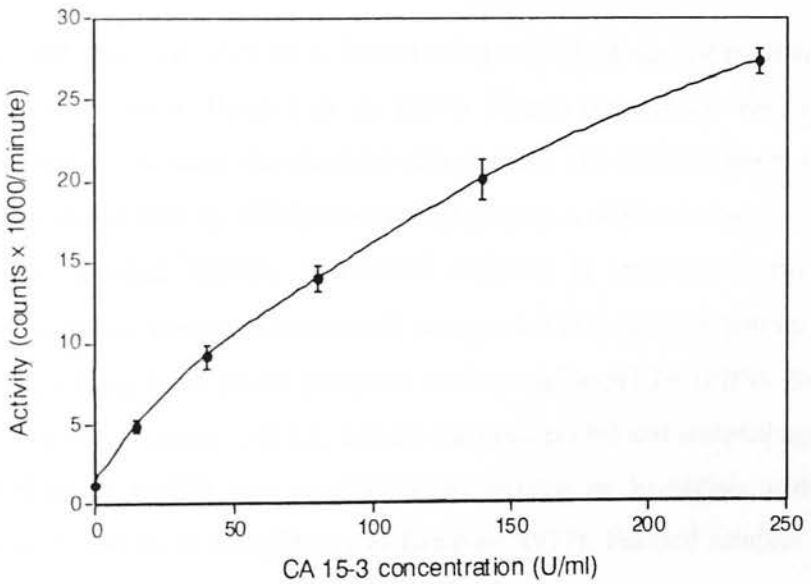


Figure 9-1: Standard curve used to calculate CA 15-3 concentrations (mean±2SE)

The tubes were placed in a gamma scintillation counter and activity counted for 60 seconds. Background gamma activity was subtracted to obtain the gamma activity for each tube. A standard curve was constructed using the values obtained from the standard dilutions (Figure 9-1), and the CA 15-3 concentration for each sample calculated from the standard curve.

9.2.2.2 The $HMFG_2$ Assay

9.2.2.2.1 Description

The asay, developed by J. Fisken (Fisken *et al:* 1993; Fisken: 1991) is a solid phase enzyme linked immunosorbent assay. The monoclonal antibody 1.10.F3 (Taylor-Papadimitriou *et al:* 1981), adsorbed on to assay plates is used as the primary antibody. The same antibody, conjugated to horseradish peroxidase is used as the tracer.

9.2.2.2.2 Assay procedure

9.2.2.2.2.1 Preparation of assay standards

$HMFG_2$ standards were prepared by J. Fisken using methods described previously (Taylor-Papadimitriou *et al:* 1981, Burchell *et al:* 1987). Human breast milk was centrifuged at 10000g for 30 minutes to isolate the skimmed milk fraction. The HMFG antigen was prepared from human skimmed milk by affinity chromatography on a sepharose column prepared by coupling of the purified $HMFG_1$ monoclonal antibody to cyanogen bromide activated sepharose (Pharmacia). Human skimmed milk was passed in batches of 100 ml through the column and the column washed with phosphate buffered saline pH 7.4 (PBS). Bound antigen was eluted using 0.1 M glycine pH 2.5, and the fractions pooled and dialysed against 0.25M acetic acid. Purified HMFG was partially deglycosylated by hydrolysis with anhydrous hydrogen fluoride for 1h at 4°C (Mort and Lamport: 1977). Purified samples were freeze dried and stored at -20°C.

HMFG concentrations were set by reference to an original preparation isolated by Dr. S. Mather (St. Bartholomew's Hospital, London). 1 mg of the freeze dried powder was arbitrarily equal to 10^6 units. Standard solutions were prepared in PBS, containing 7% bovine serum albumin and 0.01% w/v Thimerosal as preservative, and calibrated against a

preparation obtained from Dr. J. Taylor-Papadimitriou (I.C.R.F., Lincoln's Inn Fields, London). Aliquoted standards were stable for at least 2 weeks at 4°C.

9.2.2.2.2.2 Preparation of assay plates

96-well microtitre plates (M129B, Dynatech, Billingshurst, Kent, UK.) were used. $HMFG_2$ monoclonal antibody was prepared at a concentration of 5 μg/ml in 0.05M carbonate buffer pH 9.6. The plates were coated with primary antibody by adding 50μl of the antibody solution to each well and allowing to stand overnight at 4°C. At the end of the incubation period the plates were washed three times with 100μl of PBS containing 0.05% polyoxyethylene sorbitan monolaurate (Tween 20), ready for use.

9.2.2.2.2.3 Preparation of $HMFG_2$-horseradish peroxidase conjugate

Horseradish peroxidase (HRP) enzyme was conjugated to $HMFG_2$ monoclonal antibody in a 1:1 ratio. Five mg HRP (Sigma Type VI) was dissolved in 1 ml of distilled water, and oxidised by the addition of 0.4 ml freshly prepared 0.1M sodium metaperiodate for 20 minutes at room temperature in the dark, while gently stirring occasionally. Oxidised HRP was dialysed overnight at 4°C with 1 litre of 1 mM acetate buffer pH 4.4, stirring continuously. The pH was brought to pH 9.0 with 0.2M carbonate buffer pH 9.5. Five mg $HMFG_2$ antibody in 1 ml carbonate buffer was added and stirred gently for 2 hours at room temperature in the dark. Next, 0.1 ml of freshly prepared sodium borohydride (5 mg/ml in distilled water) was added and incubated at 4°C for 2 hours. The conjugate was finally dialysed with phosphate buffered saline containing 0.01% w/v Thimerosal, and was stored in this buffer at 4°C in the dark.

The peroxidase substrate consisted of 0.04% w/v 0-phenylenediamine and 0.02% v/v hydrogen peroxide in 0.15M citrate phosphate buffer pH 5.0.

9.2.2.2.2.4 The assay protocol

No-touch technique was used throughout. Patient samples were assayed in duplicate, and standards and controls in triplicate.

25μl of neat patient serum, standard, or control were added to appropriately labelled wells along with 25μl of PBS/Tween. The plates were incubated for 30 minutes at 37°C in a shaking incubator, and washed three times with PBS/Tween.

The plate wells were next covered with 50 μl of $HMFG_2$ antibody-HRP conjugate at a dilution of 1:1000 in PBS/Tween, and incubated for a further 30 minutes at 37°C. After three final washes, 100μl of peroxidase substrate was added to the wells. The reaction was stopped after 30 minutes incubation at 37°C with the addition of 50μl of 2.5M sulphuric acid.

The plates were placed in a densitometer (Titertek Multiscan), and their optical density determined at 492 nm.

The standard curve was prepared using the following concentrations of $HMFG_2$: 0.0, 50.0, 100, 200, 400 and 600 arbitrary units per ml (Figure 9-2), and the $HMFG_2$ concentration in patient samples was calculated from this standard curve.

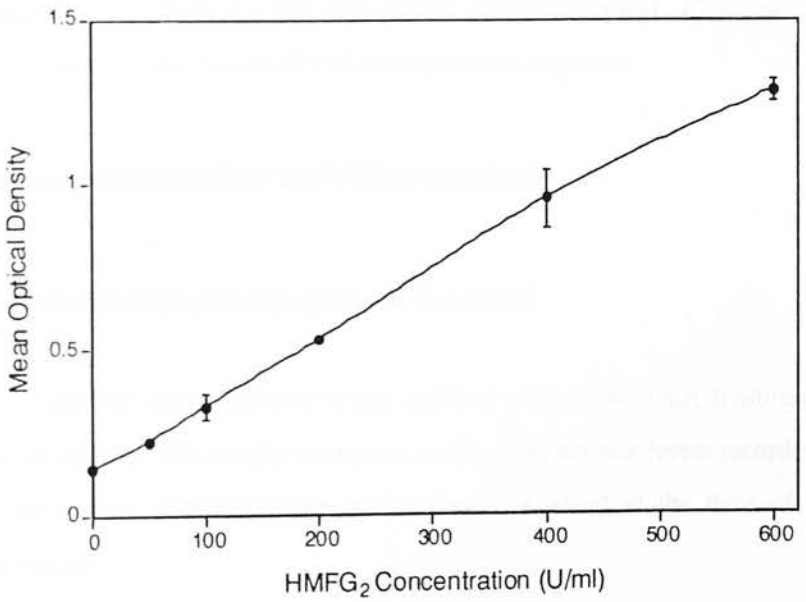


Figure 9-2: standard curve used to calculate $HMFG_2$ concentrations (mean±2SE)

9.2.3 Analysis of results

All statistical analyses were performed using the statistical software package Stata 4.0 for Windows, Stata Corporation, 702 University Drive East, College Station, Texas 77840 USA.

9.2.3.1 Definition of response

Response to primary systemic therapy was assessed by weekly measurement of tumour volume as explained previously (section 3.3.1.3). A similar technique was used to assess response in the group of patients with locally advanced breast cancer.

9.2.3.2 Sequential measurements

The marker values for patients treated within the trial were plotted against time, and using the method of least squares the rate of change of marker levels was calculated as the slope of the regression line. Where failed endocrine treatment was followed by chemotherapy, separate regression slopes were calculated for each phase of the treatment. Changes in sequential marker measurements were correlated with actual tumour response.

9.2.3.3 Measurements before and after treatment

9.2.3.3.1 Before and after primary systemic treatment

In the group of patients who received a single mode of primary systemic treatment, including the subgroup of patients with locally advanced carcinomas, marker levels recorded before the start of treatment were compared with marker levels obtained at the time of the start of locoregional therapy.

In those patients who failed to respond to endocrine therapy and went on to receive cytotoxic chemotherapy, each phase of treatment was treated as a separate treatment episode. Thus, marker levels obtained at the time of change in treatment were compared with levels obtained before the start of treatment and at the time of mastectomy.

9.2.3.3.2 Before and after mastectomy

When a patient was treated by primary mastectomy, pre mastectomy marker levels were compared with those obtained immediately following mastectomy. For patients treated by primary systemic treatment, post-mastectomy marker levels were compared with marker levels obtained before any treatment had been given.

9.3 RESULTS

9.3.1 Patients

9.3.1.1 Samples during primary systemic treatment

Sequential samples were obtained for 30 treatment episodes from 26 patients undergoing primary systemic treatment within the trial. An average of 5 samples were collected for each patient (range 2 to 8). In total 124 preoperative samples and 26 post-mastectomy samples were obtained. In addition pre and post treatment samples were obtained from 10 patients with locally advanced breast cancer.

9.3.1.2 Pre and postoperative samples

Pre and postoperative samples were available in a total of 42 patients: 26 from those given primary systemic treatment, 10 from patients treated conventionally within the trial and 6 samples from patients treated outside the trial.

9.3.2 Marker characteristics

All samples were assayed in duplicate. Marker values are recorded as the mean of two measurements and the standard error of the mean. A total of 202 corresponding measurements of CA 15-3 and $HMFG_2$ were available. The distribution of marker values was examined using a probit plot, and found to be markedly skewed, but approximated to normal on logarithmic transformation.

9.3.2.1 Assay characteristics

9.3.2.1.1 Intra-assay variability

The intra-assay variability was assessed by calculating the overall coefficient of variation from the differences in values obtained from duplicate samples (Bland: 1987). All 202 samples were used in the calculation. The coefficient of variation for CA 15-3 was 8.32±0.08%. The coefficient of variation for $HMFG_2$ was 12.74±0.37%, somewhat higher than that seen for CA 15-3.

9.3.2.1.2 Sampling variability

Since all samples were assayed simultaneously the question of inter-assay variability does not arise. It is however still possible to experience spurious variability between samples obtained at different times from the same patient.

Sequential samples obtained 3 weeks apart during primary systemic treatment are likely to be sufficiently similar in order to give a measure of sampling variability. The first and the second samples in the sequence were selected in 26 such patients undergoing primary systemic treatment. There was no significant difference between the first and second sets of samples for either CA 15-3 (n=26, z=-1.31, p=0.191 Wilcoxon signed-rank test) or for $HMFG_2$ (n=26, z=-1.22, p=0.224, Wilcoxon signed-rank test).

The coefficient of variation for CA 15-3 samples obtained at different times was 22.2±0.63%. The corresponding variability for $HMFG_2$ was 22.6±2.0%.

9.3.3 Analysis of marker values

9.3.3.1 Pre-treatment marker levels

Distribution of pre-treatment CA 15-3 and $HMFG_2$ levels in the 42 patients with operable breast cancer are shown in Figure 9-3 and Figure 9-4. Even at a conservative cut off level of 25 U/ml only 7 of the 42 patients had raised CA 15-3 values. $HMFG_2$ levels were raised above

the cut off of 40U/ml in a significantly greater proportion, with 26 of 42 patients having a raised level (p=0.000, Fisher's exact test).

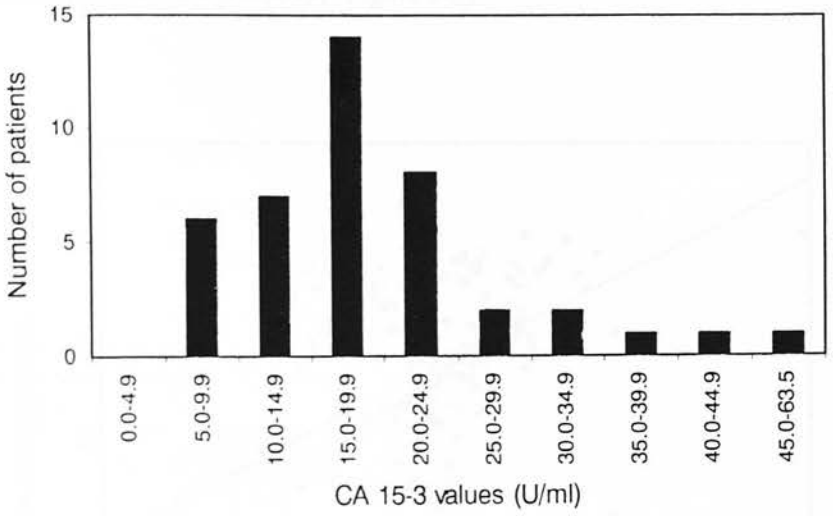


Figure 9-3: The distribution of initial CA15-3 values

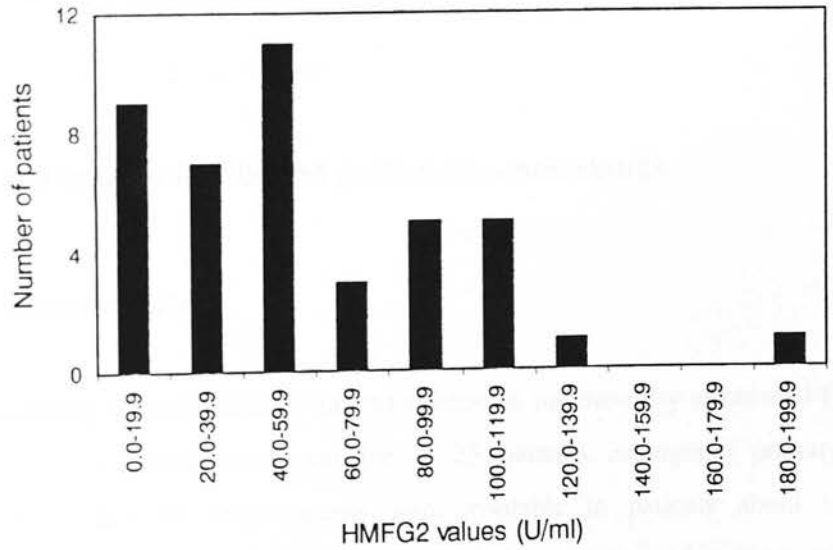


Figure 9-4: The distribution of initial $HMFG_2$ values

9.3.3.2 Relationship between CA 15-3 and $HMFG_2$

The relationship between the natural logarithm of the two markers was examined using the method of least squares There was a weak but significant correlation between CA 15-3 levels and $HMFG_2$ levels (r^2=0.140, p=0.0001, Figure 9-5).

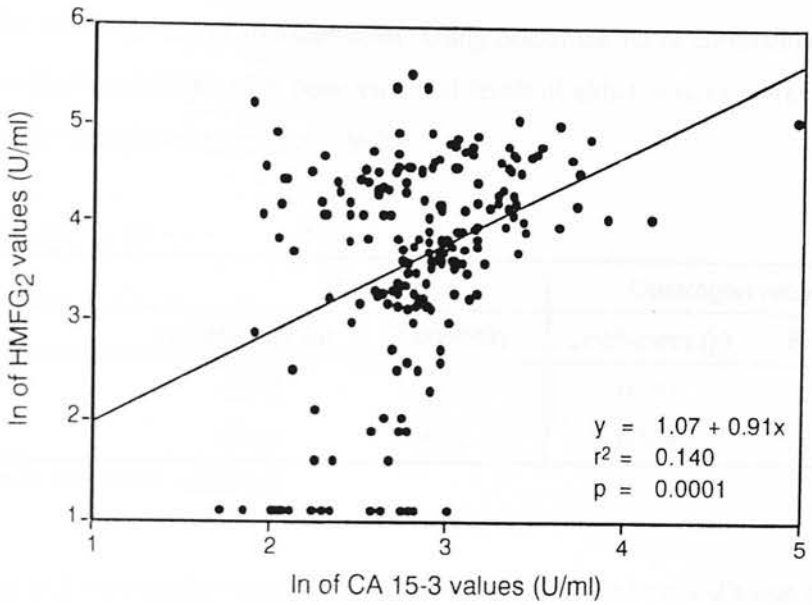


Figure 9-5: The relationship between CA 15-3 and $HMFG_2$ values

9.3.4 Initial marker levels and patient characteristics

9.3.4.1 Tumour volume

124 corresponding measurements of tumour volume as measured by ultrasound (10.2.1.2.3) and tumour marker levels were available in 26 patients undergoing primary systemic treatment. A further 10 measurements were available in patients about to undergo mastectomy. The correlation between tumour marker values and tumour volume was examined using Spearman Rank correlation coefficient.

There was no significant relationship between CA 15-3 and tumour volume (ρ=0.002, p=0.99). $HMFG_2$ levels showed a weak but significant correlation to tumour volume (ρ=0.193, p=0.027).

9.3.4.2 Age and tumour oestrogen receptor content

The relationship between tumour marker levels and these characteristics was examined in relation to the 36 initial marker measurements. Using Spearman Rank correlation coefficient, there was no significant relationship between initial levels of either tumour marker and age or tumour oestrogen receptor content (Table 9-2).

	Age		Oestrogen receptors	
	Coefficient (ρ)	Probability	Coefficient (ρ)	Probability
CA 15-3	-0.151	0.37	0.133	0.43
$HMFG_2$	-0.016	0.92	0.129	0.45

Spearman's rank correlation coefficient

Table 9-2: relationship between tumour marker levels and patient's age and tumour oestrogen receptor level

9.3.4.3 Axillary lymph node involvement

There was no significant difference in the initial levels of either tumour marker between patients with pathologically involved axillary lymph nodes and those with nodes free of tumour (Table 9-3).

Markers	Node-negative (n=16)	Node-positive (n=20)	z=	P=
CA 15-3 [median (range)]	20 (10.7-40.9)	16.9 (6.6-37.6)	-1.27	0.20
$HMFG_2$ [median (range)]	47.1 (3.0-119.9)	53.3 (5.0-185.0)	--0.07	0.95

Mann-Whitney U test.

Table 9-3: Tumour marker levels by axillary nodal status

9.3.4.4 Tumour differentiation

Tumours were divided into well, moderate and poorly differentiated categories. The difference in marker levels was examined using Kruskal-Wallis one way analysis of variance. Marker levels were similar for the three levels of differentiation (Table 9-4).

Markers	Well (n=3)	Moderate	Poor (n=8)	H=	p=
CA 15-3 [median (range)]	20.4 (17.4-40.9)	16.9 (6.6-37.6)	17.6 (12.8-34.1)	2.62	0.27
$HMFG_2$ [median (range)]	95 (3.0-105.0)	55.0 (5.0-185.0)	43.3(96.7-119.9)	0.56	0.76

Kruskal-Wallis one way analysis of variance

Table 9-4: Tumour marker levels by tumour differentiation

9.3.4.5 Tumour markers and survival

Patients were divided into those still disease free at the time of analysis and those with recurrence. Marker values were compared between the two groups using the Mann-Whitney U test. There was no difference in the initial marker values between the two groups of patients (Table 9-5).

Markers	Disease free (n=18)	Recurrence (n=18)	z=	p=
CA 15-3 [median (range)]	19.6 (10.7-40.9)	16.7 (6.6-34.1)	-1.58	0.11
$HMFG_2$ [median (range)]	55.0 (6.7-123.0)	40.0 (3.0-185.0)	-1.14	0.25

Mann-Whitney U test

Table 9-5: Tumour marker levels by recurrence free survival. There was no significant difference between the two groups

9.3.5 Changes in markers with systemic treatment

9.3.5.1 Sequential measurements

9.3.5.1.1 Significant sequential change

Sequential measurements were available for 30 treatment episodes in 26 patients. A change in marker level in relation to time from the start of treatment which was significant at the 85% level was observed in 11 of the 30 treatment episodes for CA 15-3 and in 6 of the 30 treatment episodes for $HMFG_2$. Combining the results from the two markers such that a significant change in either marker is regarded as a positive result, 14 of 30 treatment episodes were associated with a significant change in marker levels.

Twelve of these 14 treatment episodes resulted in tumour response and 2 produced no response. Marker levels showed a sequential reduction (negative slope of the regression line) in only 7 of the 12 responders. In the remaining 5, level of markers sequentially increased (positive slope). One non-responder had an increase in markers and one a decrease.

9.3.5.1.2 Rate of change and rate of volume regression

There was no significant correlation between the rate of change of marker levels and the rate of tumour response for either CA 15-3 or $HMFG_2$ ($\rho = 0.101$, $p = 0.608$ for CA 15-3; $r=0.274$, $p=0.173$ for $HMFG_2$, Spearman Rank correlation coefficient).

9.3.5.2 Pre and post treatment measurements

Marker levels before and after systemic therapy were available for 40 treatment episodes, 30 in 26 patients within the trial and 10 further episodes in 10 patients with locally advanced breast cancer. Thirty treatment episodes resulted in a tumour response, and 10 episodes produced no response.

The median and range of marker values at the start and at the completion of primary systemic treatment were compared for the entire group of patients, and separately for responding and non-responding patients, using the Wilcoxon signed-rank test.

9.3.5.2.1 CA 15-3

There was no difference in the overall median CA 15-3 values before and after treatment. Patients who subsequently failed to respond to treatment had a median initial CA 15-3 level of 14.2 U/ml (range 6.6-24.1), significantly lower than the median of 17.6 U/ml (range 7.6-142.3) for those patients who later showed a response (z=-2.11, p=0.035, Mann-Whitney U test, Table 9-6).

CA 15-3 values [median (range)]		Pre-treatment	Post-treatment	z=	p=
Entire group	(n=40)	16.7(6.6-142.3)	18.5 (8.0-37.8)	-0.57	0.57
Responders	(n=30)	17.6 (7.6-142.3)*	18.8 (8.0-37.8)	-0.79	0.43
Non-responders	(n=10)	14.2 (6.6-24.1)*	15.0 (9.3-33.1)	-2.70	0.007

* z=-2.11, p=0.035 Mann-Whitney U test

Table 9-6: Starting CA15-3 values for responders and non-responders

CA 15-3 values decreased in 15 of the 30 responding patients and increased in the remaining 15. Amongst the 10 non-responders however, CA 15-3 increased in 9 patients and decreased in only one. Overall there was a significant rise in CA 15-3 values in non-responding patients (Figure 9-6).

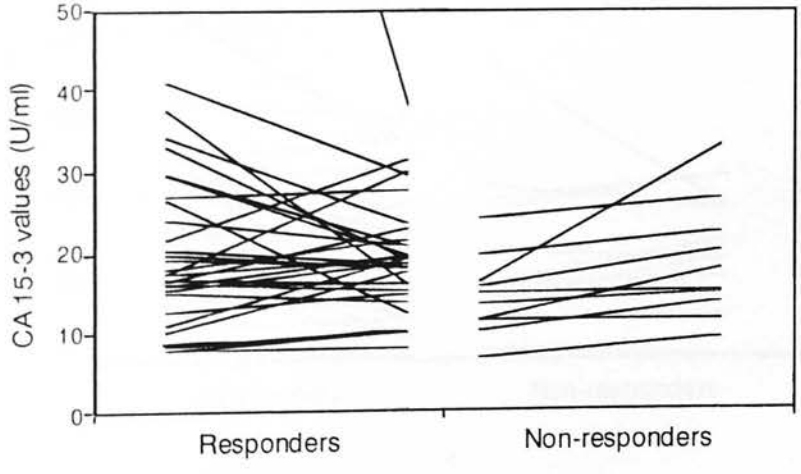


Figure 9-6: Changes in CA 15-3 values with primary systemic treatment

9.3.5.2.2 $HMFG_2$

The overall levels of $HMFG_2$ showed a tendency to fall following treatment (p=0.049). There was no significant difference in the initial $HMFG_2$ values between the responding and non-responding patients (z= 0.81, p=0.417, Mann-Whitney U test, Table 9-7).

$HMFG_2$ values [median (range)]	Pre-treatment	Post-treatment	z=	P=
Entire group (n=40)	70.4 (3.0-245.0)	63.8 (3-215)	-1.97	0.049
Responders (n=30)	77.9 (3.0-245.0)*	62.5 (3.0-215.0)	-2.38	0.017
Non-responders (n=10)	57.1 (7.5-185.0)*	67.9 (3.0-112.5)	-0.59	0.554

*z=-0.81, p=0.417, Mann-Whitney U test

Table 9-7: Starting $HMFG_2$ values for responders and non-responders

$HMFG_2$ values increased in 11 of the 30 responding patients, stayed constant in 2 and decreased in the remaining 17. Amongst the non responders, $HMFG_2$ values increased in only four patients, stayed constant in one and decreased in the remaining 5. Overall there was a significant fall in the levels of this marker amongst the responding patients (Figure 9-7).

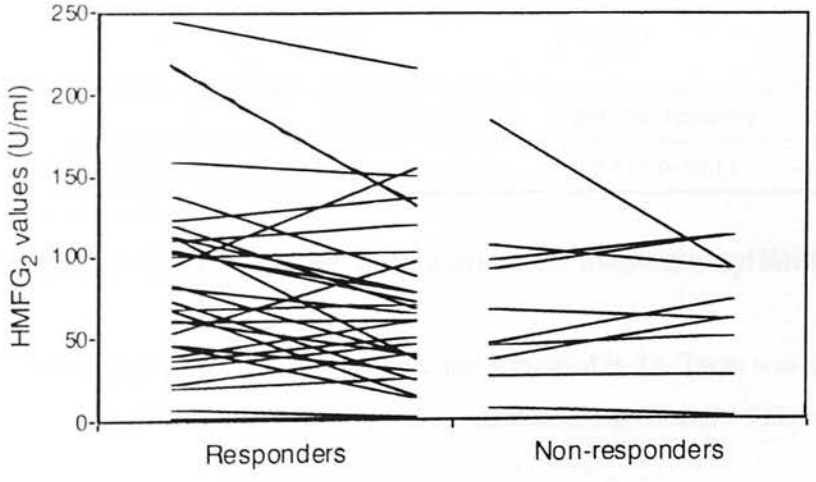


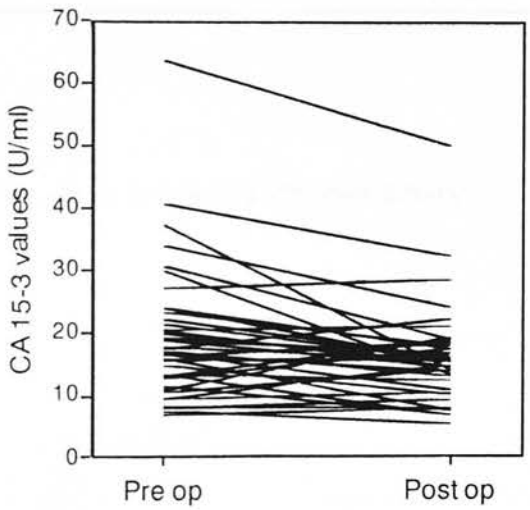
Figure 9-7: Changes in $HMFG_2$ values following completion of primary systemic treatment

9.3.6 Changes in marker levels with surgery

Pre and post-mastectomy samples were obtained in 42 patients.

9.3.6.1 CA 15-3

There was an increase in the levels of CA 15-3 in 13 of 42 patients in whom pre and postoperative samples were available. Levels stayed constant in one patient. In the remaining 28 patients, CA 15-3 values fell following surgery. Overall there was a significant drop in CA 15-3 values following mastectomy (Figure 9-8).

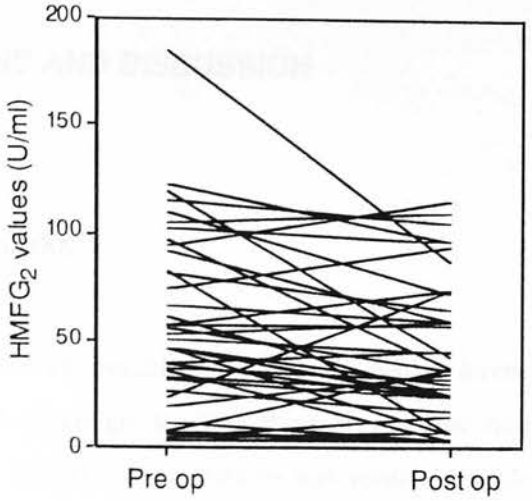


	Pre-mastectomy	Post-mastectomy	z=	P=
CA 15-3 values [median (range)]	16.9 (6.6-63.5)	15.4 (5.6-50.1)	-3.03	0.0024

Wilcoxon signed-rank test

9.3.6.2 Figure 9-8: CA 15-3 values before and after mastectomyHMFG$_2$

HMFG$_2$ levels increased in 12 of the 42 patients and decreased in 27. There was no change in the remaining 3 patients. Overall HMFG$_2$ values decreased significantly following surgery (Figure 9-9).



	Pre-mastectomy	Post-mastectomy	z=	P=
$HMFG_2$ values [median (range)]	46.6 (3.0-185.0)	33.8 (3.0-115.0)	-2.72	0.0065

Wilcoxon signed-rank test

Figure 9-9: $HMFG_2$ values before and after mastectomy

9.4 CONCLUSIONS AND DISCUSSION

9.4.1 General remarks

In this group of patients with operable breast cancers, marker levels were generally low. Few patients presented with levels greater than those seen in the normal population, and the elevation in those with initially raised markers was relatively modest. This results in a low "signal to noise ratio" in this particular patient population, thus limiting the value of CA 15-3 and $HMFG_2$ as a means of monitoring the progress of individual patients. It was nevertheless possible to detect a number of trends by examining changes in marker levels amongst the entire patient population.

9.4.1.1 CA 15-3 vs. $HMFG_2$

The performance of the two markers appeared to be similar. There was a relatively high degree of variability both within the assay and between samples. The CA 15-3 assay performance was similar to figures reported previously (Pons-Anicet *et al:* 1987; Eskelinen *et al:* 1988). Intra patient variability has also been reported for CA 15-3, and has been found to be generally greater than the intra-assay variability (Gion *et al:* 1993; Gion *et al:* 1994; Eskelinen *et al:* 1988) The correlation between the levels of the two was a relatively weak one. This is again likely to be due to the generally low marker levels, making the assays subject to non-tumour related fluctuations.

9.4.2 Tumour volume

The serum levels of tumour associated antigens are assumed to reflect the total body tumour burden (see section 9.1.1). In this patient population, tumour burden can be determined by the direct measurement of tumour volume. Volume did not correlate with CA 15-3 and only correlated weakly with $HMFG_2$. Errors in volume measurements introduced by such factors as the presence of unquantified amounts of tumour in involved axillary nodes may be partly

responsible for this lack of correlation. More importantly, it is likely that the relatively small tumour burden barely produces a detectable increase in tumour marker levels, making any relationship difficult to detect.

9.4.3 Changes in markers with treatment

9.4.3.1 Initial marker levels and response

Patients whose tumours failed to respond to treatment on average had lower initial CA 15-3 than those patients whose tumours did respond. There was however complete overlap between the range of marker values, and initial values could not be used to predict response.

9.4.3.2 Sequential marker values

The sequential measurements of markers during primary systemic treatment produced little useful information in relation to individual patients. This is likely to be due to a combination of generally low tumour marker levels and high inter-sample variability.

Tumour response was accompanied by an overall fall in $HMFG_2$ levels. No such fall was detected for CA 15-3. The change in $HMFG_2$ in response to treatment is likely to represent a true change accompanying a reduction in tumour burden with treatment.

CA 15-3 levels rose following treatment in non-responding patients. No patient actually progressed during primary systemic treatment and it is unlikely that the rise is a reflection of increasing tumour burden. Regression of a subpopulation of tumour cells, along with rapid growth of another population may produce the overall effect of a static tumour, but the resulting increase in cell turnover may be sufficient to lead to increasing release of marker antigens (Kiang *et al:* 1990). This scenario however is made less likely by the fact that there was no suggestion of a corresponding rise in $HMFG_2$. It is likely that at least part of the observed rise is in fact a spurious finding, caused by the combination of unusually low initial marker levels and the tendency for CA 15-3 values to regress towards the mean.

9.4.3.3 Changes with tumour removal

Both markers showed a significant drop following mastectomy. This observation, previously reported in other studies (O'Hanlon *et al:* 1995a; Omar *et al:* 1989a; Eskelinen *et al:* 1989a), is likely to be a true reflection of the combination of reduced tumour burden, and a reduction in baseline antigen load caused by the removal of the breast.

9.4.4 Overall conclusions

The data presented here suggest that measurement of CA 15-3 and $HMFG_2$ levels in patients with operable breast cancer provides little useful information about the state of patients' disease.

CHAPTER 10

10. Ultrasound and Tumour Monitoring

10.1 INTRODUCTION

10.1.1 Measurement of tumour size

10.1.1.1 The significance of tumour size

Tumour size is an important independent indicator of overall prognosis (Carter *et al:* 1989; Koscielny *et al:* 1984; Fisher *et al:* 1969) and the risks of locoregional failure (Clarke and Martinez: 1992; Osteen *et al:* 1987; Locker *et al:* 1989) for patients suffering from carcinoma of the breast . It is required for accurate staging of breast tumours (Beahrs *et al:* 1988; UICC: 1987), and is an important criterion for deciding between mastectomy and breast conservation (Stewart *et al:* 1989; Fisher *et al:* 1989; Osteen and Smith: 1990). Repeated measurements of tumour size may be used to assess response to preoperative radiotherapy (Cheung and Johnson: 1991a; Thomlinson: 1987a), and systemic treatment (Cheung and Johnson: 1991a; Forrest *et al:* 1986a).

10.1.1.2 Conventional measurement of tumour size

10.1.1.2.1 Clinical measurement

Tumour size has conventionally been measured clinically using engineers' callipers to measure the tumour in two diameters (Hayward *et al:* 1977; Thomlinson: 1987; Thomlinson: 1982). Such measurements provide an indirect estimate of tumour size and are influenced the presence of associated oedema and obesity (Dixon *et al:* 1984). They are highly observer dependent (Cheung and Johnson: 1991b).

10.1.1.2.2 Mammography

Mammography is well established as an objective method of assessing breast tumours (Feig: 1992). It has the potential disadvantage that the frequency with which it may be performed is limited by the radiation dose to the breast. An additional problem is that in a significant

minority of patients, the mammographic tumour outline is so diffuse as to make it impossible to estimate small variations in tumour size (Hilleren *et al:* 1991; Smith: 1991).

10.1.1.3 The place of ultrasound in measuring tumour size

Breast ultrasonography is simple to perform, provides a permanent record of tumour size, and may be performed as frequently as required (Feig: 1992; Warwick *et al:* 1988; Leucht *et al:* 1988; Vlaisavljevic: 1988). Ultrasound provides an alternative method of assessing response to primary systemic treatment, particularly in patients with dense breasts (Balu Maestro *et al:* 1991), but its exact relationship to other methods of tumour monitoring has not been previously defined.

10.1.2 Measurement of tumour response

Measurement of tumour response to preoperative treatment can provide valuable information regarding the behaviour of tumours (Cheung and Johnson: 1991b; Thomlinson: 1982b; Thomlinson: 1987b). This information can be used to modify treatment in order to select the most effective treatment regime (Smith *et al:* 1993; Cheung and Johnson: 1991; Anderson *et al:* 1991; Forrest *et al:* 1986). Accurate assessment of final response may be used to allow breast conservation following primary systemic therapy (Singletary *et al:* 1992; Schwartz *et al:* 1994; Greer *et al:* 1979; Smith *et al:* 1993). The assessment of the degree of response can in itself be used as an important indicator of the patient's final prognosis (Jacquillat *et al:* 1991b; Jacquillat *et al:* 1990b; Scholl *et al:* 1991b; Forrest and Anderson: 1991b; Hortobagyi *et al:* 1983b).

Extensive information is available on monitoring tumour response by repeated measurements of tumour size (see above), and it is this aspect of tumour monitoring that this study concentrates on.

10.1.3 The conduct of the study

The study was conducted in two parts. The first part of the study aimed to compare the accuracy of ultrasound as a method of measuring tumour size with other methods of tumour size measurement. The size of tumour in the resected specimen was used as the "gold standard". This part of the study will be referred to as the "size study".

The second part of the study examined the efficacy monitoring changes in tumour size and assessing tumour response using ultrasound. This part of the study will be referred to as the "monitoring study".

10.2 PATIENTS AND METHODS

Two overlapping groups of patients were studied.

10.2.1 The size study

10.2.1.1 Patients

Only patients with clinically palpable tumours were considered for this part of the study. All patients had clinical, mammographic and cytological confirmation of a diagnosis of breast cancer, and were about to undergo either a mastectomy or wide local excision of their breast tumour. There were no other restrictions in entering this part of the study.

Mammography was performed as part of the routine preoperative assessment of all patients. All patients had agreed to undergo breast ultrasound and detailed clinical tumour measurements, and all measurements were completed in the week immediately preceding surgery.

10.2.1.2 Methods

Clinical, mammographic and sonographic measurements were performed by single designated observers. Pathological examination of resected specimens was performed, or directly supervised by one pathologist.

10.2.1.2.1 Clinical measurement

The tumour was measured in 4 diameters at 45 degrees to each other using engineers' callipers. Mean tumour diameter was recorded as the clinical tumour size. Tumour volume was calculated using the formula for the volume of a sphere: $V=(D^3 \times \pi)/6$ (V=volume, D=mean diameter).

10.2.1.2.2 Mammographic measurement

A single oblique view was used to measure tumour diameter. The largest tumour diameter and the diameter at 90° to this axis were measured. Mammographic size was recorded as the mean of the two measurements and tumour volume calculated using the formula for the volume of a sphere. Where mammographic tumour margins were indistinguishable from the surrounding breast tissue, tumour size was considered not assessable by mammography.

10.2.1.2.3 Sonographic measurement

A Siemens (Tokyo) SL1 machine with a 7.5 MHz linear array probe was used. The probe was held orthogonal to the skin and moved over the tumour until maximum diameter was demonstrated. The diameter and the thickness of the tumour were recorded using the machine's electronic callipers. Four measurements were made at 45° intervals, and mean diameter and mean thickness calculated. Tumour volume was calculated using the formula for the volume of an ellipsoid $V=(D^2 x d x \pi)/6$ (V=volume, D=mean diameter, d=mean thickness).

Where the sonographic image of a tumour could not be fitted in to a single screen (diameter over 6 cm), the tumour was considered not assessable by ultrasound.

10.2.1.2.4 Measurements on the resected specimen

Following surgery, fresh specimens were serially sectioned at 0.5-1 cm intervals, and at right angles to the skin. The length, width and thickness of the tumour were recorded. Mean diameter was calculated from the length and the width and volume calculated using the formula for the volume of an ellipsoid.

If the macroscopic margins of the tumour could not be determined with reasonable confidence on visual inspection of the sectioned tumour, that tumour was excluded from the study.

10.2.1.2.5 Analysis of results

All statistical analyses were performed using the statistical software package Stata 4.0 for Windows, Stata Corporation, 702 University Drive East, College Station, Texas 77840 USA.

Distribution of the data was assessed for normality using a probit plot and skewed data normalised using logarithmic transformation. Mean tumour diameter measured by the pathologist was designated "actual size", and the relationship between this and diameters measured by other methods was established using linear regression by the method of least squares. To assess whether a method over- or underestimated tumour diameter, mean pathological, clinical, mammographic and ultrasonographic diameters were compared using Friedman two-way analysis of variance.

10.2.2 The monitoring study

10.2.2.1 Patients

The patients were those receiving primary systemic treatment in the main clinical trial. The entry criteria are described in section 3.2.

10.2.2.2 Methods

10.2.2.2.1 Sequential assessment

Patients were seen once a week and their tumour diameter measured by calliper and by ultrasound as described above. Single oblique mammography was performed once every 4 weeks. Primary systemic treatment was continued for 12 weeks at the end of which time a mastectomy was performed. The natural logarithm of tumour volume was plotted against time, and response defined as a significant negative correlation between time from start of treatment and the natural logarithm of volume, as described in section 3.3.1.3.

Tumours with diffuse mammographic margins or with initial diameters larger than one ultrasound screen were considered not assessable by these modalities.

10.2.2.2.2 Definition of response

Response to primary systemic treatment as assessed by sequential measurement of tumour volume was compared with "actual response". This was determined by estimating the pre-

treatment tumour volume and standard error (SE) from the initial mammographic and ultrasonographic measurements, using data obtained from the "size study". Following primary systemic treatment macroscopic size and microscopic extent of tumour were measured in the surgical specimen, and volume of residual tumour calculated. If this was equal to the estimated initial volume ± 2SE, the disease was classed as static. Residual volumes less or greater than this were classed as regression and progression respectively.

10.3 RESULTS

10.3.1 The size study

10.3.1.1 Patients

Sixty three tumours were measured in 62 patients. The sample included 42 patients treated by initial surgery, and 20 patients who had completed 12 weeks of primary systemic therapy.

10.3.1.2 Tumour assessment

Of the 63 surgical specimens examined, 5 contained no macroscopically detectable residual tumour and in a further 3 the tumour margins were too diffuse for accurate assessment. Fifty-five (87%) of the tumours were assessable.

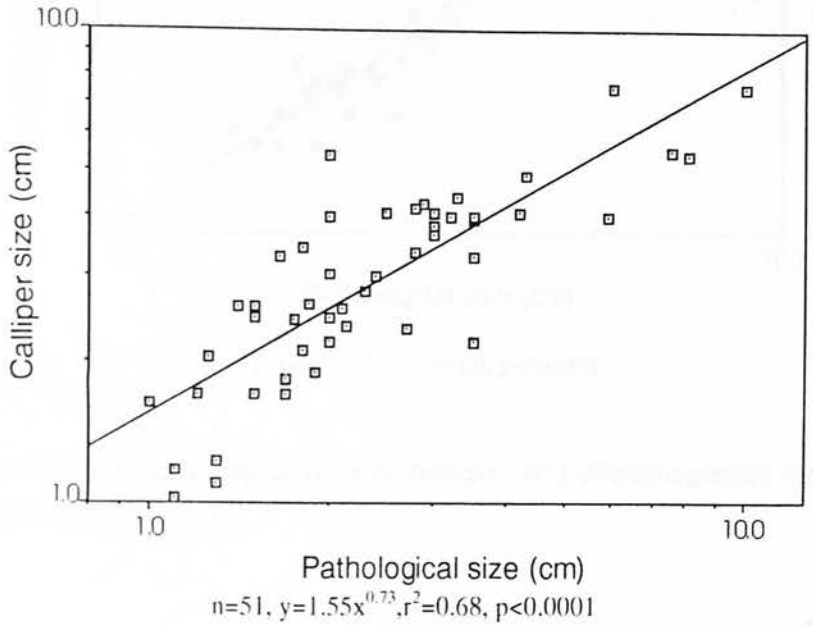
Two patients had clinically palpable lesions which did not correspond to tumours detected in resected specimens and two tumours presenting in one breast were clinically indistinguishable. Ten tumours had diffuse mammographic outlines and could not be measured by this method. Three tumours were larger than the maximum diameter of the ultrasound screen (6 cm), and were not assessable by sonography. Fifty one clinical, 45 mammographic and 52 sonographic measurements were available for analysis.

10.3.1.3 The relationship between different methods of size measurement

10.3.1.3.1 Measurements of tumour diameter

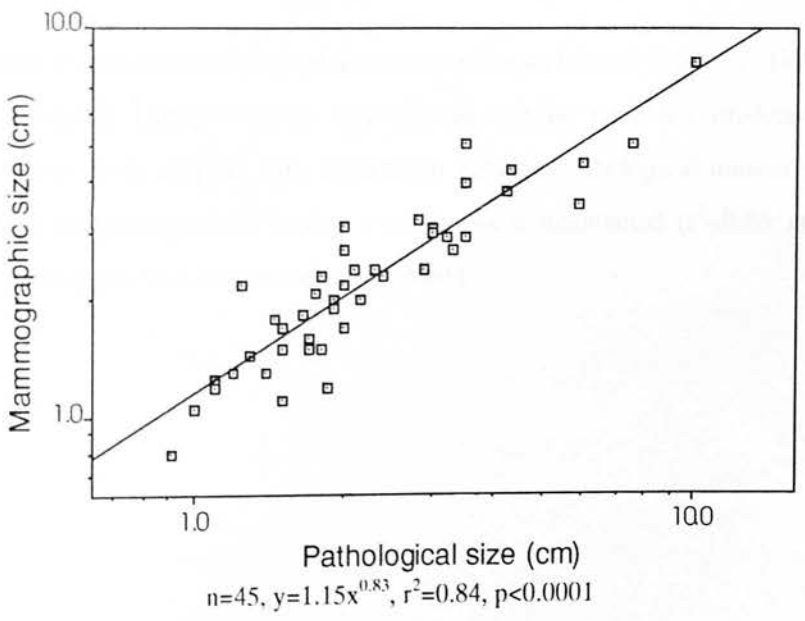
The actual measurements obtained using different methods are presented in the appendix (14.4). Diameter followed a positively skewed distribution curve and log-transformed data were used for linear regression. The following figures show the relationship between actual size and mean clinical, mammographic and sonographic tumour diameters. Diameter measured by calliper showed a moderate degree of correlation with actual size (r^2=0.68,

p<0.0001, Figure 10-1). Mammographic and ultrasonographic measurements correlated much more closely with actual size (r^2=0.84, p<0.0001, Figure 10-2 and r^2=0.89, p<0.0001, Figure 10-3 respectively).



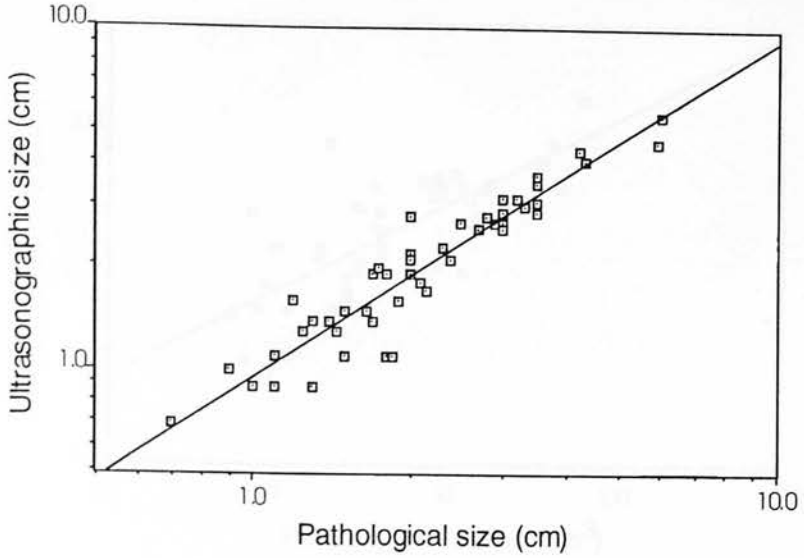
n=51, $y=1.55x^{0.73}$, r^2=0.68, p<0.0001

Figure 10-1: Relationship between pathological and clinical mean tumour diameter



n=45, $y=1.15x^{0.83}$, r^2=0.84, p<0.0001

Figure 10-2: Relationship between pathological and mammographic mean tumour diameter



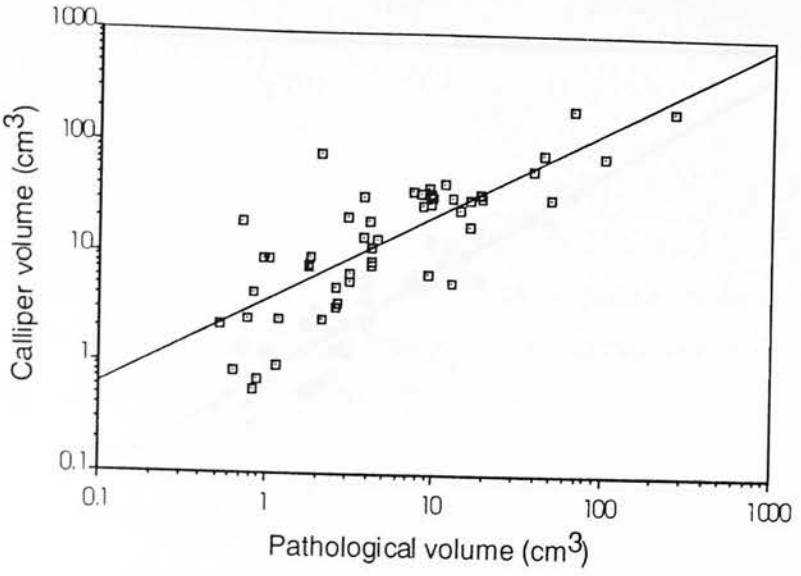
n=52, $y=0.95x^{0.99}$, $r^2=0.89$, $p<0.0001$

Figure 10-3: Relationship between pathological and ultrasonographic mean tumour diameter

10.3.1.3.2 Measurement of tumour volume

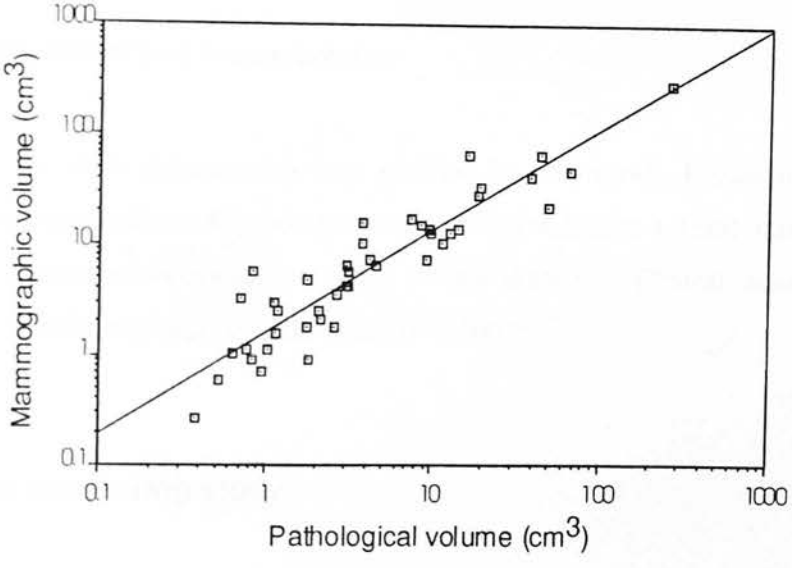
Values for tumour volume also followed a positively skewed distribution curve, and logarithmic transformations of the data were used for linear regression.

Tumour volume measurements followed the same pattern as tumour diameter. The correlation between pathological tumour volume and clinical volume remained moderate ($r^2=0.63$, $p<0.0001$, Figure 10-4), and the close correlation between pathological tumour volume and mammographic and sonographic tumour volumes were maintained ($r^2=0.85$ and $r^2=0.87$, Figure 10-5 and Figure 10-6 respectively, $p<0.0001$).



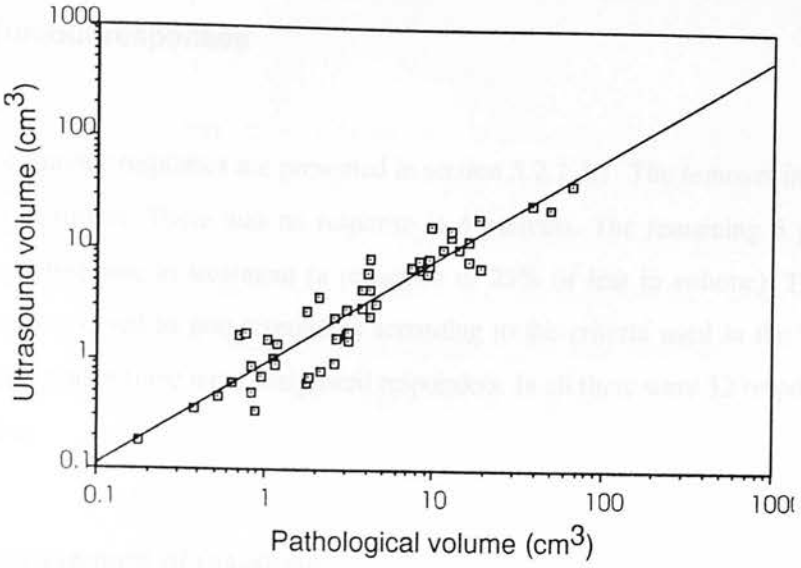
n=51, $y=3.72x^{0.78}$, $r^2=0.63$, $p<0.0001$

Figure 10-4: Relationship between pathological and clinical tumour volume



n=45, $y=1.58x^{0.92}$, $r^2=0.85$, $p<0.0001$

Figure 10-5: Relationship between pathological and mammographic tumour volume



n=52, $y=1.10x^{0.92}$, $r^2=0.87$, $p<0.0001$

Figure 10-6: Relationship between pathological and ultrasonographic tumour volume

10.3.1.3.3 Consistent bias in measurement

For 45 cases in which measurements were available by all methods, Friedman analysis of variance found no significant difference between pathological (mean: 1.9 cm), mammographic (mean: 1.9 cm) and ultrasonographic (mean: 1.8 cm) diameters. Clinical diameter (mean: 2.7 cm) was significantly larger than the others ($p<0.0001$).

10.3.2 The monitoring study

10.3.2.1 Patients

Sequential measurements were performed over a period of 2 years on 38 patients (including 20 cases included in the "size study").

10.3.2.2 Tumour responses

The details of tumour responses are presented in section 5.2.1.3.1. The tumours in 29 patients responded to treatment. There was no response in 4 patients. The remaining 5 patients had shown minimal response to treatment (a reduction of 25% or less in volume). Two of these patients were considered as non-responders according to the criteria used in the "monitoring study", while the other three were designated responders. In all there were 32 responders and 6 non responders.

10.3.2.3 Assessment of response

10.3.2.3.1 Clinical measurement

Sequential clinical measurement was possible in all 38 patients. Clinical measurements correctly classified response in 30 responders and 4 non responders. Two non responders and 2 responders were misclassified.

10.3.2.3.2 Mammography

Twenty six tumours were assessable by mammography. Mammography correctly detected response in 20 responders and three non-responders. Mammography suggested a response in one non-responding patient, and failed to detect response in 2 responders.

10.3.2.3.3 Ultrasound

Thirty six tumours were assessable by ultrasound, and response was correctly detected in 31 responders and 3 non-responders. Of the 12 patients not assessable by mammography 10 were correctly assessed by ultrasound. The other two were not assessable by either ultrasound or mammography. Ultrasound failed to detect response in one responding patient and suggested a response in one non-responder.

10.3.2.3.4 Difficult to assess tumours

Two tumours were incorrectly assessed by all three techniques. Two further tumours were not assessable by ultrasound and mammography, and were incorrectly assessed by clinical examination. Of these four tumours two were non-responders and two were responders. Histological examination revealed diffuse infiltration of the breast by two tumours which were incorrectly assessed as responders. The two patients who were incorrectly assessed as non-responders had discrete residual breast masses which were shown to consist of hyalinized stroma, with very few residual malignant cells.

10.4 CONCLUSIONS AND DISCUSSION

10.4.1 The size study

The correlation between tumour diameter measured by ultrasonography, and actual tumour diameter on excision, was greater in this study than in those previously reported (Pain *et al:* 1992; Nishimura *et al:* 1988; Fornage *et al:* 1987). Ultrasonography was found to be the most accurate method of measuring tumour size in one study (Fornage *et al:* 1987), but a more recent study found all three methods to have the same degree of inaccuracy (Pain *et al:* 1992). These studies were retrospective and relied on sizes recorded in routine clinical notes. Actual size may often have been approximate, as evidenced by significant clustering of pathological sizes around whole numbers (Pain *et al:* 1992; Fornage *et al:* 1987). Pathological size was often reported in one plane only and, in one study, was measured on fixed specimens. Two studies had used a 5 MHz ultrasound probe which may have further contributed to the lower accuracy.

Size was recorded prospectively in the present study. Tumours were measured in several planes, thus minimising errors due to irregularities in tumour shape.

Ultrasonography was the best method of measuring tumour diameter but mammography can also estimate the pathological mean tumour diameter and tumour volume with a much higher degree of accuracy than clinical measurement.

10.4.2 The monitoring study

The aim of repeated measurements is to assess the overall pattern of response. To this end the present study confirms the accuracy of sequential calliper measurements performed by the same person in monitoring response to primary systemic treatment. Imaging techniques are nevertheless important in providing independent and objective verification of clinically observed responses. Mammography and ultrasonography were equally good in assessing response in mammographically discrete tumours, but ultrasonography could also be used to

assess the response of diffuse tumours, and was therefore successful in significantly more patients. Failure to correctly assess response appeared to be a function of the tumour architecture rather than the measurement technique. It is likely that such failures can only be avoided by monitoring parameters other than tumour dimensions.

The assessment of the extent of pathological response requires full histological examination of resected breast tissue, and none of the currently available imaging techniques are sensitive enough to be used as a substitute for this (Helvie *et al:* 1996; Vinnicombe *et al:* 1996).

10.4.3 Overall conclusion

Mammographic or ultrasonographic tumour diameter, rather than clinical diameter, should be used in clinical staging of breast cancer and in planning future clinical trials. Ultrasonography is the method of choice for monitoring the response of breast tumours to primary systemic treatment.

CHAPTER 11

11. Optimum Monitoring Frequency

11.1 FREQUENCY OF TUMOUR MONITORING

11.1.1 Rationale for weekly monitoring

An important concern with regard to the use of primary systemic treatment is that the delay in surgery may result in local tumour progression. Partly for this reason, the current protocol requires the examination of the patient and measurement of tumour volume once a week. The requirement for weekly outpatient attendance is however burdensome to patients and costly in terms of the time of health service resources.

The optimum interval for tumour monitoring is examined in this part of the study.

11.1.2 Patients and methods

Sequential clinical and sonographic weekly tumour measurements were available on patients who had received primary systemic treatment within the main trial. Tumour response was defined according to the criteria set out in section 3.3.1.3, using sonographic measurements. In two cases where ultrasound was deemed unreliable, clinical measurements were used.

11.1.2.1 Re-sampling of measurements

Sequential measurements were re-sampled as follows

Weekly:	(Actual response)
Every 2 weeks :	Weeks 0, 2, 4, 6, 8, 10 and 12
Every 3 weeks:	Weeks 0, 3, 6, 9 and 12
Every 4 weeks:	Weeks 0, 4, 8 and 12

When a patient's treatment was changed because of lack of response, tumour sizes from each phase of treatment were treated as a distinct set of measurements.

11.1.2.2 Analysis of results

For each simulated sample the slope of the regression line and its significance were calculated and tumour half life determined as explained in section 3.3.1.4.2. For sets of measurements obtained weekly or once every two weeks, a significance level of 95% or better was considered to indicate a clinically relevant change in tumour volume. For samples taken once every 3 or 4 weeks, a significance level of 90% or better was considered acceptable.

The simulated therapeutic decisions were compared with actual therapeutic decisions to assess whether a lower frequency of examination had any implications for treatment safety.

11.1.3 Results

11.1.3.1 Patients

All 38 patients treated by primary systemic therapy in the first part of the trial were studied. This sample included five patients who had received and failed to respond to endocrine therapy, and subsequently received chemotherapy. There were 43 sets of measurements available for re-analysis, covering 9 phases of non-response and 34 phases of tumour response.

11.1.3.2 Decisions regarding response

The numbers of responders and non-responders according to each simulated sample are presented in Table 11-1. The number of phases of treatment categorised as producing a response or not resulting in response did not change when tumours were measured once every two, or once every three weeks. Sampling once every 4 weeks considerably reduced the sensitivity of detecting a response. With this frequency of monitoring, four phases of endocrine treatment and two phases of chemotherapy would have been erroneously categorised as resulting in no response. Furthermore, 9 treatment phases which were categorised as producing a response had regression lines which were significant at 90 to 95% level, further reducing the reliability of sampling once every 4 weeks.

	Weekly	Every 2 wks	Every 3 wks	Every 4 wks
Response	34	34	34*	28§
No response, Chemo	4	4	4	6
No response, Endocrine	5	5	5	9

*: Regression in 3 patients was significant at 93 to 95% level

§: Regression in 9 patients was significant at 90 to 95% level.

Table 11-1: Tumour assessment using less frequent sampling than once a week

11.1.3.3 Tumour half lives

Half lives for the nine phases of treatment resulting in no response could not be calculated and they were excluded from further analysis. For the remaining 34 treatment phases, tumour half lives calculated from weekly measurements were not significantly different from half lives obtained from less frequent monitoring. (Table 11-2). Furthermore, the individual values obtained from weekly measurements closely correlated with values obtained by less frequent monitoring (Table 11-2).

	Weekly	Every 2 wks	Every 3 wks	Every 4 wks
Half lives: median (range)	39 (5-105)	38 (5-117)	40 (5-105)	42 (5-113)
Wilcoxon signed-rank test (weekly vs. others)	-	z=-1.09 p=0.28	z=-0.13 p=0.90	z=-1.37 p=0.17
Spearman Rank correlation coefficient (weekly vs others)	-	ρ=0.98 p<0.0001	ρ=0.98 p<0.0001	ρ=0.95 p<0.0001

Table 11-2: The relationship between tumour half lives calculated from weekly and less frequent monitoring

11.1.4 Conclusions

It is clear that weekly tumour monitoring is unnecessarily intensive. Monitoring the tumour once every three weeks is as informative as more frequent regimes, and does not compromise treatment safety. Outpatient visits may be scheduled to coincide with hospital attendance for other purposes such as receiving cytotoxic chemotherapy, and will be much less disruptive to patients.

It is recommended that a regime of monitoring the tumour once every three weeks be adopted for future studies.

11.2 MONITORING STUDIES: OVERALL CONCLUSIONS

Accurate measurement of response is critical to the success of response based regimes of primary systemic treatment. The accessibility of primary tumours makes direct measurement of size a suitable method for monitoring tumour response. In the last three sections an attempt was made to improve the way tumours are monitored during primary systemic therapy

The question of improving the accuracy of clinical size measurement for monitoring tumour response was addressed in chapter 9.

In many patients, the primary tumour represents only part of the total body tumour burden. Tumour markers can reflect the total body burden of tumour. The utility of tumour markers in monitoring tumour burden during primary systemic treatment was examined in chapter 8.

The present study used an intensive weekly tumour monitoring regime. The need for such an intensive regime was questioned in the current chapter .

The three main conclusions of these studies are as follows:

1. Ultrasound is the most effective method of monitoring tumours during primary systemic therapy, and should also be used for the initial measurement of tumour size.

2. It is not necessary to monitor the tumour more than once every three weeks.

3. Tumour markers CA 15-3 and $HMFG_2$ are not sufficiently sensitive to be used for tumour monitoring during primary systemic treatment.

11.2.1 Other methods of tumour monitoring

The techniques of monitoring examined in this part of the thesis concentrate in detecting changes in tumour bulk. An alternative approach will be invasive tumour monitoring. Attempts have been made to assess changes in tumour biology by sequential needle biopsies (Baildam *et al:* 1989), or fine needle aspirates (Forouhi *et al:* 1992; Jordan *et al:* 1986; Zbieranowski *et al:* 1992; Spyratos *et al:* 1992; Briffod *et al:* 1989; Heyderman *et al:* 1989).

These techniques however involve considerable inconvenience to patients, and carry risks of potential morbidity. Colour Doppler ultrasound (Srivastava *et al:* 1988), and magnetic resonance imaging of tumour circulation (Knopp *et al:* 1994) are non invasive methods of assessing changes in tumour architecture which may reflect ultimate response,. and are worthy of further investigation.

12.

CONCLUDING REMARKS

12.1 SUMMARY OF RESULTS

The package of treatment which was investigated in this study evolved out of Sir Patrick Forrest's initial experiments with reversing the traditional order of breast cancer treatment in order to use the breast primary as a guide to best treatment in a "Human tumour model" (Forrest *et al:* 1986). Over the past decade initial systemic treatment of operable breast cancer has become more widely used, but many questions remain to be answered. In this thesis, a group of patients randomised to receive either the new package or conventional treatment were studied in an attempt to answer some of these questions.

12.1.1 Practical disadvantages of primary systemic therapy

In section 1.6.2.2 three potential practical disadvantages of primary systemic therapy were pointed out. All three have been addressed as follows:

12.1.1.1 Loss of potential prognostic indicators

It was shown in section 5.2.1 that the characteristics of tumours which are of prognostic significance are substantially changed by primary systemic therapy. The tumours become smaller, the number of involved lymph nodes are fewer, more well differentiated tumours are recovered, and ER values tend to become lower. In some cases no evidence of tumour remains.

Despite these changes the post treatment tumour characteristics bear the same relationship to prognosis as do their pre-treatment counterparts. Thus prognosis appears to relate to the number of post treatment involved lymph nodes in the same way as it relates to pre-treatment nodes. Patients with fewer than 4 involved nodes have a prognosis which is only marginally worse than those with no nodes involved. In the same way post treatment ER correlates with prognosis, with patients with ER rich tumours continuing to do substantially better than those with ER poor cancers. What is more, speed of response provides an additional marker of prognosis.

In a significant proportion of patients not enough tissue was available for post treatment ER measurements, but this problem can be overcome by the use of a cytochemical assay, which was shown to provide the same quality of prognostic information as the traditional enzyme immuno-assay.

The quality of prognostic indicators are not significantly affected by primary systemic therapy.

12.1.1.2 Potential psychiatric morbidity

The most significant aspects of cancer related psychological problems, mood and adjustment disorders, were examined using well validated instruments. Treatment was an anxious time for patients, but significant morbidity was low, and levels of anxiety returned to baseline after treatment was completed. Primary systemic treatment had no adverse psychological sequelae.

Primary systemic treatment required protracted hospital attendance. Despite this, even at the short follow-up of 37 months, patients in the two arms of the study had almost identical mean TWiST times. Longer follow-up is needed to consolidate these results.

An interesting coincidental finding was the relationship between being anxiously preoccupied with cancer and shorter event free survival.

12.1.1.3 Potential surgical morbidity

Although problems after mastectomy were not uncommon, there was no significant difference in the number of complications between the two arms of the trial, and any non-significant trends were in favour of PST. If PST can be used to allow breast conservation where mastectomy was required before, it may in fact reduce the overall surgical morbidity experienced by individual patients.

Obese patients were particularly at risk of developing surgical complications.

12.1.2 Optimising the treatment

An important advantage of primary systemic treatment is the ability to directly assess response to therapy. Ultrasound was shown to be a highly effective means of doing so. Weekly monitoring was shown to be unnecessary, with assessment once every three weeks providing the same amount of information, without putting patients at risk. Serological tumour markers were shown to be ineffective in monitoring response.

12.1.3 Efficacy of primary systemic therapy

The main outcome of this trial is survival. The 78 evaluable patients treated in the first part of the study have been followed up for 57 months. No significant difference in disease free or overall survival has emerged, although there has been a consistent trend in favour of primary systemic therapy. With this sample size the likelihood of detecting a significant difference of the size suggested by this trend is less than 20%.

The entire cohort of patients have been followed up for 37 months. No differences in survival have emerged at this stage, but it is unlikely that any differences will be detectable before 5 years of follow-up.

12.1.4 The power of the study

An important shortcoming of comparative studies reported in this thesis is the relatively small number of patients who were studied, giving the negative results limited confidence.

The trial was initiated with realistic objectives. When it failed to meet initial recruitment objectives, timely action was taken to increase recruitment rate. Unfortunately despite these efforts the trial failed to recruit the number of patients stipulated as necessary to provide it with reasonable power. Thus even on maturity, the power of the trial will not exceed 45%, and is likely to be even lower because of protocol violations.

Not withstanding, the trial and associated studies remain of considerable value in an area where controlled studies are few. They have provided a considerable amount of new controlled data about important aspects of primary systemic treatment, thus expanding the total body of knowledge about this important potential advance in the treatment of breast cancer.

Even if these data prove inadequate on their own, combined with data from other similar studies, they will help establish the definitive role for primary systemic therapy in the treatment of breast cancer.

12.2 DIRECTION FOR FUTURE RESEARCH

Axillary lymph nodes remain the single most important indicator of prognosis in breast cancer, and continue to be used as the main criterion for selecting patients for aggressive chemotherapy (Bonadonna and Valagussa: 1995; Steward: 1995; Bonadonna: 1992). Although post treatment nodal status continues to indicate the patient's prognosis, it would be desirable to have a method of identifying high risk patients who may be candidates for aggressive chemotherapy before treatment is started. Developments in imaging technology such as colour Doppler (Walsh *et al:* 1994), and positron emission tomography (Alder *et al:* 1993; Nieweg *et al:* 1993) may be able to identify some patients, although false negatives relative to surgery however remain high. What may decide the ultimate usefulness of these non-invasive tests will be the relationship between "radiological nodal status" and prognosis.

Single centre trials such as this one have the advantage of being able to successfully implement complex treatment regimes, and to carry out detailed studies of outcomes other than survival, such as the comparative studies of psychological and surgical morbidity presented in this thesis. Realistic comparisons of useful treatment gains however require much larger numbers of patients than a single centre is ever likely to recruit. For example, A reduction in the odds of death from 50% to 40% will provide substantial benefits to large numbers of women, but will require over 800 patients in order to have an 80% chance of being detected.

Primary systemic treatment can be used to provide relatively rapid assessment of new treatment regimes relative to each other, by assessing the direct effect on the tumour. For example it will not be unreasonable to expect an improvement in response rate from 40% to 70% with two different chemotherapy regimes. Such a difference will be detectable with 80% power in 100 patients. Of course such a trial may well be too small to detect a survival advantage, but provided that the design is kept simple, will point the way for larger collaborative trials, as well as adding to the pool of data for future meta-analyses.

This thesis has concentrated on the clinical aspects of primary systemic treatment. One of the most attractive aspects of this treatment is the unique opportunity it offers for studying the biology of a tumour during systemic therapy. Through such studies it may ultimately be

possible to predict the behaviour of a tumour and to tailor-make treatment to specific tumours. Many questions must be answered before this vision can be realised.

Any serious study of tumour biology however will require examination of tissue samples. For patients already worn down by the rigors of their breast cancer treatment even a minimally invasive test such as a fine needle aspirate represents a significant imposition. Establishing an adequate method of tumour sampling is the first priority if such studies are to be performed. Some work has been done on the cell yield of fine needle aspirates (Mullen and Miller: 1989; Hartley *et al:* 1988) and limited attempts have been made to study biological markers in breast aspirates, often in conjunction with flow cytometry (Forouhi *et al:* 1992; Zbieranowski *et al:* 1992; Fuhr *et al:* 1992; Spyratos *et al:* 1992; Palmer *et al:* 1988; Remvikos *et al:* 1989; Fernando *et al:* 1995; Bozzetti *et al:* 1994). Much work is still needed to assess the efficacy of minimally invasive sampling methods and to develop techniques of biological study before meaningful numbers of patients can be approached to undergo repeated tumour sampling.

At the time of starting this trial primary systemic therapy for operable breast cancer was regarded as a highly experimental technique. Although it is now more frequently used, much more data are needed before its role in the treatment of breast cancer is clarified. This should be forthcoming as this and other trials of primary systemic therapy mature. In the mean time it is important that the efficacy and morbidity of primary systemic therapy continues to be closely monitored.

13.

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14.

APPENDIX

14.1 LIFE TABLES

The life tables relating to the survival curves displayed in the body of the thesis are presented in this section. The material included in each life table and the figure to which each life table refers is provided in the caption.

The following notation is used for the life tables:

Interval:	time interval, in months, for which the risk is calculated
No:	Number of patients at risk at the starty of the interval
Ev:	Number of events (recurrence, death etc.) during the interval
Ce:	Number of patients cencored during the interval
PS:	Probability of remaining free of events during the interval
95% CI	95% confidence intervals for "PS".

The life tables are presented in the following pages.

Interval	No	Ev	Ce	PS	95%CI
1 to 2	78	1	0	0.99	0.91 - 1.00
2 to 3	77	1	0	0.97	0.90 - 0.99
8 to 9	76	1	0	0.96	0.89 - 0.99
9 to 10	75	1	0	0.95	0.87 - 0.98
10 to 11	74	2	0	0.92	0.84 - 0.96
11 to 12	72	1	0	0.91	0.82 - 0.96
12 to 13	71	1	0	0.90	0.81 - 0.95
13 to 14	70	2	0	0.87	0.77 - 0.93
14 to 15	68	1	0	0.86	0.76 - 0.92
15 to 16	67	1	0	0.85	0.75 - 0.91
16 to 17	66	1	0	0.83	0.73 - 0.90
17 to 18	65	1	0	0.82	0.72 - 0.89
18 to 19	64	1	0	0.81	0.70 - 0.88
20 to 21	63	2	0	0.78	0.67 - 0.86
21 to 22	61	1	0	0.77	0.66 - 0.85
24 to 25	60	1	0	0.76	0.65 - 0.84
26 to 27	59	1	0	0.74	0.63 - 0.83
27 to 28	58	1	0	0.73	0.62 - 0.82
28 to 29	57	2	0	0.71	0.59 - 0.79
34 to 35	55	2	0	0.68	0.56 - 0.77
43 to 44	53	2	0	0.65	0.54 - 0.75
44 to 45	51	1	0	0.64	0.52 - 0.74
47 to 48	50	1	0	0.63	0.51 - 0.72
48 to 49	49	1	0	0.62	0.50 - 0.71
49 to 50	48	1	0	0.60	0.49 - 0.70
50 to 51	47	2	2	0.58	0.46 - 0.68
51 to 52	43	0	1	0.58	0.46 - 0.68
52 to 53	42	1	1	0.56	0.45 - 0.66
53 to 54	40	0	1	0.56	0.45 - 0.66
55 to 56	39	0	1	0.56	0.45 - 0.66
56 to 57	38	0	5	0.56	0.45 - 0.66
58 to 59	33	1	0	0.55	0.43 - 0.65
59 to 60	32	0	1	0.55	0.43 - 0.65
60 to 61	31	0	2	0.55	0.43 - 0.65
61 to 62	29	0	1	0.55	0.43 - 0.65
63 to 64	28	0	1	0.55	0.43 - 0.65
64 to 65	27	0	4	0.55	0.43 - 0.65
65 to 66	23	0	1	0.55	0.43 - 0.65
66 to 67	22	0	1	0.55	0.43 - 0.65
67 to 68	21	0	1	0.55	0.43 - 0.65
68 to 69	20	1	3	0.52	0.39 - 0.63
69 to 70	16	0	1	0.52	0.39 - 0.63
70 to 71	15	0	3	0.52	0.39 - 0.63
71 to 72	12	0	1	0.52	0.39 - 0.63
72 to 73	11	0	3	0.52	0.39 - 0.63
73 to 74	8	0	1	0.52	0.39 - 0.63
75 to 76	7	0	3	0.52	0.39 - 0.63
76 to 77	4	0	4	0.52	0.39 - 0.63

Table 14-1 Recurrence free survival for the cohort of patients in the first part of the trial

Interval	No	Ev	Ce	PS	95% CI
5 to 6	78	1	0	0.99	0.91 - 1.00
9 to 10	77	1	0	0.97	0.90 - 0.99
10 to 11	76	3	0	0.94	0.85 - 0.97
12 to 13	73	1	0	0.92	0.84 - 0.96
16 to 17	72	1	0	0.91	0.82 - 0.96
17 to 18	71	2	0	0.88	0.79 - 0.94
19 to 20	69	1	0	0.87	0.77 - 0.93
21 to 22	68	1	0	0.86	0.76 - 0.92
22 to 23	67	1	0	0.85	0.75 - 0.91
25 to 26	66	2	0	0.82	0.72 - 0.89
27 to 28	64	1	0	0.81	0.70 - 0.88
29 to 30	63	1	0	0.79	0.69 - 0.87
30 to 31	62	1	0	0.78	0.67 - 0.86
31 to 32	61	2	0	0.76	0.65 - 0.84
36 to 37	59	1	0	0.74	0.63 - 0.83
41 to 42	58	1	0	0.73	0.62 - 0.82
45 to 46	57	1	0	0.72	0.60 - 0.80
48 to 49	56	1	0	0.71	0.59 - 0.79
49 to 50	55	1	0	0.69	0.58 - 0.78
50 to 51	54	0	2	0.69	0.58 - 0.78
51 to 52	52	2	1	0.67	0.55 - 0.76
52 to 53	49	0	2	0.67	0.55 - 0.76
53 to 54	47	1	1	0.65	0.53 - 0.75
55 to 56	45	1	1	0.64	0.52 - 0.73
56 to 57	43	0	5	0.64	0.52 - 0.73
59 to 60	38	1	1	0.62	0.50 - 0.72
60 to 61	36	0	2	0.62	0.50 - 0.72
61 to 62	34	0	1	0.62	0.50 - 0.72
63 to 64	33	2	1	0.58	0.46 - 0.69
64 to 65	30	0	4	0.58	0.46 - 0.69
65 to 66	26	0	1	0.58	0.46 - 0.69
66 to 67	25	0	1	0.58	0.46 - 0.69
67 to 68	24	1	1	0.56	0.43 - 0.67
68 to 69	22	0	4	0.56	0.43 - 0.67
69 to 70	18	0	1	0.56	0.43 - 0.67
70 to 71	17	0	3	0.56	0.43 - 0.67
71 to 72	14	0	1	0.56	0.43 - 0.67
72 to 73	13	0	5	0.56	0.43 - 0.67
73 to 74	8	0	1	0.56	0.43 - 0.67
75 to 76	7	1	3	0.46	0.25 - 0.64
76 to 77	3	0	3	0.46	0.25 - 0.64

Table 14-2 Overall survival for patients in the first part of the trial

Interval	No	Ev	Ce	PS	95% CI
Conventional treatment					
1 to 2	38	1	0	0.97	0.83 - 1.00
2 to 3	37	1	0	0.95	0.81 - 0.99
8 to 9	36	1	0	0.92	0.77 - 0.97
10 to 11	35	2	0	0.87	0.71 - 0.94
11 to 12	33	1	0	0.84	0.68 - 0.93
13 to 14	32	2	0	0.79	0.62 - 0.89
16 to 17	30	1	0	0.76	0.59 - 0.87
17 to 18	29	1	0	0.74	0.57 - 0.85
24 to 25	28	1	0	0.71	0.54 - 0.83
26 to 27	27	1	0	0.68	0.51 - 0.81
34 to 35	26	2	0	0.63	0.46 - 0.76
43 to 44	24	1	0	0.61	0.43 - 0.74
47 to 48	23	1	0	0.58	0.41 - 0.72
48 to 49	22	1	0	0.55	0.38 - 0.69
49 to 50	21	1	0	0.53	0.36 - 0.67
50 to 51	20	0	2	0.53	0.36 - 0.67
52 to 53	18	1	0	0.50	0.33 - 0.64
53 to 54	17	0	1	0.50	0.33 - 0.64
56 to 57	16	0	1	0.50	0.33 - 0.64
59 to 60	15	0	1	0.50	0.33 - 0.64
60 to 61	14	0	1	0.50	0.33 - 0.64
61 to 62	13	0	1	0.50	0.33 - 0.64
64 to 65	12	0	2	0.50	0.33 - 0.64
65 to 66	10	0	1	0.50	0.33 - 0.64
67 to 68	9	0	1	0.50	0.33 - 0.64
68 to 69	8	1	1	0.43	0.25 - 0.60
69 to 70	6	0	1	0.43	0.25 - 0.60
70 to 71	5	0	2	0.43	0.25 - 0.60
72 to 73	3	0	1	0.43	0.25 - 0.60
76 to 77	2	0	2	0.43	0.25 - 0.60

Interval	No	Ev	Ce	PS	95% CI
Primary systemic treatment					
9 to 10	40	1	0	0.98	0.84 - 1.00
12 to 13	39	1	0	0.95	0.81 - 0.99
14 to 15	38	1	0	0.93	0.79 - 0.98
15 to 16	37	1	0	0.90	0.76 - 0.96
18 to 19	36	1	0	0.88	0.73 - 0.95
20 to 21	35	2	0	0.83	0.67 - 0.91
21 to 22	33	1	0	0.80	0.64 - 0.89
27 to 28	32	1	0	0.78	0.61 - 0.88
28 to 29	31	2	0	0.73	0.56 - 0.84
43 to 44	29	1	0	0.70	0.53 - 0.82
44 to 45	28	1	0	0.68	0.51 - 0.80
50 to 51	27	2	0	0.63	0.46 - 0.75
51 to 52	25	0	1	0.63	0.46 - 0.75
52 to 53	24	0	1	0.63	0.46 - 0.75
55 to 56	23	0	1	0.63	0.46 - 0.75
56 to 57	22	0	4	0.63	0.46 - 0.75
58 to 59	18	1	0	0.59	0.42 - 0.73
60 to 61	17	0	1	0.59	0.42 - 0.73
63 to 64	16	0	1	0.59	0.42 - 0.73
64 to 65	15	0	2	0.59	0.42 - 0.73
66 to 67	13	0	1	0.59	0.42 - 0.73
68 to 69	12	0	2	0.59	0.42 - 0.73
70 to 71	10	0	1	0.59	0.42 - 0.73
71 to 72	9	0	1	0.59	0.42 - 0.73
72 to 73	8	0	2	0.59	0.42 - 0.73
73 to 74	6	0	1	0.59	0.42 - 0.73
75 to 76	5	0	3	0.59	0.42 - 0.73
76 to 77	2	0	2	0.59	0.42 - 0.73

Table 14-3: Recurrence free survival by intention to treat for patients in the first part of the trial

Interval	No	Ev	Ce	PS	95% CI
Conventional treatment					
1 to 2	40	1	0	0.98	0.84 - 1.00
2 to 3	39	1	0	0.95	0.81 - 0.99
8 to 9	38	1	0	0.93	0.79 - 0.98
10 to 11	37	2	0	0.88	0.73 - 0.95
11 to 12	35	1	0	0.85	0.70 - 0.93
13 to 14	34	2	0	0.80	0.64 - 0.89
16 to 17	32	1	0	0.78	0.61 - 0.88
17 to 18	31	1	0	0.75	0.59 - 0.86
24 to 25	30	1	0	0.73	0.56 - 0.84
26 to 27	29	1	0	0.70	0.53 - 0.82
34 to 35	28	1	0	0.68	0.51 - 0.80
43 to 44	27	1	0	0.65	0.48 - 0.78
44 to 45	26	1	0	0.63	0.46 - 0.75
47 to 48	25	1	0	0.60	0.43 - 0.73
48 to 49	24	1	0	0.58	0.41 - 0.71
49 to 50	23	1	0	0.55	0.38 - 0.69
50 to 51	22	0	2	0.55	0.38 - 0.69
51 to 52	20	0	1	0.55	0.38 - 0.69
52 to 53	19	1	0	0.52	0.36 - 0.66
53 to 54	18	0	1	0.52	0.36 - 0.66
56 to 57	17	0	1	0.52	0.36 - 0.66
59 to 60	16	0	1	0.52	0.36 - 0.66
60 to 61	15	0	1	0.52	0.36 - 0.66
61 to 62	14	0	1	0.52	0.36 - 0.66
64 to 65	13	0	3	0.52	0.36 - 0.66
65 to 66	10	0	1	0.52	0.36 - 0.66
67 to 68	9	0	1	0.52	0.36 - 0.66
68 to 69	8	1	1	0.45	0.26 - 0.62
69 to 70	6	0	1	0.45	0.26 - 0.62
70 to 71	5	0	2	0.45	0.26 - 0.62
72 to 73	3	0	1	0.45	0.26 - 0.62
76 to 77	2	0	2	0.45	0.26 - 0.62
Primary systemic treatment					
9 to 10	38	1	0	0.97	0.83 - 1.00
12 to 13	37	1	0	0.95	0.81 - 0.99
14 to 15	36	1	0	0.92	0.77 - 0.97
15 to 16	35	1	0	0.89	0.74 - 0.96
18 to 19	34	1	0	0.87	0.71 - 0.94
20 to 21	33	2	0	0.82	0.65 - 0.91
21 to 22	31	1	0	0.79	0.62 - 0.89
27 to 28	30	1	0	0.76	0.59 - 0.87
28 to 29	29	2	0	0.71	0.54 - 0.83
34 to 35	27	1	0	0.68	0.51 - 0.81
43 to 44	26	1	0	0.66	0.48 - 0.78
50 to 51	25	2	0	0.61	0.43 - 0.74
52 to 53	23	0	1	0.61	0.43 - 0.74
55 to 56	22	0	1	0.61	0.43 - 0.74
56 to 57	21	0	4	0.61	0.43 - 0.74
58 to 59	17	1	0	0.57	0.39 - 0.71
60 to 61	16	0	1	0.57	0.39 - 0.71
63 to 64	15	0	1	0.57	0.39 - 0.71
64 to 65	14	0	1	0.57	0.39 - 0.71
66 to 67	13	0	1	0.57	0.39 - 0.71
68 to 69	12	0	2	0.57	0.39 - 0.71
70 to 71	10	0	1	0.57	0.39 - 0.71
71 to 72	9	0	1	0.57	0.39 - 0.71
72 to 73	8	0	2	0.57	0.39 - 0.71
73 to 74	6	0	1	0.57	0.39 - 0.71
75 to 76	5	0	3	0.57	0.39 - 0.71
76 to 77	2	0	2	0.57	0.39 - 0.71

Table 14-4: Recurrence free survival by actual treatments given for patients in the first part of the trial

Interval			No	Ev	Ce	PS	95% CI
Conventional treatment							
5	to	6	86	1	0	0.99	0.92 - 1.00
9	to	10	85	2	0	0.97	0.90 - 0.99
10	to	11	83	3	1	0.93	0.85 - 0.97
11	to	12	79	0	5	0.93	0.85 - 0.97
12	to	13	74	1	2	0.92	0.83 - 0.96
13	to	14	71	0	1	0.92	0.83 - 0.96
14	to	15	70	0	1	0.92	0.83 - 0.96
16	to	17	69	1	0	0.90	0.82 - 0.95
17	to	18	68	1	2	0.89	0.80 - 0.94
18	to	19	65	0	1	0.89	0.80 - 0.94
19	to	20	64	0	1	0.89	0.80 - 0.94
20	to	21	63	0	2	0.89	0.80 - 0.94
21	to	22	61	1	2	0.88	0.78 - 0.93
22	to	23	58	2	0	0.85	0.74 - 0.91
23	to	24	56	0	2	0.85	0.74 - 0.91
24	to	25	54	2	1	0.81	0.70 - 0.89
25	to	26	51	1	0	0.80	0.69 - 0.87
27	to	28	50	0	3	0.80	0.69 - 0.87
29	to	30	47	0	1	0.80	0.69 - 0.87
31	to	32	46	0	1	0.80	0.69 - 0.87
34	to	35	45	1	1	0.78	0.66 - 0.86
35	to	36	43	0	1	0.78	0.66 - 0.86
36	to	37	42	1	2	0.76	0.64 - 0.85
37	to	38	39	0	1	0.76	0.64 - 0.85
40	to	41	38	0	1	0.76	0.64 - 0.85
41	to	42	37	0	1	0.76	0.64 - 0.85
43	to	44	36	0	2	0.76	0.64 - 0.85
44	to	45	34	0	2	0.76	0.64 - 0.85
46	to	47	32	0	1	0.76	0.64 - 0.85
47	to	48	31	0	2	0.76	0.64 - 0.85
48	to	49	29	1	0	0.73	0.61 - 0.83
49	to	50	28	1	1	0.71	0.57 - 0.81
50	to	51	26	0	2	0.71	0.57 - 0.81
52	to	53	24	0	1	0.71	0.57 - 0.81
53	to	54	23	1	1	0.68	0.53 - 0.79
55	to	56	21	1	1	0.64	0.49 - 0.76
56	to	57	19	0	1	0.64	0.49 - 0.76
59	to	60	18	1	1	0.61	0.44 - 0.74
60	to	61	16	0	1	0.61	0.44 - 0.74
61	to	62	15	0	1	0.61	0.44 - 0.74
63	to	64	14	1	0	0.56	0.39 - 0.70
64	to	65	13	0	2	0.56	0.39 - 0.70
65	to	66	11	0	1	0.56	0.39 - 0.70
67	to	68	10	1	1	0.50	0.32 - 0.67
68	to	69	8	0	1	0.50	0.32 - 0.67
69	to	70	7	0	1	0.50	0.32 - 0.67
70	to	71	6	0	2	0.50	0.32 - 0.67
72	to	73	4	0	2	0.50	0.32 - 0.67
76	to	77	2	0	2	0.50	0.32 - 0.67
Primary systemic treatment							
9	to	10	85	0	1	1.00	. - .
10	to	11	84	1	0	0.99	0.92 - 1.00
11	to	12	83	1	0	0.98	0.91 - 0.99
12	to	13	82	0	3	0.98	0.91 - 0.99
14	to	15	79	0	3	0.98	0.91 - 0.99
15	to	16	76	0	2	0.98	0.91 - 0.99
16	to	17	74	0	1	0.98	0.91 - 0.99
17	to	18	73	1	0	0.96	0.89 - 0.99
18	to	19	72	0	3	0.96	0.89 - 0.99
19	to	20	69	1	1	0.95	0.87 - 0.98
20	to	21	67	0	1	0.95	0.87 - 0.98
21	to	22	66	0	1	0.95	0.87 - 0.98
22	to	23	65	0	1	0.95	0.87 - 0.98
23	to	24	64	1	2	0.93	0.85 - 0.97
24	to	25	61	0	1	0.93	0.85 - 0.97
25	to	26	60	2	2	0.90	0.80 - 0.95
26	to	27	56	0	1	0.90	0.80 - 0.95
27	to	28	55	1	1	0.89	0.78 - 0.94
29	to	30	53	1	0	0.87	0.76 - 0.93
30	to	31	52	1	2	0.85	0.74 - 0.92
31	to	32	49	3	0	0.80	0.68 - 0.88
34	to	35	46	0	1	0.80	0.68 - 0.88
35	to	36	45	0	1	0.80	0.68 - 0.88
38	to	39	44	0	1	0.80	0.68 - 0.88
39	to	40	43	1	0	0.78	0.66 - 0.87
40	to	41	42	0	1	0.78	0.66 - 0.87
41	to	42	41	1	1	0.76	0.63 - 0.85
42	to	43	39	0	2	0.76	0.63 - 0.85
43	to	44	37	0	3	0.76	0.63 - 0.85
44	to	45	34	0	1	0.76	0.63 - 0.85
45	to	46	33	1	0	0.74	0.61 - 0.83
48	to	49	32	0	3	0.74	0.61 - 0.83
51	to	52	29	2	1	0.69	0.54 - 0.79
52	to	53	26	0	1	0.69	0.54 - 0.79
55	to	56	25	0	1	0.69	0.54 - 0.79
56	to	57	24	0	4	0.69	0.54 - 0.79
60	to	61	20	0	1	0.69	0.54 - 0.79
63	to	64	19	1	1	0.65	0.49 - 0.77
64	to	65	17	0	2	0.65	0.49 - 0.77
66	to	67	15	0	1	0.65	0.49 - 0.77
68	to	69	14	0	3	0.65	0.49 - 0.77
70	to	71	11	0	1	0.65	0.49 - 0.77
71	to	72	10	0	1	0.65	0.49 - 0.77
72	to	73	9	0	3	0.65	0.49 - 0.77
73	to	74	6	0	1	0.65	0.49 - 0.77
75	to	76	5	1	3	0.46	0.15 - 0.73
76	to	77	1	0	1	0.46	0.15 - 0.73

Table 14-5: Overall survival by intention to treat for patients in the first part of the trial

Interval	No	Ev	Ce	PS	95% CI
Conventional treatment					
5 to 6	91	1	0	0.99	0.92 - 1.00
9 to 10	90	2	0	0.97	0.90 - 0.99
10 to 11	88	3	1	0.93	0.86 - 0.97
11 to 12	84	0	5	0.93	0.86 - 0.97
12 to 13	79	1	3	0.92	0.84 - 0.96
13 to 14	75	0	1	0.92	0.84 - 0.96
14 to 15	74	0	1	0.92	0.84 - 0.96
16 to 17	73	1	0	0.91	0.83 - 0.95
17 to 18	72	1	2	0.90	0.81 - 0.94
18 to 19	69	0	1	0.90	0.81 - 0.94
19 to 20	68	0	1	0.90	0.81 - 0.94
20 to 21	67	0	2	0.90	0.81 - 0.94
21 to 22	65	1	2	0.88	0.79 - 0.94
22 to 23	62	2	0	0.85	0.76 - 0.91
23 to 24	60	0	3	0.85	0.76 - 0.91
24 to 25	57	2	1	0.82	0.72 - 0.89
25 to 26	54	1	0	0.81	0.70 - 0.88
27 to 28	53	0	3	0.81	0.70 - 0.88
29 to 30	50	0	1	0.81	0.70 - 0.88
31 to 32	49	1	1	0.79	0.68 - 0.87
34 to 35	47	1	1	0.77	0.66 - 0.85
35 to 36	45	0	1	0.77	0.66 - 0.85
36 to 37	44	1	2	0.76	0.64 - 0.84
37 to 38	41	0	1	0.76	0.64 - 0.84
40 to 41	40	0	1	0.76	0.64 - 0.84
41 to 42	39	0	1	0.76	0.64 - 0.84
43 to 44	38	0	2	0.76	0.64 - 0.84
44 to 45	36	0	2	0.76	0.64 - 0.84
45 to 46	34	1	0	0.73	0.61 - 0.82
46 to 47	33	0	1	0.73	0.61 - 0.82
47 to 48	32	0	2	0.73	0.61 - 0.82
49 to 50	30	1	1	0.71	0.58 - 0.81
50 to 51	28	0	2	0.71	0.58 - 0.81
51 to 52	26	0	1	0.71	0.58 - 0.81
52 to 53	25	0	1	0.71	0.58 - 0.81
53 to 54	24	1	1	0.68	0.54 - 0.79
55 to 56	22	1	1	0.65	0.50 - 0.76
56 to 57	20	0	1	0.65	0.50 - 0.76
59 to 60	19	1	1	0.61	0.46 - 0.74
60 to 61	17	0	1	0.61	0.46 - 0.74
61 to 62	16	0	1	0.61	0.46 - 0.74
63 to 64	15	1	0	0.57	0.41 - 0.71
64 to 65	14	0	3	0.57	0.41 - 0.71
65 to 66	11	0	1	0.57	0.41 - 0.71
67 to 68	10	1	1	0.51	0.33 - 0.67
68 to 69	8	0	1	0.51	0.33 - 0.67
69 to 70	7	0	1	0.51	0.33 - 0.67
70 to 71	6	0	2	0.51	0.33 - 0.67
72 to 73	4	0	2	0.51	0.33 - 0.67
76 to 77	2	0	2	0.51	0.33 - 0.67
primary systemic treatment					

Interval	No	Ev	Ce	PS	95% CI
9 to 10	80	0	1	1.00	. - .
10 to 11	79	1	0	0.99	0.91 - 1.00
11 to 12	78	1	0	0.97	0.90 - 0.99
12 to 13	77	0	2	0.97	0.90 - 0.99
14 to 15	75	0	3	0.97	0.90 - 0.99
15 to 16	72	0	2	0.97	0.90 - 0.99
16 to 17	70	0	1	0.97	0.90 - 0.99
17 to 18	69	1	0	0.96	0.88 - 0.99
18 to 19	68	0	3	0.96	0.88 - 0.99
19 to 20	65	1	1	0.95	0.86 - 0.98
20 to 21	63	0	1	0.95	0.86 - 0.98
21 to 22	62	0	1	0.95	0.86 - 0.98
22 to 23	61	0	1	0.95	0.86 - 0.98
23 to 24	60	1	1	0.93	0.84 - 0.97
24 to 25	58	0	1	0.93	0.84 - 0.97
25 to 26	57	2	2	0.90	0.79 - 0.95
26 to 27	53	0	1	0.90	0.79 - 0.95
27 to 28	52	1	1	0.88	0.77 - 0.94
29 to 30	50	1	0	0.86	0.75 - 0.93
30 to 31	49	1	2	0.84	0.73 - 0.91
31 to 32	46	2	0	0.81	0.68 - 0.89
34 to 35	44	0	1	0.81	0.68 - 0.89
35 to 36	43	0	1	0.81	0.68 - 0.89
38 to 39	42	0	1	0.81	0.68 - 0.89
39 to 40	41	1	0	0.79	0.66 - 0.87
40 to 41	40	0	1	0.79	0.66 - 0.87
41 to 42	39	1	1	0.77	0.64 - 0.86
42 to 43	37	0	2	0.77	0.64 - 0.86
43 to 44	35	0	3	0.77	0.64 - 0.86
44 to 45	32	0	1	0.77	0.64 - 0.86
48 to 49	31	1	3	0.74	0.60 - 0.84
51 to 52	27	2	0	0.69	0.54 - 0.80
52 to 53	25	0	1	0.69	0.54 - 0.80
55 to 56	24	0	1	0.69	0.54 - 0.80
56 to 57	23	0	4	0.69	0.54 - 0.80
60 to 61	19	0	1	0.69	0.54 - 0.80
63 to 64	18	1	1	0.65	0.48 - 0.77
64 to 65	16	0	1	0.65	0.48 - 0.77
66 to 67	15	0	1	0.65	0.48 - 0.77
68 to 69	14	0	3	0.65	0.48 - 0.77
70 to 71	11	0	1	0.65	0.48 - 0.77
71 to 72	10	0	1	0.65	0.48 - 0.77
72 to 73	9	0	3	0.65	0.48 - 0.77
73 to 74	6	0	1	0.65	0.48 - 0.77
75 to 76	5	1	3	0.46	0.15 - 0.73
76 to 77	1	0	1	0.46	0.15 - 0.73

Table 14-6: Overall survival by actual treatments given for patients in the first part of the trial

Interval	No	Ev	Ce	PS	95% CI
1 to 2	170	1	0	0.99	0.96 - 1.00
2 to 3	169	2	0	0.98	0.95 - 0.99
5 to 6	167	2	0	0.97	0.93 - 0.99
8 to 9	165	2	0	0.96	0.92 - 0.98
9 to 10	163	1	1	0.95	0.91 - 0.98
10 to 11	161	3	1	0.94	0.89 - 0.96
11 to 12	157	2	5	0.92	0.87 - 0.95
12 to 13	150	2	5	0.91	0.86 - 0.95
13 to 14	143	2	1	0.90	0.84 - 0.94
14 to 15	140	2	4	0.88	0.83 - 0.92
15 to 16	134	2	1	0.87	0.81 - 0.91
16 to 17	131	1	1	0.86	0.80 - 0.91
17 to 18	129	2	1	0.85	0.79 - 0.90
18 to 19	126	1	4	0.84	0.78 - 0.89
19 to 20	121	0	2	0.84	0.78 - 0.89
20 to 21	119	2	3	0.83	0.76 - 0.88
21 to 22	114	1	3	0.82	0.75 - 0.87
22 to 23	110	0	1	0.82	0.75 - 0.87
23 to 24	109	0	4	0.82	0.75 - 0.87
24 to 25	105	3	3	0.80	0.73 - 0.85
25 to 26	99	0	2	0.80	0.73 - 0.85
26 to 27	97	1	1	0.79	0.72 - 0.85
27 to 28	95	2	4	0.77	0.70 - 0.83
28 to 29	89	2	0	0.76	0.68 - 0.82
29 to 30	87	0	1	0.76	0.68 - 0.82
30 to 31	86	0	1	0.76	0.68 - 0.82
31 to 32	85	0	1	0.76	0.68 - 0.82
34 to 35	84	2	2	0.74	0.66 - 0.80
35 to 36	80	0	2	0.74	0.66 - 0.80
36 to 37	78	0	2	0.74	0.66 - 0.80
37 to 38	76	0	1	0.74	0.66 - 0.80
38 to 39	75	0	1	0.74	0.66 - 0.80
40 to 41	74	0	2	0.74	0.66 - 0.80
41 to 42	72	0	2	0.74	0.66 - 0.80
42 to 43	70	0	2	0.74	0.66 - 0.80
43 to 44	68	3	4	0.70	0.62 - 0.78
44 to 45	61	1	3	0.69	0.60 - 0.77
46 to 47	57	0	1	0.69	0.60 - 0.77
47 to 48	56	1	1	0.68	0.59 - 0.76
48 to 49	54	1	3	0.67	0.57 - 0.74
49 to 50	50	2	1	0.64	0.54 - 0.72
50 to 51	47	2	2	0.61	0.51 - 0.70
51 to 52	43	0	1	0.61	0.51 - 0.70
52 to 53	42	1	1	0.60	0.49 - 0.69
53 to 54	40	0	1	0.60	0.49 - 0.69
55 to 56	39	0	1	0.60	0.49 - 0.69
56 to 57	38	0	5	0.60	0.49 - 0.69
58 to 59	33	1	0	0.58	0.47 - 0.67
59 to 60	32	0	1	0.58	0.47 - 0.67
60 to 61	31	0	2	0.58	0.47 - 0.67
61 to 62	29	0	1	0.58	0.47 - 0.67
63 to 64	28	0	1	0.58	0.47 - 0.67
64 to 65	27	0	4	0.58	0.47 - 0.67
65 to 66	23	0	1	0.58	0.47 - 0.67
66 to 67	22	0	1	0.58	0.47 - 0.67
67 to 68	21	0	1	0.58	0.47 - 0.67
68 to 69	20	1	3	0.55	0.43 - 0.65
69 to 70	16	0	1	0.55	0.43 - 0.65
70 to 71	15	0	3	0.55	0.43 - 0.65
71 to 72	12	0	1	0.55	0.43 - 0.65
72 to 73	11	0	3	0.55	0.43 - 0.65
73 to 74	8	0	1	0.55	0.43 - 0.65
75 to 76	7	0	3	0.55	0.43 - 0.65
76 to 77	4	0	4	0.55	0.43 - 0.65

Table 14-7: Disease free survival for all patients in the trial

Interval	No	Ev	Ce	PS	95% CI
5 to 6	170	1	0	0.99	0.96 - 1.00
9 to 10	169	2	1	0.98	0.95 - 0.99
10 to 11	166	4	1	0.96	0.92 - 0.98
11 to 12	161	1	5	0.95	0.91 - 0.98
12 to 13	155	1	5	0.95	0.90 - 0.97
13 to 14	149	0	1	0.95	0.90 - 0.97
14 to 15	148	0	4	0.95	0.90 - 0.97
15 to 16	144	0	2	0.95	0.90 - 0.97
16 to 17	142	1	1	0.94	0.89 - 0.97
17 to 18	140	2	2	0.93	0.87 - 0.96
18 to 19	136	0	4	0.93	0.87 - 0.96
19 to 20	132	1	2	0.92	0.86 - 0.95
20 to 21	129	0	3	0.92	0.86 - 0.95
21 to 22	126	1	3	0.91	0.86 - 0.95
22 to 23	122	2	1	0.90	0.84 - 0.94
23 to 24	119	1	4	0.89	0.83 - 0.93
24 to 25	114	2	2	0.87	0.81 - 0.92
25 to 26	110	3	2	0.85	0.78 - 0.90
26 to 27	105	0	1	0.85	0.78 - 0.90
27 to 28	104	1	4	0.84	0.77 - 0.89
29 to 30	99	1	1	0.83	0.76 - 0.89
30 to 31	97	1	2	0.82	0.75 - 0.88
31 to 32	94	3	1	0.80	0.72 - 0.86
34 to 35	90	1	2	0.79	0.71 - 0.85
35 to 36	87	0	2	0.79	0.71 - 0.85
36 to 37	85	1	2	0.78	0.70 - 0.84
37 to 38	82	0	1	0.78	0.70 - 0.84
38 to 39	81	0	1	0.78	0.70 - 0.84
39 to 40	80	1	0	0.77	0.69 - 0.83
40 to 41	79	0	2	0.77	0.69 - 0.83
41 to 42	77	1	2	0.76	0.67 - 0.82
42 to 43	74	0	2	0.76	0.67 - 0.82
43 to 44	72	0	5	0.76	0.67 - 0.82
44 to 45	67	0	3	0.76	0.67 - 0.82
45 to 46	64	1	0	0.75	0.66 - 0.82
46 to 47	63	0	1	0.75	0.66 - 0.82
47 to 48	62	0	2	0.75	0.66 - 0.82
48 to 49	60	1	3	0.73	0.64 - 0.80
49 to 50	56	1	1	0.72	0.63 - 0.79
50 to 51	54	0	2	0.72	0.63 - 0.79
51 to 52	52	2	1	0.69	0.60 - 0.77
52 to 53	49	0	2	0.69	0.60 - 0.77
53 to 54	47	1	1	0.68	0.58 - 0.76
55 to 56	45	1	1	0.66	0.56 - 0.75
56 to 57	43	0	5	0.66	0.56 - 0.75
59 to 60	38	1	1	0.65	0.54 - 0.73
60 to 61	36	0	2	0.65	0.54 - 0.73
61 to 62	34	0	1	0.65	0.54 - 0.73
63 to 64	33	2	1	0.61	0.49 - 0.70
64 to 65	30	0	4	0.61	0.49 - 0.70
65 to 66	26	0	1	0.61	0.49 - 0.70
66 to 67	25	0	1	0.61	0.49 - 0.70
67 to 68	24	1	1	0.58	0.46 - 0.68
68 to 69	22	0	4	0.58	0.46 - 0.68
69 to 70	18	0	1	0.58	0.46 - 0.68
70 to 71	17	0	3	0.58	0.46 - 0.68
71 to 72	14	0	1	0.58	0.46 - 0.68
72 to 73	13	0	5	0.58	0.46 - 0.68
73 to 74	8	0	1	0.58	0.46 - 0.68
75 to 76	7	1	3	0.47	0.26 - 0.66
76 to 77	3	0	3	0.47	0.26 - 0.66

Table 14-8: Overall survival for all patients in the trial

Interval			No	Ev	Ce	PS	95% CI
Conventionl treatment							
1	to	2	85	1	0	0.99	0.92 - 1.00
2	to	3	84	1	0	0.98	0.91 - 0.99
8	to	9	83	2	0	0.95	0.88 - 0.98
10	to	11	81	3	1	0.92	0.83 - 0.96
11	to	12	77	2	5	0.89	0.80 - 0.94
12	to	13	70	1	2	0.88	0.79 - 0.93
13	to	14	67	2	1	0.85	0.76 - 0.91
14	to	15	64	0	1	0.85	0.76 - 0.91
15	to	16	63	1	0	0.84	0.74 - 0.90
16	to	17	62	1	0	0.83	0.72 - 0.89
17	to	18	61	2	1	0.80	0.69 - 0.87
18	to	19	58	0	1	0.80	0.69 - 0.87
19	to	20	57	0	1	0.80	0.69 - 0.87
20	to	21	56	0	2	0.80	0.69 - 0.87
21	to	22	54	0	2	0.80	0.69 - 0.87
23	to	24	52	0	2	0.80	0.69 - 0.87
24	to	25	50	1	2	0.78	0.67 - 0.86
26	to	27	47	1	0	0.77	0.65 - 0.85
27	to	28	46	0	3	0.77	0.65 - 0.85
29	to	30	43	0	1	0.77	0.65 - 0.85
31	to	32	42	0	1	0.77	0.65 - 0.85
34	to	35	41	2	1	0.73	0.61 - 0.82
35	to	36	38	0	1	0.73	0.61 - 0.82
36	to	37	37	0	2	0.73	0.61 - 0.82
37	to	38	35	0	1	0.73	0.61 - 0.82
40	to	41	34	0	1	0.73	0.61 - 0.82
41	to	42	33	0	1	0.73	0.61 - 0.82
43	to	44	32	2	2	0.68	0.55 - 0.78
44	to	45	28	0	2	0.68	0.55 - 0.78
46	to	47	26	0	1	0.68	0.55 - 0.78
47	to	48	25	1	1	0.65	0.51 - 0.76
48	to	49	23	1	0	0.63	0.48 - 0.74
49	to	50	22	1	1	0.60	0.45 - 0.72
50	to	51	20	0	2	0.60	0.45 - 0.72
52	to	53	18	1	0	0.56	0.41 - 0.69
53	to	54	17	0	1	0.56	0.41 - 0.69
56	to	57	16	0	1	0.56	0.41 - 0.69
59	to	60	15	0	1	0.56	0.41 - 0.69
60	to	61	14	0	1	0.56	0.41 - 0.69
61	to	62	13	0	1	0.56	0.41 - 0.69
64	to	65	12	0	2	0.56	0.41 - 0.69
65	to	66	10	0	1	0.56	0.41 - 0.69
67	to	68	9	0	1	0.56	0.41 - 0.69
68	to	69	8	1	1	0.49	0.30 - 0.65
69	to	70	6	0	1	0.49	0.30 - 0.65
70	to	71	5	0	2	0.49	0.30 - 0.65
72	to	73	3	0	1	0.49	0.30 - 0.65
76	to	77	2	0	2	0.49	0.30 - 0.65
Primary systemic treatment							
2	to	3	85	1	0	0.99	0.92 - 1.00

Interval			No	Ev	Ce	PS	95% CI
5	to	6	84	2	0	0.96	0.89 - 0.99
9	to	10	82	1	1	0.95	0.88 - 0.98
12	to	13	80	1	3	0.94	0.86 - 0.97
14	to	15	76	2	3	0.92	0.83 - 0.96
15	to	16	71	1	1	0.90	0.81 - 0.95
16	to	17	69	0	1	0.90	0.81 - 0.95
18	to	19	68	1	3	0.89	0.80 - 0.94
19	to	20	64	0	1	0.89	0.80 - 0.94
20	to	21	63	2	1	0.86	0.76 - 0.92
21	to	22	60	1	1	0.85	0.74 - 0.91
22	to	23	58	0	1	0.85	0.74 - 0.91
23	to	24	57	0	2	0.85	0.74 - 0.91
24	to	25	55	2	1	0.82	0.71 - 0.89
25	to	26	52	0	2	0.82	0.71 - 0.89
26	to	27	50	0	1	0.82	0.71 - 0.89
27	to	28	49	2	1	0.78	0.67 - 0.86
28	to	29	46	2	0	0.75	0.63 - 0.83
30	to	31	44	0	1	0.75	0.63 - 0.83
34	to	35	43	0	1	0.75	0.63 - 0.83
35	to	36	42	0	1	0.75	0.63 - 0.83
38	to	39	41	0	1	0.75	0.63 - 0.83
40	to	41	40	0	1	0.75	0.63 - 0.83
41	to	42	39	0	1	0.75	0.63 - 0.83
42	to	43	38	0	2	0.75	0.63 - 0.83
43	to	44	36	1	2	0.73	0.60 - 0.82
44	to	45	33	1	1	0.70	0.57 - 0.80
48	to	49	31	0	3	0.70	0.57 - 0.80
49	to	50	28	1	0	0.68	0.54 - 0.78
50	to	51	27	2	0	0.63	0.48 - 0.74
51	to	52	25	0	1	0.63	0.48 - 0.74
52	to	53	24	0	1	0.63	0.48 - 0.74
55	to	56	23	0	1	0.63	0.48 - 0.74
56	to	57	22	0	4	0.63	0.48 - 0.74
58	to	59	18	1	0	0.59	0.44 - 0.72
60	to	61	17	0	1	0.59	0.44 - 0.72
63	to	64	16	0	1	0.59	0.44 - 0.72
64	to	65	15	0	2	0.59	0.44 - 0.72
66	to	67	13	0	1	0.59	0.44 - 0.72
68	to	69	12	0	2	0.59	0.44 - 0.72
70	to	71	10	0	1	0.59	0.44 - 0.72
71	to	72	9	0	1	0.59	0.44 - 0.72
72	to	73	8	0	2	0.59	0.44 - 0.72
73	to	74	6	0	1	0.59	0.44 - 0.72
75	to	76	5	0	3	0.59	0.44 - 0.72
76	to	77	2	0	2	0.59	0.44 - 0.72

Table 14-9: Recurrence free survival for all patients in the trial by intention to treat

Interval	No	Ev	Ce	PS	95% CI
Conventional treatment					
5 to 6	85	1	0	0.99	0.92 - 1.00
9 to 10	84	2	0	0.96	0.89 - 0.99
10 to 11	82	3	1	0.93	0.85 - 0.97
11 to 12	78	0	5	0.93	0.85 - 0.97
12 to 13	73	1	2	0.92	0.83 - 0.96
13 to 14	70	0	1	0.92	0.83 - 0.96
14 to 15	69	0	1	0.92	0.83 - 0.96
16 to 17	68	1	0	0.90	0.81 - 0.95
17 to 18	67	1	2	0.89	0.80 - 0.94
18 to 19	64	0	1	0.89	0.80 - 0.94
19 to 20	63	0	1	0.89	0.80 - 0.94
20 to 21	62	0	2	0.89	0.80 - 0.94
21 to 22	60	1	2	0.87	0.78 - 0.93
22 to 23	57	2	0	0.84	0.74 - 0.91
23 to 24	55	0	2	0.84	0.74 - 0.91
24 to 25	53	2	1	0.81	0.70 - 0.88
25 to 26	50	1	0	0.80	0.68 - 0.87
27 to 28	49	0	3	0.80	0.68 - 0.87
29 to 30	46	0	1	0.80	0.68 - 0.87
31 to 32	45	0	1	0.80	0.68 - 0.87
34 to 35	44	1	1	0.78	0.66 - 0.86
35 to 36	42	0	1	0.78	0.66 - 0.86
36 to 37	41	1	2	0.76	0.64 - 0.84
37 to 38	38	0	1	0.76	0.64 - 0.84
40 to 41	37	0	1	0.76	0.64 - 0.84
41 to 42	36	0	1	0.76	0.64 - 0.84
43 to 44	35	0	2	0.76	0.64 - 0.84
44 to 45	33	0	2	0.76	0.64 - 0.84
46 to 47	31	0	1	0.76	0.64 - 0.84
47 to 48	30	0	2	0.76	0.64 - 0.84
48 to 49	28	1	0	0.73	0.60 - 0.82
49 to 50	27	1	1	0.70	0.56 - 0.80
50 to 51	25	0	2	0.70	0.56 - 0.80
52 to 53	23	0	1	0.70	0.56 - 0.80
53 to 54	22	1	1	0.67	0.52 - 0.78
55 to 56	20	1	0	0.64	0.48 - 0.76
56 to 57	19	0	1	0.64	0.48 - 0.76
59 to 60	18	1	1	0.60	0.44 - 0.73
60 to 61	16	0	1	0.60	0.44 - 0.73
61 to 62	15	0	1	0.60	0.44 - 0.73
63 to 64	14	1	0	0.56	0.38 - 0.70
64 to 65	13	0	2	0.56	0.38 - 0.70
65 to 66	11	0	1	0.56	0.38 - 0.70
67 to 68	10	1	1	0.50	0.31 - 0.66
68 to 69	8	0	1	0.50	0.31 - 0.66
69 to 70	7	0	1	0.50	0.31 - 0.66
70 to 71	6	0	2	0.50	0.31 - 0.66
72 to 73	4	0	2	0.50	0.31 - 0.66
76 to 77	2	0	2	0.50	0.31 - 0.66
Primary systemic treatment					
9 to 10	85	0	1	1.00	

Interval	No	Ev	Ce	PS	95% CI
10 to 11	84	1	0	0.99	0.92 - 1.00
11 to 12	83	1	0	0.98	0.91 - 0.99
12 to 13	82	0	3	0.98	0.91 - 0.99
14 to 15	79	0	3	0.98	0.91 - 0.99
15 to 16	76	0	2	0.98	0.91 - 0.99
16 to 17	74	0	1	0.98	0.91 - 0.99
17 to 18	73	1	0	0.96	0.89 - 0.99
18 to 19	72	0	3	0.96	0.89 - 0.99
19 to 20	69	1	1	0.95	0.87 - 0.98
20 to 21	67	0	1	0.95	0.87 - 0.98
21 to 22	66	0	1	0.95	0.87 - 0.98
22 to 23	65	0	1	0.95	0.87 - 0.98
23 to 24	64	1	2	0.93	0.85 - 0.97
24 to 25	61	0	1	0.93	0.85 - 0.97
25 to 26	60	2	2	0.90	0.80 - 0.95
26 to 27	56	0	1	0.90	0.80 - 0.95
27 to 28	55	1	1	0.89	0.78 - 0.94
29 to 30	53	1	0	0.87	0.76 - 0.93
30 to 31	52	1	2	0.85	0.74 - 0.92
31 to 32	49	3	0	0.80	0.68 - 0.88
34 to 35	46	0	1	0.80	0.68 - 0.88
35 to 36	45	0	1	0.80	0.68 - 0.88
38 to 39	44	0	1	0.80	0.68 - 0.88
39 to 40	43	1	0	0.78	0.66 - 0.87
40 to 41	42	0	1	0.78	0.66 - 0.87
41 to 42	41	1	1	0.76	0.63 - 0.85
42 to 43	39	0	2	0.76	0.63 - 0.85
43 to 44	37	0	3	0.76	0.63 - 0.85
44 to 45	34	0	1	0.76	0.63 - 0.85
45 to 46	33	1	0	0.74	0.61 - 0.83
48 to 49	32	0	3	0.74	0.61 - 0.83
51 to 52	29	2	1	0.69	0.54 - 0.79
52 to 53	26	0	1	0.69	0.54 - 0.79
55 to 56	25	0	1	0.69	0.54 - 0.79
56 to 57	24	0	4	0.69	0.54 - 0.79
60 to 61	20	0	1	0.69	0.54 - 0.79
63 to 64	19	1	1	0.65	0.49 - 0.77
64 to 65	17	0	2	0.65	0.49 - 0.77
66 to 67	15	0	1	0.65	0.49 - 0.77
68 to 69	14	0	3	0.65	0.49 - 0.77
70 to 71	11	0	1	0.65	0.49 - 0.77
71 to 72	10	0	1	0.65	0.49 - 0.77
72 to 73	9	0	3	0.65	0.49 - 0.77
73 to 74	6	0	1	0.65	0.49 - 0.77
75 to 76	5	1	3	0.46	0.15 - 0.73
76 to 77	1	0	1	0.46	0.15 - 0.73

Table 14-10: Overall survival for all patients in the trial by intention to treat

Interval	No	Ev	Ce	PS	95% CI
ER negative patients					
5 to 6	75	1	0	0.99	0.91 - 1.00
9 to 10	74	2	1	0.96	0.88 - 0.99
10 to 11	71	4	1	0.91	0.81 - 0.95
11 to 12	66	0	1	0.91	0.81 - 0.95
12 to 13	65	0	2	0.91	0.81 - 0.95
14 to 15	63	0	2	0.91	0.81 - 0.95
15 to 16	61	0	1	0.91	0.81 - 0.95
16 to 17	60	1	0	0.89	0.79 - 0.94
17 to 18	59	2	2	0.86	0.75 - 0.92
19 to 20	55	1	0	0.84	0.74 - 0.91
20 to 21	54	0	1	0.84	0.74 - 0.91
21 to 22	53	0	3	0.84	0.74 - 0.91
22 to 23	50	1	1	0.83	0.71 - 0.90
23 to 24	48	1	1	0.81	0.69 - 0.89
24 to 25	46	2	0	0.77	0.65 - 0.86
25 to 26	44	1	1	0.76	0.63 - 0.84
27 to 28	42	1	0	0.74	0.61 - 0.83
29 to 30	41	1	0	0.72	0.59 - 0.82
30 to 31	40	1	0	0.70	0.57 - 0.80
31 to 32	39	3	0	0.65	0.51 - 0.75
34 to 35	36	1	0	0.63	0.50 - 0.74
35 to 36	35	0	1	0.63	0.50 - 0.74
36 to 37	34	1	1	0.61	0.48 - 0.72
38 to 39	32	0	1	0.61	0.48 - 0.72
39 to 40	31	1	0	0.59	0.46 - 0.71
41 to 42	30	1	1	0.57	0.43 - 0.69
42 to 43	28	0	2	0.57	0.43 - 0.69
43 to 44	26	0	2	0.57	0.43 - 0.69
44 to 45	24	0	1	0.57	0.43 - 0.69
45 to 46	23	1	0	0.55	0.41 - 0.67
47 to 48	22	0	1	0.55	0.41 - 0.67
48 to 49	21	1	1	0.52	0.38 - 0.64
50 to 51	19	0	1	0.52	0.38 - 0.64
53 to 54	18	0	1	0.52	0.38 - 0.64
55 to 56	17	1	0	0.49	0.35 - 0.62
59 to 60	16	0	1	0.49	0.35 - 0.62
63 to 64	15	0	1	0.49	0.35 - 0.62
64 to 65	14	0	1	0.49	0.35 - 0.62
66 to 67	13	0	1	0.49	0.35 - 0.62
67 to 68	12	0	1	0.49	0.35 - 0.62
70 to 71	11	0	2	0.49	0.35 - 0.62
71 to 72	9	0	1	0.49	0.35 - 0.62
72 to 73	8	0	2	0.49	0.35 - 0.62
73 to 74	6	0	1	0.49	0.35 - 0.62
75 to 76	5	1	2	0.37	0.15 - 0.59
76 to 77	2	0	2	0.37	0.15 - 0.59
ER positive patients					
11 to 12	93	1	4	0.99	0.92 - 1.00
12 to 13	88	1	3	0.98	0.91 - 0.99
13 to 14	84	0	1	0.98	0.91 - 0.99
14 to 15	83	0	2	0.98	0.91 - 0.99
16 to 17	81	0	1	0.98	0.91 - 0.99
18 to 19	80	0	3	0.98	0.91 - 0.99
19 to 20	77	0	2	0.98	0.91 - 0.99
20 to 21	75	0	2	0.98	0.91 - 0.99
21 to 22	73	1	0	0.96	0.89 - 0.99
22 to 23	72	0	1	0.96	0.89 - 0.99
23 to 24	71	0	3	0.96	0.89 - 0.99
24 to 25	68	0	2	0.96	0.89 - 0.99
25 to 26	66	2	1	0.93	0.85 - 0.97
26 to 27	63	0	1	0.93	0.85 - 0.97
27 to 28	62	0	4	0.93	0.85 - 0.97
29 to 30	58	0	1	0.93	0.85 - 0.97
30 to 31	57	0	2	0.93	0.85 - 0.97
31 to 32	55	0	1	0.93	0.85 - 0.97
34 to 35	54	0	2	0.93	0.85 - 0.97
35 to 36	52	0	1	0.93	0.85 - 0.97
36 to 37	51	0	1	0.93	0.85 - 0.97
37 to 38	50	0	1	0.93	0.85 - 0.97
40 to 41	49	0	2	0.93	0.85 - 0.97
41 to 42	47	0	1	0.93	0.85 - 0.97
43 to 44	46	0	3	0.93	0.85 - 0.97
44 to 45	43	0	2	0.93	0.85 - 0.97
46 to 47	41	0	1	0.93	0.85 - 0.97
47 to 48	40	0	1	0.93	0.85 - 0.97
48 to 49	39	0	2	0.93	0.85 - 0.97
49 to 50	37	1	1	0.91	0.80 - 0.96
50 to 51	35	0	1	0.91	0.80 - 0.96
51 to 52	34	2	1	0.85	0.72 - 0.93
52 to 53	31	0	2	0.85	0.72 - 0.93
53 to 54	29	0	1	0.85	0.72 - 0.93
55 to 56	28	0	1	0.85	0.72 - 0.93
56 to 57	27	0	5	0.85	0.72 - 0.93
59 to 60	22	1	0	0.82	0.66 - 0.91
60 to 61	21	0	2	0.82	0.66 - 0.91
61 to 62	19	0	1	0.82	0.66 - 0.91
63 to 64	18	1	1	0.77	0.58 - 0.88
64 to 65	16	0	3	0.77	0.58 - 0.88
65 to 66	13	0	1	0.77	0.58 - 0.88
67 to 68	12	1	0	0.71	0.49 - 0.84
68 to 69	11	0	4	0.71	0.49 - 0.84
69 to 70	7	0	1	0.71	0.49 - 0.84
70 to 71	6	0	1	0.71	0.49 - 0.84
72 to 73	5	0	3	0.71	0.49 - 0.84
75 to 76	2	0	1	0.71	0.49 - 0.84
76 to 77	1	0	1	0.71	0.49 - 0.84

Table 14-11: Overall survival by oestrogen receptor status

Interval	No	Ev	Ce	PS	95% CI
ERICA ER negative					
5 to 6	35	1	0	0.97	0.81 - 1.00
10 to 11	34	2	1	0.91	0.76 - 0.97
11 to 12	31	1	1	0.88	0.72 - 0.95
12 to 13	29	0	1	0.88	0.72 - 0.95
14 to 15	28	0	1	0.88	0.72 - 0.95
15 to 16	27	0	1	0.88	0.72 - 0.95
17 to 18	26	2	0	0.82	0.63 - 0.91
19 to 20	24	1	0	0.78	0.59 - 0.89
21 to 22	23	1	1	0.75	0.55 - 0.87
22 to 23	21	1	1	0.71	0.51 - 0.84
23 to 24	19	0	1	0.71	0.51 - 0.84
24 to 25	18	1	0	0.67	0.47 - 0.81
25 to 26	17	1	0	0.63	0.43 - 0.78
30 to 31	16	0	1	0.63	0.43 - 0.78
39 to 40	15	1	0	0.59	0.39 - 0.75
41 to 42	14	1	0	0.55	0.34 - 0.71
42 to 43	13	0	1	0.55	0.34 - 0.71
43 to 44	12	0	1	0.55	0.34 - 0.71
44 to 45	11	0	1	0.55	0.34 - 0.71
45 to 46	10	1	0	0.49	0.29 - 0.67
47 to 48	9	0	1	0.49	0.29 - 0.67
52 to 53	8	0	1	0.49	0.29 - 0.67
53 to 54	7	0	1	0.49	0.29 - 0.67
63 to 64	6	0	1	0.49	0.29 - 0.67
70 to 71	5	0	1	0.49	0.29 - 0.67
72 to 73	4	0	1	0.49	0.29 - 0.67
75 to 76	3	0	2	0.49	0.29 - 0.67
76 to 77	1	0	1	0.49	0.29 - 0.67
ERICA ER positive					
9 to 10	61	1	0	0.98	0.89 - 1.00
11 to 12	60	0	1	0.98	0.89 - 1.00
12 to 13	59	0	3	0.98	0.89 - 1.00
14 to 15	56	0	2	0.98	0.89 - 1.00
15 to 16	54	0	1	0.98	0.89 - 1.00
16 to 17	53	1	0	0.97	0.87 - 0.99
18 to 19	52	0	4	0.97	0.87 - 0.99
19 to 20	48	0	1	0.97	0.87 - 0.99
20 to 21	47	0	1	0.97	0.87 - 0.99
23 to 24	46	0	1	0.97	0.87 - 0.99
24 to 25	45	0	2	0.97	0.87 - 0.99
25 to 26	43	1	1	0.94	0.83 - 0.98
26 to 27	41	0	1	0.94	0.83 - 0.98
27 to 28	40	0	2	0.94	0.83 - 0.98
31 to 32	38	0	1	0.94	0.83 - 0.98
34 to 35	37	0	2	0.94	0.83 - 0.98
35 to 36	35	0	1	0.94	0.83 - 0.98
36 to 37	34	1	1	0.91	0.78 - 0.97
37 to 38	32	0	1	0.91	0.78 - 0.97
43 to 44	31	0	2	0.91	0.78 - 0.97
44 to 45	29	0	1	0.91	0.78 - 0.97
48 to 49	28	1	1	0.88	0.73 - 0.95
49 to 50	26	1	0	0.85	0.68 - 0.93
50 to 51	25	0	1	0.85	0.68 - 0.93
51 to 52	24	1	1	0.81	0.63 - 0.91
52 to 53	22	0	1	0.81	0.63 - 0.91
53 to 54	21	0	1	0.81	0.63 - 0.91
55 to 56	20	1	1	0.77	0.58 - 0.88
56 to 57	18	0	5	0.77	0.58 - 0.88
59 to 60	13	1	0	0.71	0.49 - 0.85
60 to 61	12	0	1	0.71	0.49 - 0.85
61 to 62	11	0	1	0.71	0.49 - 0.85
64 to 65	10	0	1	0.71	0.49 - 0.85
66 to 67	9	0	1	0.71	0.49 - 0.85
67 to 68	8	1	1	0.62	0.35 - 0.80
68 to 69	6	0	2	0.62	0.35 - 0.80
70 to 71	4	0	1	0.62	0.35 - 0.80
72 to 73	3	0	3	0.62	0.35 - 0.80

Table 14-12: Overall survival by oestrogen receptor status defined by the ERICA assay as ER negative (0-1% of cells staining), and ER positive (2% or more cells staining)

Interval	No	Ev	Ce	PS	95% CI
Node negative patients					
10 to 11	79	1	0	0.99	0.91 - 1.00
11 to 12	78	0	3	0.99	0.91 - 1.00
12 to 13	75	0	1	0.99	0.91 - 1.00
14 to 15	74	0	2	0.99	0.91 - 1.00
17 to 18	72	0	2	0.99	0.91 - 1.00
18 to 19	70	0	4	0.99	0.91 - 1.00
19 to 20	66	1	2	0.97	0.89 - 0.99
20 to 21	63	0	2	0.97	0.89 - 0.99
21 to 22	61	0	1	0.97	0.89 - 0.99
22 to 23	60	0	1	0.97	0.89 - 0.99
23 to 24	59	0	2	0.97	0.89 - 0.99
25 to 26	57	1	1	0.95	0.87 - 0.99
26 to 27	55	0	1	0.95	0.87 - 0.99
27 to 28	54	0	3	0.95	0.87 - 0.99
30 to 31	51	1	0	0.94	0.84 - 0.98
34 to 35	50	0	2	0.94	0.84 - 0.98
35 to 36	48	0	1	0.94	0.84 - 0.98
36 to 37	47	1	2	0.92	0.81 - 0.96
38 to 39	44	0	1	0.92	0.81 - 0.96
39 to 40	43	1	0	0.89	0.78 - 0.95
40 to 41	42	0	2	0.89	0.78 - 0.95
41 to 42	40	0	2	0.89	0.78 - 0.95
42 to 43	38	0	2	0.89	0.78 - 0.95
43 to 44	36	0	3	0.89	0.78 - 0.95
44 to 45	33	0	2	0.89	0.78 - 0.95
48 to 49	31	0	2	0.89	0.78 - 0.95
50 to 51	29	0	2	0.89	0.78 - 0.95
51 to 52	27	0	1	0.89	0.78 - 0.95
52 to 53	26	0	2	0.89	0.78 - 0.95
53 to 54	24	0	1	0.89	0.78 - 0.95
56 to 57	23	0	1	0.89	0.78 - 0.95
59 to 60	22	1	1	0.85	0.70 - 0.93
60 to 61	20	0	1	0.85	0.70 - 0.93
63 to 64	19	1	1	0.81	0.62 - 0.91
64 to 65	17	0	4	0.81	0.62 - 0.91
65 to 66	13	0	1	0.81	0.62 - 0.91
66 to 67	12	0	1	0.81	0.62 - 0.91
70 to 71	11	0	1	0.81	0.62 - 0.91
71 to 72	10	0	1	0.81	0.62 - 0.91
72 to 73	9	0	3	0.81	0.62 - 0.91
73 to 74	6	0	1	0.81	0.62 - 0.91
75 to 76	5	1	2	0.61	0.20 - 0.86
76 to 77	2	0	2	0.61	0.20 - 0.86
Node positive patients					
5 to 6	89	1	0	0.99	0.92 - 1.00
9 to 10	88	2	1	0.97	0.90 - 0.99

Interval	No	Ev	Ce	PS	95% CI
10 to 11	85	3	1	0.93	0.85 - 0.97
11 to 12	81	0	2	0.93	0.85 - 0.97
12 to 13	79	1	4	0.92	0.84 - 0.96
13 to 14	74	0	1	0.92	0.84 - 0.96
14 to 15	73	0	2	0.92	0.84 - 0.96
15 to 16	71	0	2	0.92	0.84 - 0.96
16 to 17	69	1	1	0.91	0.82 - 0.95
17 to 18	67	2	0	0.88	0.79 - 0.93
20 to 21	65	0	1	0.88	0.79 - 0.93
21 to 22	64	1	2	0.87	0.77 - 0.92
22 to 23	61	1	1	0.85	0.75 - 0.91
23 to 24	59	1	2	0.84	0.73 - 0.90
24 to 25	56	2	2	0.81	0.70 - 0.88
25 to 26	52	1	1	0.79	0.68 - 0.87
27 to 28	50	1	1	0.77	0.66 - 0.85
29 to 30	48	1	1	0.76	0.64 - 0.84
30 to 31	46	0	2	0.76	0.64 - 0.84
31 to 32	44	3	1	0.71	0.58 - 0.80
34 to 35	40	1	0	0.69	0.56 - 0.78
35 to 36	39	0	1	0.69	0.56 - 0.78
37 to 38	38	0	1	0.69	0.56 - 0.78
41 to 42	37	1	0	0.67	0.54 - 0.77
43 to 44	36	0	2	0.67	0.54 - 0.77
44 to 45	34	0	1	0.67	0.54 - 0.77
45 to 46	33	1	0	0.65	0.52 - 0.75
46 to 47	32	0	1	0.65	0.52 - 0.75
47 to 48	31	0	2	0.65	0.52 - 0.75
48 to 49	29	1	1	0.63	0.49 - 0.73
49 to 50	27	1	1	0.60	0.47 - 0.71
51 to 52	25	2	0	0.55	0.41 - 0.67
53 to 54	23	0	1	0.55	0.41 - 0.67
55 to 56	22	1	1	0.53	0.39 - 0.65
56 to 57	20	0	4	0.53	0.39 - 0.65
60 to 61	16	0	1	0.53	0.39 - 0.65
61 to 62	15	0	1	0.53	0.39 - 0.65
63 to 64	14	0	1	0.53	0.39 - 0.65
67 to 68	13	1	1	0.49	0.33 - 0.62
68 to 69	11	0	4	0.49	0.33 - 0.62
69 to 70	7	0	1	0.49	0.33 - 0.62
70 to 71	6	0	2	0.49	0.33 - 0.62
72 to 73	4	0	2	0.49	0.33 - 0.62
75 to 76	2	0	1	0.49	0.33 - 0.62
76 to 77	1	0	1	0.49	0.33 - 0.62

Table 14-13: Overall survival for patients with and without axillary nodal involvement

Interval	No	Ev	Ce	PS	95% CI
No involved nodes					
10 to 11	76	1	0	0.99	0.91 - 1.00
11 to 12	75	0	3	0.99	0.91 - 1.00

Interval	No	Ev	Ce	PS	95% CI
14 to 15	72	0	2	0.99	0.91 - 1.00
17 to 18	70	0	2	0.99	0.91 - 1.00
18 to 19	68	0	4	0.99	0.91 - 1.00

Interval	No	Ev	Ce	PS	95% CI
19 to 20	64	1	2	0.97	0.89 - 0.99
20 to 21	61	0	2	0.97	0.89 - 0.99
21 to 22	59	0	1	0.97	0.89 - 0.99
22 to 23	58	0	1	0.97	0.89 - 0.99
23 to 24	57	0	2	0.97	0.89 - 0.99
25 to 26	55	1	1	0.95	0.86 - 0.98
26 to 27	53	0	1	0.95	0.86 - 0.98
27 to 28	52	0	3	0.95	0.86 - 0.98
30 to 31	49	1	0	0.93	0.83 - 0.98
34 to 35	48	0	2	0.93	0.83 - 0.98
35 to 36	46	0	1	0.93	0.83 - 0.98
36 to 37	45	1	2	0.91	0.80 - 0.96
38 to 39	42	0	1	0.91	0.80 - 0.96
39 to 40	41	1	0	0.89	0.77 - 0.95
40 to 41	40	0	2	0.89	0.77 - 0.95
41 to 42	38	0	2	0.89	0.77 - 0.95
42 to 43	36	0	2	0.89	0.77 - 0.95
43 to 44	34	0	3	0.89	0.77 - 0.95
44 to 45	31	0	2	0.89	0.77 - 0.95
48 to 49	29	0	2	0.89	0.77 - 0.95
50 to 51	27	0	2	0.89	0.77 - 0.95
51 to 52	25	0	1	0.89	0.77 - 0.95
52 to 53	24	0	2	0.89	0.77 - 0.95
53 to 54	22	0	1	0.89	0.77 - 0.95
56 to 57	21	0	1	0.89	0.77 - 0.95
59 to 60	20	1	1	0.84	0.68 - 0.93
60 to 61	18	0	1	0.84	0.68 - 0.93
63 to 64	17	1	1	0.79	0.60 - 0.90
64 to 65	15	0	4	0.79	0.60 - 0.90
65 to 66	11	0	1	0.79	0.60 - 0.90
66 to 67	10	0	1	0.79	0.60 - 0.90
70 to 71	9	0	1	0.79	0.60 - 0.90
71 to 72	8	0	1	0.79	0.60 - 0.90
72 to 73	7	0	2	0.79	0.60 - 0.90
73 to 74	5	0	1	0.79	0.60 - 0.90
75 to 76	4	1	2	0.53	0.10 - 0.84
76 to 77	1	0	1	0.53	0.10 - 0.84
1-3 involved nodes					
11 to 12	43	0	1	1.00	. - .
12 to 13	42	1	3	0.98	0.84 - 1.00
13 to 14	38	0	1	0.98	0.84 - 1.00
14 to 15	37	0	2	0.98	0.84 - 1.00
16 to 17	35	0	1	0.98	0.84 - 1.00
22 to 23	34	1	1	0.95	0.80 - 0.99
23 to 24	32	0	1	0.95	0.80 - 0.99
24 to 25	31	1	2	0.91	0.76 - 0.97
25 to 26	28	1	0	0.88	0.71 - 0.95
27 to 28	27	0	1	0.88	0.71 - 0.95
29 to 30	26	1	1	0.85	0.67 - 0.93
30 to 31	24	0	1	0.85	0.67 - 0.93
31 to 32	23	1	1	0.81	0.62 - 0.91
43 to 44	21	0	1	0.81	0.62 - 0.91
44 to 45	20	0	1	0.81	0.62 - 0.91
47 to 48	19	0	1	0.81	0.62 - 0.91
48 to 49	18	0	1	0.81	0.62 - 0.91
51 to 52	17	1	0	0.76	0.56 - 0.88
53 to 54	16	0	1	0.76	0.56 - 0.88
55 to 56	15	1	0	0.71	0.49 - 0.85

Interval	No	Ev	Ce	PS	95% CI
56 to 57	14	0	2	0.71	0.49 - 0.85
60 to 61	12	0	1	0.71	0.49 - 0.85
67 to 68	11	0	1	0.71	0.49 - 0.85
68 to 69	10	0	4	0.71	0.49 - 0.85
70 to 71	6	0	2	0.71	0.49 - 0.85
72 to 73	4	0	2	0.71	0.49 - 0.85
75 to 76	2	0	1	0.71	0.49 - 0.85
76 to 77	1	0	1	0.71	0.49 - 0.85
4-9 involved nodes					
9 to 10	29	1	0	0.97	0.78 - 1.00
10 to 11	28	1	1	0.93	0.75 - 0.98
12 to 13	26	0	2	0.93	0.75 - 0.98
15 to 16	24	0	1	0.93	0.75 - 0.98
16 to 17	23	1	0	0.89	0.70 - 0.96
17 to 18	22	1	0	0.85	0.65 - 0.94
21 to 22	21	1	1	0.81	0.60 - 0.92
23 to 24	19	0	1	0.81	0.60 - 0.92
24 to 25	18	1	0	0.76	0.54 - 0.89
25 to 26	17	0	1	0.76	0.54 - 0.89
30 to 31	16	0	1	0.76	0.54 - 0.89
35 to 36	15	0	1	0.76	0.54 - 0.89
37 to 38	14	0	1	0.76	0.54 - 0.89
41 to 42	13	1	0	0.70	0.47 - 0.85
43 to 44	12	0	1	0.70	0.47 - 0.85
45 to 46	11	1	0	0.64	0.39 - 0.81
46 to 47	10	0	1	0.64	0.39 - 0.81
47 to 48	9	0	1	0.64	0.39 - 0.81
48 to 49	8	1	0	0.56	0.30 - 0.76
51 to 52	7	1	0	0.48	0.23 - 0.70
55 to 56	6	0	1	0.48	0.23 - 0.70
56 to 57	5	0	2	0.48	0.23 - 0.70
61 to 62	3	0	1	0.48	0.23 - 0.70
63 to 64	2	0	1	0.48	0.23 - 0.70
69 to 70	1	0	1	0.48	0.23 - 0.70
Ten or more involved nodes					
5 to 6	20	1	0	0.95	0.69 - 0.99
9 to 10	19	1	1	0.90	0.65 - 0.97
10 to 11	17	2	0	0.79	0.54 - 0.92
11 to 12	15	0	1	0.79	0.54 - 0.92
15 to 16	14	0	1	0.79	0.54 - 0.92
17 to 18	13	1	0	0.73	0.47 - 0.88
20 to 21	12	0	1	0.73	0.47 - 0.88
21 to 22	11	0	1	0.73	0.47 - 0.88
23 to 24	10	1	0	0.66	0.38 - 0.83
27 to 28	9	1	0	0.59	0.31 - 0.78
31 to 32	8	2	0	0.44	0.19 - 0.66
34 to 35	6	1	0	0.37	0.14 - 0.60
49 to 50	5	1	1	0.28	0.09 - 0.53
67 to 68	3	1	0	0.19	0.04 - 0.44
72 to 73	2	0	1	0.19	0.04 - 0.44
76 to 77	1	0	1	0.19	0.04 - 0.44

Table 14-14: Overall survival by the number of involved axillary nodes

Interval	No	Ev	Ce	PS	95% CI
ER negative patients					
10 to 11	19	1	0	0.95	0.68 - 0.99
14 to 15	18	0	1	0.95	0.68 - 0.99
15 to 16	17	0	2	0.95	0.68 - 0.99
19 to 20	15	1	0	0.88	0.61 - 0.97
21 to 22	14	0	1	0.88	0.61 - 0.97
27 to 28	13	1	0	0.82	0.53 - 0.94
29 to 30	12	1	0	0.75	0.46 - 0.90
30 to 31	11	1	2	0.67	0.38 - 0.85
31 to 32	8	1	0	0.59	0.30 - 0.79
38 to 39	7	0	1	0.59	0.30 - 0.79
41 to 42	6	1	1	0.48	0.19 - 0.72
42 to 43	4	0	1	0.48	0.19 - 0.72
60 to 61	3	0	1	0.48	0.19 - 0.72
63 to 64	2	0	1	0.48	0.19 - 0.72
75 to 76	1	0	1	0.48	0.19 - 0.72
ER positive patients					
9 to 10	30	0	1	1.00	. - .
12 to 13	29	0	1	1.00	. - .
14 to 15	28	0	1	1.00	. - .
18 to 19	27	0	2	1.00	. - .
20 to 21	25	0	1	1.00	. - .
25 to 26	24	0	1	1.00	. - .
26 to 27	23	0	1	1.00	. - .
31 to 32	22	1	0	0.95	0.72 - 0.99
34 to 35	21	0	1	0.95	0.72 - 0.99
43 to 44	20	0	2	0.95	0.72 - 0.99
48 to 49	18	1	1	0.90	0.65 - 0.97
51 to 52	16	2	0	0.79	0.53 - 0.92
52 to 53	14	0	1	0.79	0.53 - 0.92
55 to 56	13	0	1	0.79	0.53 - 0.92
56 to 57	12	0	4	0.79	0.53 - 0.92
66 to 67	8	0	1	0.79	0.53 - 0.92
68 to 69	7	0	3	0.79	0.53 - 0.92
70 to 71	4	0	1	0.79	0.53 - 0.92
72 to 73	3	0	2	0.79	0.53 - 0.92
75 to 76	1	0	1	0.79	0.53 - 0.92

Table 14-15: Overall survival by post treatment oestrogen receptor status

Interval	No	Ev	Ce	PS	95% CI
Node negative patients					
10 to 11	41	1	0	0.98	0.84 - 1.00
12 to 13	40	0	1	0.98	0.84 - 1.00
14 to 15	39	0	2	0.98	0.84 - 1.00
18 to 19	37	0	3	0.98	0.84 - 1.00
19 to 20	34	1	1	0.95	0.80 - 0.99
20 to 21	32	0	1	0.95	0.80 - 0.99
21 to 22	31	0	1	0.95	0.80 - 0.99
23 to 24	30	0	1	0.95	0.80 - 0.99
25 to 26	29	0	1	0.95	0.80 - 0.99
26 to 27	28	0	1	0.95	0.80 - 0.99
30 to 31	27	1	0	0.91	0.75 - 0.97
34 to 35	26	0	1	0.91	0.75 - 0.97
35 to 36	25	0	1	0.91	0.75 - 0.97
38 to 39	24	0	1	0.91	0.75 - 0.97
39 to 40	23	1	0	0.87	0.69 - 0.95
40 to 41	22	0	1	0.87	0.69 - 0.95
41 to 42	21	0	1	0.87	0.69 - 0.95
42 to 43	20	0	2	0.87	0.69 - 0.95
43 to 44	18	0	1	0.87	0.69 - 0.95
44 to 45	17	0	1	0.87	0.69 - 0.95
48 to 49	16	0	2	0.87	0.69 - 0.95
52 to 53	14	0	1	0.87	0.69 - 0.95
56 to 57	13	0	1	0.87	0.69 - 0.95
60 to 61	12	0	1	0.87	0.69 - 0.95
63 to 64	11	0	1	0.87	0.69 - 0.95
64 to 65	10	0	1	0.87	0.69 - 0.95
66 to 67	9	0	1	0.87	0.69 - 0.95
71 to 72	8	0	1	0.87	0.69 - 0.95
72 to 73	7	0	2	0.87	0.69 - 0.95
73 to 74	5	0	1	0.87	0.69 - 0.95
75 to 76	4	1	2	0.58	0.09 - 0.89
76 to 77	1	0	1	0.58	0.09 - 0.89
Node positive patients					
9 to 10	37	0	1	1.00	. - .
12 to 13	36	0	1	1.00	. - .
14 to 15	35	0	1	1.00	. - .
15 to 16	34	0	2	1.00	. - .
16 to 17	32	0	1	1.00	. - .
17 to 18	31	1	0	0.97	0.79 - 1.00
22 to 23	30	0	1	0.97	0.79 - 1.00
23 to 24	29	1	0	0.93	0.76 - 0.98
24 to 25	28	0	1	0.93	0.76 - 0.98
25 to 26	27	1	1	0.90	0.72 - 0.97
27 to 28	25	1	1	0.86	0.67 - 0.95
29 to 30	23	1	0	0.82	0.63 - 0.92
30 to 31	22	0	2	0.82	0.63 - 0.92
31 to 32	20	2	0	0.74	0.53 - 0.87
41 to 42	18	1	0	0.70	0.49 - 0.84
43 to 44	17	0	2	0.70	0.49 - 0.84
48 to 49	15	1	1	0.65	0.43 - 0.80
51 to 52	13	2	0	0.55	0.33 - 0.73
55 to 56	11	0	1	0.55	0.33 - 0.73
56 to 57	10	0	3	0.55	0.33 - 0.73
63 to 64	7	0	1	0.55	0.33 - 0.73
68 to 69	6	0	3	0.55	0.33 - 0.73
70 to 71	3	0	1	0.55	0.33 - 0.73
72 to 73	2	0	1	0.55	0.33 - 0.73
75 to 76	1	0	1	0.55	0.33 - 0.73

Table 14-16: Overall survival by post-treatment lymph node status

Interval	No	Ev	Ce	PS	95% CI
No involved nodes					
10 to 11	79	1	0	0.99	0.91 - 1.00
11 to 12	78	0	3	0.99	0.91 - 1.00
12 to 13	75	0	1	0.99	0.91 - 1.00
14 to 15	74	0	2	0.99	0.91 - 1.00
17 to 18	72	0	2	0.99	0.91 - 1.00
18 to 19	70	0	4	0.99	0.91 - 1.00
19 to 20	66	1	2	0.97	0.89 - 0.99
20 to 21	63	0	2	0.97	0.89 - 0.99
21 to 22	61	0	1	0.97	0.89 - 0.99
22 to 23	60	0	1	0.97	0.89 - 0.99
23 to 24	59	0	2	0.97	0.89 - 0.99
25 to 26	57	1	1	0.95	0.87 - 0.99
26 to 27	55	0	1	0.95	0.87 - 0.99
27 to 28	54	0	3	0.95	0.87 - 0.99
30 to 31	51	1	0	0.94	0.84 - 0.98
34 to 35	50	0	2	0.94	0.84 - 0.98
35 to 36	48	0	1	0.94	0.84 - 0.98
36 to 37	47	1	2	0.92	0.81 - 0.96
38 to 39	44	0	1	0.92	0.81 - 0.96
39 to 40	43	1	0	0.89	0.78 - 0.95
40 to 41	42	0	2	0.89	0.78 - 0.95
41 to 42	40	0	2	0.89	0.78 - 0.95
42 to 43	38	0	2	0.89	0.78 - 0.95
43 to 44	36	0	3	0.89	0.78 - 0.95
44 to 45	33	0	2	0.89	0.78 - 0.95
48 to 49	31	0	2	0.89	0.78 - 0.95
50 to 51	29	0	2	0.89	0.78 - 0.95
51 to 52	27	0	1	0.89	0.78 - 0.95
52 to 53	26	0	2	0.89	0.78 - 0.95
53 to 54	24	0	1	0.89	0.78 - 0.95
56 to 57	23	0	1	0.89	0.78 - 0.95
59 to 60	22	1	1	0.85	0.70 - 0.93
60 to 61	20	0	1	0.85	0.70 - 0.93
63 to 64	19	1	1	0.81	0.62 - 0.91
64 to 65	17	0	4	0.81	0.62 - 0.91
65 to 66	13	0	1	0.81	0.62 - 0.91
66 to 67	12	0	1	0.81	0.62 - 0.91
70 to 71	11	0	1	0.81	0.62 - 0.91
71 to 72	10	0	1	0.81	0.62 - 0.91
72 to 73	9	0	3	0.81	0.62 - 0.91
73 to 74	6	0	1	0.81	0.62 - 0.91
75 to 76	5	1	2	0.61	0.20 - 0.86
76 to 77	2	0	2	0.61	0.20 - 0.86
1-3 involved nodes					
11 to 12	40	0	1	1.00	. - .
12 to 13	39	1	2	0.97	0.83 - 1.00
13 to 14	36	0	1	0.97	0.83 - 1.00
14 to 15	35	0	2	0.97	0.83 - 1.00
16 to 17	33	0	1	0.97	0.83 - 1.00
22 to 23	32	1	1	0.94	0.79 - 0.99
23 to 24	30	0	1	0.94	0.79 - 0.99
24 to 25	29	1	2	0.91	0.74 - 0.97
25 to 26	26	1	0	0.87	0.70 - 0.95
27 to 28	25	0	1	0.87	0.70 - 0.95
29 to 30	24	1	1	0.84	0.65 - 0.93
30 to 31	22	0	1	0.84	0.65 - 0.93
31 to 32	21	1	1	0.80	0.60 - 0.90
43 to 44	19	0	1	0.80	0.60 - 0.90
44 to 45	18	0	1	0.80	0.60 - 0.90
47 to 48	17	0	1	0.80	0.60 - 0.90
48 to 49	16	0	1	0.80	0.60 - 0.90
51 to 52	15	1	0	0.74	0.53 - 0.87
53 to 54	14	0	1	0.74	0.53 - 0.87
55 to 56	13	1	0	0.69	0.45 - 0.84
56 to 57	12	0	2	0.69	0.45 - 0.84
60 to 61	10	0	1	0.69	0.45 - 0.84
67 to 68	9	0	1	0.69	0.45 - 0.84
68 to 69	8	0	4	0.69	0.45 - 0.84
70 to 71	4	0	2	0.69	0.45 - 0.84
72 to 73	2	0	1	0.69	0.45 - 0.84
75 to 76	1	0	1	0.69	0.45 - 0.84
4-9 involved nodes					
9 to 10	29	1	0	0.97	0.78 - 1.00
10 to 11	28	1	1	0.93	0.75 - 0.98
12 to 13	26	0	2	0.93	0.75 - 0.98
15 to 16	24	0	1	0.93	0.75 - 0.98
16 to 17	23	1	0	0.89	0.70 - 0.96
17 to 18	22	1	0	0.85	0.65 - 0.94
21 to 22	21	1	1	0.81	0.60 - 0.92
23 to 24	19	0	1	0.81	0.60 - 0.92
24 to 25	18	1	0	0.76	0.54 - 0.89
25 to 26	17	0	1	0.76	0.54 - 0.89
30 to 31	16	0	1	0.76	0.54 - 0.89
35 to 36	15	0	1	0.76	0.54 - 0.89
37 to 38	14	0	1	0.76	0.54 - 0.89
41 to 42	13	1	0	0.70	0.47 - 0.85
43 to 44	12	0	1	0.70	0.47 - 0.85
45 to 46	11	1	0	0.64	0.39 - 0.81
46 to 47	10	0	1	0.64	0.39 - 0.81
47 to 48	9	0	1	0.64	0.39 - 0.81
48 to 49	8	1	0	0.56	0.30 - 0.76
51 to 52	7	1	0	0.48	0.23 - 0.70
55 to 56	6	0	1	0.48	0.23 - 0.70
56 to 57	5	0	2	0.48	0.23 - 0.70
61 to 62	3	0	1	0.48	0.23 - 0.70
63 to 64	2	0	1	0.48	0.23 - 0.70
69 to 70	1	0	1	0.48	0.23 - 0.70
10 or more involved nodes					
5 to 6	20	1	0	0.95	0.69 - 0.99
9 to 10	19	1	1	0.90	0.65 - 0.97
10 to 11	17	2	0	0.79	0.54 - 0.92
11 to 12	15	0	1	0.79	0.54 - 0.92
15 to 16	14	0	1	0.79	0.54 - 0.92
17 to 18	13	1	0	0.73	0.47 - 0.88
20 to 21	12	0	1	0.73	0.47 - 0.88
21 to 22	11	0	1	0.73	0.47 - 0.88
23 to 24	10	1	0	0.66	0.38 - 0.83
27 to 28	9	1	0	0.59	0.31 - 0.78
31 to 32	8	2	0	0.44	0.19 - 0.66
34 to 35	6	1	0	0.37	0.14 - 0.60
49 to 50	5	1	1	0.28	0.09 - 0.53
67 to 68	3	1	0	0.19	0.04 - 0.44
72 to 73	2	0	1	0.19	0.04 - 0.44
76 to 77	1	0	1	0.19	0.04 - 0.44

Table 14-17: Overall survival by post-treatment nodal category

Interval	No	Ev	Ce	PS	95% CI
Fast response					
21 to 22	19	1	0	0.95	0.68 - 0.99
43 to 44	18	1	0	0.89	0.64 - 0.97
50 to 51	17	1	0	0.84	0.59 - 0.95
52 to 53	16	0	1	0.84	0.59 - 0.95
55 to 56	15	0	1	0.84	0.59 - 0.95
56 to 57	14	0	2	0.84	0.59 - 0.95
63 to 64	12	0	1	0.84	0.59 - 0.95
64 to 65	11	0	1	0.84	0.59 - 0.95
68 to 69	10	0	2	0.84	0.59 - 0.95
71 to 72	8	0	1	0.84	0.59 - 0.95
72 to 73	7	0	2	0.84	0.59 - 0.95
73 to 74	5	0	1	0.84	0.59 - 0.95
75 to 76	4	0	2	0.84	0.59 - 0.95
76 to 77	2	0	2	0.84	0.59 - 0.95
Slow response					

Interval	No	Ev	Ce	PS	95% CI
9 to 10	19	1	0	0.95	0.68 - 0.99
12 to 13	18	1	0	0.89	0.64 - 0.97
14 to 15	17	1	0	0.84	0.59 - 0.95
15 to 16	16	1	0	0.79	0.53 - 0.92
18 to 19	15	1	0	0.74	0.48 - 0.88
20 to 21	14	2	0	0.63	0.38 - 0.80
27 to 28	12	1	0	0.58	0.33 - 0.76
28 to 29	11	2	0	0.47	0.24 - 0.67
34 to 35	9	1	0	0.42	0.20 - 0.62
50 to 51	8	1	0	0.37	0.17 - 0.57
56 to 57	7	0	2	0.37	0.17 - 0.57
58 to 59	5	1	0	0.29	0.11 - 0.51
60 to 61	4	0	1	0.29	0.11 - 0.51
66 to 67	3	0	1	0.29	0.11 - 0.51
70 to 71	2	0	1	0.29	0.11 - 0.51
75 to 76	1	0	1	0.29	0.11 - 0.51

Table 14-18: Distant disease free survival acording to the speed of response to primary systemic treatment

Interval	No	Ev	Ce	PS	95% CI
Fast response					
21 to 22	19	1	0	0.95	0.68 - 0.99
43 to 44	18	1	0	0.89	0.64 - 0.97
50 to 51	17	1	0	0.84	0.59 - 0.95
52 to 53	16	0	1	0.84	0.59 - 0.95
55 to 56	15	0	1	0.84	0.59 - 0.95
56 to 57	14	0	2	0.84	0.59 - 0.95
63 to 64	12	0	1	0.84	0.59 - 0.95
64 to 65	11	0	1	0.84	0.59 - 0.95
68 to 69	10	0	2	0.84	0.59 - 0.95
71 to 72	8	0	1	0.84	0.59 - 0.95
72 to 73	7	0	2	0.84	0.59 - 0.95
73 to 74	5	0	1	0.84	0.59 - 0.95
75 to 76	4	0	2	0.84	0.59 - 0.95
76 to 77	2	0	2	0.84	0.59 - 0.95
Slow response					

Interval	No	Ev	Ce	PS	95% CI
9 to 10	19	1	0	0.95	0.68 - 0.99
12 to 13	18	1	0	0.89	0.64 - 0.97
14 to 15	17	1	0	0.84	0.59 - 0.95
15 to 16	16	1	0	0.79	0.53 - 0.92
18 to 19	15	1	0	0.74	0.48 - 0.88
20 to 21	14	2	0	0.63	0.38 - 0.80
27 to 28	12	1	0	0.58	0.33 - 0.76
28 to 29	11	2	0	0.47	0.24 - 0.67
34 to 35	9	1	0	0.42	0.20 - 0.62
50 to 51	8	1	0	0.37	0.17 - 0.57
56 to 57	7	0	2	0.37	0.17 - 0.57
58 to 59	5	1	0	0.29	0.11 - 0.51
60 to 61	4	0	1	0.29	0.11 - 0.51
66 to 67	3	0	1	0.29	0.11 - 0.51
70 to 71	2	0	1	0.29	0.11 - 0.51
75 to 76	1	0	1	0.29	0.11 - 0.51

Table 14-19: Distant disease free survival acording to the speed of response to primary systemic treatment, adjusted for age, tumour size, initial ER status, axillary lymph node status and tumour differentiation

Interval	No	Ev	Ce	PS	95% CI
Fast response					
31 to 32	19	1	0	0.95	0.68 - 0.99
52 to 53	18	0	1	0.95	0.68 - 0.99
55 to 56	17	0	1	0.95	0.68 - 0.99
56 to 57	16	0	2	0.95	0.68 - 0.99
63 to 64	14	0	2	0.95	0.68 - 0.99
64 to 65	12	0	1	0.95	0.68 - 0.99
68 to 69	11	0	3	0.95	0.68 - 0.99
71 to 72	8	0	1	0.95	0.68 - 0.99
72 to 73	7	0	2	0.95	0.68 - 0.99
73 to 74	5	0	1	0.95	0.68 - 0.99
75 to 76	4	1	2	0.63	0.07 - 0.92
76 to 77	1	0	1	0.63	0.07 - 0.92
Slow response					
10 to 11	19	1	0	0.95	0.68 - 0.99
17 to 18	18	1	0	0.89	0.64 - 0.97
19 to 20	17	1	0	0.84	0.59 - 0.95
25 to 26	16	1	0	0.79	0.53 - 0.92
27 to 28	15	1	0	0.74	0.48 - 0.88
29 to 30	14	1	0	0.68	0.43 - 0.84
30 to 31	13	1	0	0.63	0.38 - 0.80
31 to 32	12	1	0	0.58	0.33 - 0.76
41 to 42	11	1	0	0.53	0.29 - 0.72
48 to 49	10	1	0	0.47	0.24 - 0.67
51 to 52	9	2	0	0.37	0.17 - 0.57
56 to 57	7	0	2	0.37	0.17 - 0.57
60 to 61	5	0	1	0.37	0.17 - 0.57
66 to 67	4	0	1	0.37	0.17 - 0.57
70 to 71	3	0	1	0.37	0.17 - 0.57
72 to 73	2	0	1	0.37	0.17 - 0.57
75 to 76	1	0	1	0.37	0.17 - 0.57

Table 14-20: Overall survival acording to the speed of response to primary systemic treatment

Interval	No	Ev	Ce	PS	95% CI
Fast response					
31 to 32	18	1	0	0.94	0.67 - 0.99
52 to 53	17	0	1	0.94	0.67 - 0.99
55 to 56	16	0	1	0.94	0.67 - 0.99
56 to 57	15	0	2	0.94	0.67 - 0.99
63 to 64	13	0	1	0.94	0.67 - 0.99
64 to 65	12	0	1	0.94	0.67 - 0.99
68 to 69	11	0	3	0.94	0.67 - 0.99
71 to 72	8	0	1	0.94	0.67 - 0.99
72 to 73	7	0	2	0.94	0.67 - 0.99
73 to 74	5	0	1	0.94	0.67 - 0.99
75 to 76	4	1	2	0.63	0.07 - 0.92
76 to 77	1	0	1	0.63	0.07 - 0.92
Slow response					
10 to 11	19	1	0	0.95	0.68 - 0.99
17 to 18	18	1	0	0.89	0.64 - 0.97
19 to 20	17	1	0	0.84	0.59 - 0.95
25 to 26	16	1	0	0.79	0.53 - 0.92
27 to 28	15	1	0	0.74	0.48 - 0.88
29 to 30	14	1	0	0.68	0.43 - 0.84
30 to 31	13	1	0	0.63	0.38 - 0.80
31 to 32	12	1	0	0.58	0.33 - 0.76
41 to 42	11	1	0	0.53	0.29 - 0.72
48 to 49	10	1	0	0.47	0.24 - 0.67
51 to 52	9	2	0	0.37	0.17 - 0.57
56 to 57	7	0	2	0.37	0.17 - 0.57
60 to 61	5	0	1	0.37	0.17 - 0.57
66 to 67	4	0	1	0.37	0.17 - 0.57
70 to 71	3	0	1	0.37	0.17 - 0.57
72 to 73	2	0	1	0.37	0.17 - 0.57
75 to 76	1	0	1	0.37	0.17 - 0.57

Table 14-21: Overall survival acording to the speed of response to primary systemic treatment, adjusted for age, tumour size, initial ER status, axillary lymph node status and tumour differentiation

Interval	No	Ev	Ce	PS	95% CI
Low levels of anxious preoccupation					
13 to 14	28	1	0	0.96	0.77 - 0.99
17 to 18	27	1	0	0.93	0.74 - 0.98
20 to 21	26	1	0	0.89	0.70 - 0.96
27 to 28	25	1	0	0.86	0.66 - 0.94
28 to 29	24	1	0	0.82	0.62 - 0.92
34 to 35	23	1	0	0.79	0.58 - 0.90
50 to 51	22	1	0	0.75	0.55 - 0.87
53 to 54	21	0	1	0.75	0.55 - 0.87
56 to 57	20	0	4	0.75	0.55 - 0.87
58 to 59	16	1	0	0.70	0.49 - 0.84
59 to 60	15	0	1	0.70	0.49 - 0.84
64 to 65	14	0	1	0.70	0.49 - 0.84
65 to 66	13	0	1	0.70	0.49 - 0.84
68 to 69	12	0	2	0.70	0.49 - 0.84
70 to 71	10	0	2	0.70	0.49 - 0.84
71 to 72	8	0	1	0.70	0.49 - 0.84
72 to 73	7	0	2	0.70	0.49 - 0.84
73 to 74	5	0	1	0.70	0.49 - 0.84
75 to 76	4	0	2	0.70	0.49 - 0.84
76 to 77	2	0	2	0.70	0.49 - 0.84
High levels of anxious preoccupation					
10 to 11	29	1	0	0.97	0.78 - 1.00

Interval	No	Ev	Ce	PS	95% CI
11 to 12	28	1	0	0.93	0.75 - 0.98
13 to 14	27	1	0	0.90	0.71 - 0.97
15 to 16	26	1	0	0.86	0.67 - 0.95
16 to 17	25	1	0	0.83	0.63 - 0.92
18 to 19	24	1	0	0.79	0.60 - 0.90
21 to 22	23	1	0	0.76	0.56 - 0.88
24 to 25	22	1	0	0.72	0.52 - 0.85
26 to 27	21	1	0	0.69	0.49 - 0.82
28 to 29	20	1	0	0.66	0.45 - 0.80
34 to 35	19	1	0	0.62	0.42 - 0.77
41 to 42	18	1	0	0.59	0.39 - 0.74
43 to 44	17	3	0	0.48	0.29 - 0.65
50 to 51	14	1	0	0.45	0.27 - 0.62
60 to 61	13	0	1	0.45	0.27 - 0.62
63 to 64	12	0	1	0.45	0.27 - 0.62
64 to 65	11	0	3	0.45	0.27 - 0.62
66 to 67	8	0	1	0.45	0.27 - 0.62
67 to 68	7	0	1	0.45	0.27 - 0.62
68 to 69	6	0	1	0.45	0.27 - 0.62
69 to 70	5	0	1	0.45	0.27 - 0.62
72 to 73	4	0	1	0.45	0.27 - 0.62
75 to 76	3	0	1	0.45	0.27 - 0.62
76 to 77	2	0	2	0.45	0.27 - 0.62

Table 14-22: Event free survival by the levels of anxious preoccupation

Interval	No	Ev	Ce	PS	95% CI
Low levels of anxious preoccupation					
21 to 22	28	1	0	0.96	0.77 - 0.99
22 to 23	27	1	0	0.93	0.74 - 0.98
30 to 31	26	1	0	0.89	0.70 - 0.96
31 to 32	25	1	0	0.86	0.66 - 0.94
51 to 52	24	2	0	0.79	0.58 - 0.90
53 to 54	22	0	1	0.79	0.58 - 0.90
55 to 56	21	1	0	0.75	0.54 - 0.87
56 to 57	20	0	4	0.75	0.54 - 0.87
59 to 60	16	0	1	0.75	0.54 - 0.87
63 to 64	15	1	0	0.70	0.48 - 0.84
64 to 65	14	0	1	0.70	0.48 - 0.84
65 to 66	13	0	1	0.70	0.48 - 0.84
68 to 69	12	0	2	0.70	0.48 - 0.84
70 to 71	10	0	2	0.70	0.48 - 0.84
71 to 72	8	0	1	0.70	0.48 - 0.84
72 to 73	7	0	3	0.70	0.48 - 0.84
73 to 74	4	0	1	0.70	0.48 - 0.84
75 to 76	3	0	2	0.70	0.48 - 0.84
76 to 77	1	0	1	0.70	0.48 - 0.84
High levels of anxious preoccupation					
10 to 11	29	1	0	0.97	0.78 - 1.00

Interval	No	Ev	Ce	PS	95% CI
12 to 13	28	1	0	0.93	0.75 - 0.98
16 to 17	27	1	0	0.90	0.71 - 0.97
17 to 18	26	1	0	0.86	0.67 - 0.95
25 to 26	25	1	0	0.83	0.63 - 0.92
27 to 28	24	1	0	0.79	0.60 - 0.90
29 to 30	23	1	0	0.76	0.56 - 0.88
31 to 32	22	1	0	0.72	0.52 - 0.85
36 to 37	21	1	0	0.69	0.49 - 0.82
41 to 42	20	1	0	0.66	0.45 - 0.80
48 to 49	19	1	0	0.62	0.42 - 0.77
60 to 61	18	0	1	0.62	0.42 - 0.77
61 to 62	17	0	1	0.62	0.42 - 0.77
63 to 64	16	1	1	0.58	0.38 - 0.74
64 to 65	14	0	3	0.58	0.38 - 0.74
66 to 67	11	0	1	0.58	0.38 - 0.74
67 to 68	10	1	1	0.52	0.31 - 0.69
68 to 69	8	0	2	0.52	0.31 - 0.69
69 to 70	6	0	1	0.52	0.31 - 0.69
72 to 73	5	0	1	0.52	0.31 - 0.69
75 to 76	4	1	1	0.37	0.12 - 0.63
76 to 77	2	0	2	0.37	0.12 - 0.63

Table 14-23: Overall survival by levels of anxious preoccupation

Interval	No	Ev	Ce	PS	95% CI
Low levels of anxious preoccupation					
13 to 14	25	1	0	0.96	0.75 - 0.99
20 to 21	24	1	0	0.92	0.72 - 0.98
27 to 28	23	1	0	0.88	0.67 - 0.96
28 to 29	22	1	0	0.84	0.63 - 0.94
34 to 35	21	1	0	0.80	0.58 - 0.91
50 to 51	20	1	0	0.76	0.54 - 0.88
53 to 54	19	0	1	0.76	0.54 - 0.88
56 to 57	18	0	4	0.76	0.54 - 0.88
58 to 59	14	1	0	0.71	0.48 - 0.85
59 to 60	13	0	1	0.71	0.48 - 0.85
64 to 65	12	0	1	0.71	0.48 - 0.85
65 to 66	11	0	1	0.71	0.48 - 0.85
68 to 69	10	0	2	0.71	0.48 - 0.85
70 to 71	8	0	2	0.71	0.48 - 0.85
72 to 73	6	0	2	0.71	0.48 - 0.85
73 to 74	4	0	1	0.71	0.48 - 0.85
75 to 76	3	0	1	0.71	0.48 - 0.85
76 to 77	2	0	2	0.71	0.48 - 0.85
High levels of anxious preoccupation					

Interval	No	Ev	Ce	PS	95% CI
10 to 11	24	1	0	0.96	0.74 - 0.99
11 to 12	23	1	0	0.92	0.71 - 0.98
13 to 14	22	1	0	0.88	0.66 - 0.96
18 to 19	21	1	0	0.83	0.61 - 0.93
21 to 22	20	1	0	0.79	0.57 - 0.91
26 to 27	19	1	0	0.75	0.53 - 0.88
28 to 29	18	1	0	0.71	0.48 - 0.85
34 to 35	17	1	0	0.67	0.44 - 0.82
41 to 42	16	1	0	0.63	0.40 - 0.78
43 to 44	15	3	0	0.50	0.29 - 0.68
60 to 61	12	0	1	0.50	0.29 - 0.68
64 to 65	11	0	3	0.50	0.29 - 0.68
66 to 67	8	0	1	0.50	0.29 - 0.68
67 to 68	7	0	1	0.50	0.29 - 0.68
68 to 69	6	0	1	0.50	0.29 - 0.68
69 to 70	5	0	1	0.50	0.29 - 0.68
72 to 73	4	0	1	0.50	0.29 - 0.68
75 to 76	3	0	1	0.50	0.29 - 0.68
76 to 77	2	0	2	0.50	0.29 - 0.68

Table 14-24: Event free survival by anxious preoccupation, adjusted for trial option, axillary nodal status and *ln* of initial ER

14.2 PSYCHOLOGICAL QUESTINNAIRES

14.2.1 The Hospital Anxiety and Depression (HAD) Scale

The HAD scale consists of an explanatory statement followed by 14 questionnaire items. Each item is followed by a choice of 4 remarks indicating strong agreement, mild agreement, mild disagreement and strong disagreement with the item Seven items are designed to assess anxiety. These alternate with the remaining seven which are aimed at evaluating depression. Scoring is from zero to 3, with directly scored questions alternating with reversed score questions.

The details of the questionnaire are as follows:

14.2.1.1 Explanatory statement

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more.

This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week.

Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

14.2.1.2 Questionnaire items

Type refers to whether the item addresses anxiety (Anx) or depression (Dep). The "score" does not appear on the questionnaire given to patients. The items are detailed in the next two pages.

The HAD Scale			
Type	**Questionnaire item**	**Replies**	**Score**
1. Anx	**I feel tense or 'wound up':**	Most of the time	3
		A lot of the time	2
		Time to time, Occasionally	1
		Not at all	0
2. Dep	**I still enjoy the things I used to enjoy:**	Definitely as much	0
		Not quite so much	1
		Only a little	2
		Hardly at all	3
3. Anx	**I get a sort of frightened feeling as if something awful is about to happen:**	Very definitely and quite badly	3
		Yes, but not too badly	2
		A little, but it doesn't worry me	1
		Not at all .	0
4. Dep	**I can laugh and see the funny side of things:**	As much as I always could	0
		Not quite so much now	1
		Definitely not so much now	2
		Not at all	3
5. Anx	**Worrying thoughts go through my mind:**	A great deal of the time	3
		A lot of the time	2
		From time to time but not too often	1
		Only occasionally	0
6. Dep	**I feel cheerful:**	Not at all	3
		Not often	2
		Sometimes	1
		Most of the time	0
7. Anx	**I can sit at ease and feel relaxed:**	Definitely	0
		Usually	1
		Not often	2
		Not at all	3
8. Dep	**I feel as if I am slowed down:**	Nearly all the time	3
		Very often	2
		Sometimes	1
		Not at all	0

The HAD Scale			
Type	**Questionnaire item**	**Replies**	**Score**
9. Anx	**I get a sort of frightened feeling like butterflies' in the stomach:**	Not at all	0
		Occasionally	1
		Quite often	2
		Very often	3
10. Dep	**I have lost interest in my appearance:**	Definitely	3
		I don't take so much care as I should	2
		I may not take quite as much care	1
		I take just as much care as ever	0
11. Anx	**I feel restless as if I have to be on the move:**	Very much indeed	3
		Quite a lot	2
		Not very much	1
		Not at all	0
12. Dep	**I look forward with enjoyment to things:**	As much as ever I did	0
		Rather less than I used to	1
		Definitely less than I used to	2
		Hardly at all	3
13. Anx	**I get sudden feelings of panic:**	Very often indeed	3
		Quite often	2
		Not very often	1
		Not at all	0
14. Dep	**I can enjoy a good book or radio or TV programme:**	Often	0
		Sometimes	1
		Not often	2
		Very seldom	3

14.2.2 The Mental Adjustment to Cancer (MAC) Scale

The MAC scale consists of an explanatory statement followed by 40 questionnaire items. Each item may be scored from 1 to 4, with no reverse scored items as follows:

1. Definitely does not apply to me

2. Does not apply to me

3. Applies to me

4. Definitely applies to me

The items fall into one of five categories appearing in random order:

1. Fighting spirit:	16 items
2. Helplessness / Hopelessness	6 items
3. Anxious Preoccupation	9 items
4. Fatalistic	8 items
5. Avoidance	one item

The details of the questionnaire are as follows:

14.2.2.1 Explanatory statement

A number of statements are given below which describe people's reactions to having cancer. Please circle the appropriate number to the right of each statement, indicating how far it applies to you at present For example, if the statement definitely does not apply to you then you should circle 1 in the first column.

14.2.2.2 Questionnaire items

"Type" refers to the aspect of mental adjustment addressed by the question, as follows:

FS: Fighting spirit, H: Hopelessness/Helplessness, AP: Anxious preoccupation, F: Fatalistic, A: Avoidance

The MAC Scale	
Type	**Item**
1. AP	I have been doing things that I believe will improve my health e.g. changed my diet
2. H	I feel I can't do anything to cheer myself up
3. AP	I feel that problems with my health prevent me from planning ahead
4. FS	I believe that my positive attitude will benefit my health
5. FS	I don't dwell on my illness
6. FS	I firmly believe that I will get better
7. F	I feel that nothing I can do will make any difference
8. F	I've left it all to my doctors
9. H	I feel that life is hopeless
10. AP	I have been doing things that I believe will improve my health, e.g. exercised
11. FS	Since my cancer diagnosis I now realise how precious life is and I'm making the most of it
12. F	I've put myself in the hands of God
13. FS	I have plans for the future, e.g. holiday, jobs, housing
14. AP	I worry about the cancer returning or getting worse
15. F	I've had a good life what's left is a bonus
16. FS	I think my state of mind can make a lot of difference to my health
17. H	I feel that there is nothing I can do to help myself
18. FS	I try to carry on my life as I've always done
19. AP	I would like to make contact with others in the same boat
20. FS	I am determined to put it all behind me
21. AP	I have difficulty in believing that this happened to me
22. AP	I suffer great anxiety about it
23. H	I am not very hopeful about the future

The MAC Scale	
Type	**Item**
24. F	At the moment I take one day at a time
25. H	I feel like giving up
26. FS	I try to keep a sense of humour about it
27. FS	Other people worry about me more than I do
28. FS	I think of other people who are worse off
29. AP	I am trying to get as much information as I can about cancer
30. F	I feel that I can't control what is happening
31. FS	I try to have a very positive attitude
32. FS	I keep quite busy, so I don't have time to think about it
33. F	I avoid finding out more about it
34. FS	I see my illness as a challenge
35. F	I feel fatalistic about it
36. H	I feel completely at a loss about what to do
37. AP	I feel very angry about what has happened to me
38. A	I don't really believe I had cancer
39. FS	I count my blessings
40. FS	I try to fight the illness

14.3 THE Q-TWIST PROGRAM

The Q-TWiST analysis was performed using a routine (called an ado file) written for the statistical software package Stata 4, Stata Corporation, 702 University Drive East, College Station, Texas 77840 USA.

"twist" is the name of the routine which contains the Q-TWiST programme. Its details are given below. All are "Stata" commands and should be placed in a text file named **twist.ado** exactly as written. twist.ado should be placed either in the *drive:\path*`\ado\t` directory, or in the same directory as the dataset being analysed.

```
program define twist
      if "`1'"=="?" {
            global S_1 "QTWiST"
            exit
      }
      sort trex
      survcurv trex rex
      gen var1=trex[_n-1]
      recode var1 .=0
      gen var2=trex-var1
      gen var3=var2*_surv
      gen var4=sum(var3)
      gen ar1=var4 in 1
      recode ar1 .=max
      drop var1 var2 var3 var4
      sort trec
      survcurv trec rec
      gen var1=trec[_n-1]
      recode var1 .=0
      gen var2=trec-var1
      gen var3=var2*_surv
      gen var4=sum(var3)
      gen ar2=var4 in 1
      recode ar2 .=max
      drop var1 var2 var3 var4
      sort tdead
      survcurv tdead dead
      gen var1=tdead[_n-1]
      recode var1 .=0
      gen var2=tdead-var1
      gen var3=var2*_surv
      gen var4=sum(var3)
      gen ar3=var4 in 1
      recode ar3 .=max
      drop var1 var2 var3 var4
      gen arrec=ar3-ar2
      gen artwist=ar2-ar1
      gen final=(ar1*urex)+artwist+(arrec*urec)
      sum final
      post `1' _result(3)
end
```

Once the twist.ado file is available the following commands need to be entered for the calculation of Q-TWiST. Stata commands appear in **bold**, while characters which appear in *italics* indicate variables to be entered by the user.

gen trec= *name of variable indicating time to recurrence in days*
gen tdead= *name of variable indicating time to death in days*
gen trex= *name of variable indicating duration of treatment in days*
gen rec= *name of censoring variable for recurrence, coded 1 for an event 0 for censoring*
gen dead= *name of censoring variable for death, coded 1 for an event 0 for censoring*
gen rex= *name of censoring variable for treatment, coded 1 for an event 0 for censoring*
gen urec= *number between 0 and 1, indicating the utility coefficient for recurrence*
gen urex= *number between 0 and 1, indicating the utility coefficient for treatment*
keep trec tdead trex rec dead rex urec urex
bstrap twist, reps(*number of bootstrap replications***) d**

The results returns the mean Q-TWiST, and bootstrap standard deviation which is by definition the standard error of the mean.

14.4 TUMOUR SIZE MEASUREMENTS

Actual tumour size measurements by different modalities. Path: diameter measured by the pathologist. Clin: clinical tumour size. Mam: Mammographic tumour size. US: Ultrasound tumour size.

No	**Path**	Clin	Mam	US	No	**Path**	Clin	Mam	US
1	**0.7**	—	—	0.7	29	**2.1**	2.6	2.4	1.8
2	**0.9**	—	0.8	1.0	30	**2.2**	2.4	2.0	1.7
3	**1.0**	1.6	1.1	0.9	31	**2.3**	2.8	2.4	2.3
4	**1.1**	1.0	1.2	0.9	32	**2.4**	3.0	2.3	2.1
5	**1.1**	1.2	1.5	1.1	33	**2.5**	4.1	—	2.7
6	**1.2**	1.7	1.3	1.6	34	**2.7**	2.3	—	2.6
7	**1.3**	2.0	2.2	1.3	35	**2.8**	4.2	3.2	2.8
8	**1.3**	1.2	1.5	1.4	36	**2.8**	3.4	—	2.8
9	**1.3**	1.1	—	0.9	37	**2.9**	4.3	2.4	2.7
10	**1.4**	2.6	1.3	1.4	38	**3.0**	3.8	3.1	2.7
11	**1.5**	—	1.8	1.3	39	**3.0**	3.8	—	2.6
12	**1.5**	2.5	1.5	1.1	40	**3.0**	4.1	3.0	2.9
13	**1.5**	2.6	1.1	1.1	41	**3.0**	3.7	3.0	3.2
14	**1.5**	1.7	1.7	1.5	42	**3.2**	4.0	2.9	3.2
15	**1.7**	3.3	1.9	1.5	43	**3.3**	4.4	2.7	3.0
16	**1.7**	1.8	1.5	1.9	44	**3.5**	4.0	—	3.1
17	**1.7**	1.7	1.6	1.4	45	**3.5**	3.3	5.0	3.7
18	**1.8**	2.4	2.1	2.0	46	**3.5**	2.2	—	3.5
19	**1.8**	3.5	2.3	1.9	47	**3.5**	4.0	2.9	3.7
20	**1.8**	2.1	1.5	1.1	48	**3.5**	4.0	4.0	2.9
21	**1.9**	2.6	1.2	1.1	49	**4.2**	4.1	3.8	4.4
22	**1.9**	1.9	1.9	1.6	50	**4.3**	4.9	4.3	4.1
23	**1.9**	—	2.0	1.6	51	**5.9**	4.0	3.5	4.6
24	**2.0**	4.0	3.1	2.2	52	**6.0**	7.5	4.5	5.5
25	**2.0**	5.4	1.7	2.1	53	**7.5**	5.5	5.0	—
26	**2.0**	3.0	2.7	1.9	54	**8.0**	5.4	—	—
27	**2.0**	2.5	—	2.8	55	**10.0**	7.5	8.2	—
28	**2.0**	2.2	2.2	1.9					

14.5 PUBLISHED PAPERS

Reprints of papers published from the work presented in this thesis are appended.

British Journal of Surgery 1994, **81**, 223–225

Ultrasonography as a method of measuring breast tumour size and monitoring response to primary systemic treatment

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Accurate measurement of change in tumour size is a prerequisite for the use of response-based regimens of primary systemic therapy for breast cancer. This study evaluated the accuracy of clinical assessment, mammography and ultrasonography in measuring tumour size and in monitoring response to treatment. Size was determined during the week preceding surgery and actual size measured from resected specimens. Sequential measurements were performed in 35 patients undergoing primary systemic treatment. There was moderate correlation between pathological and clinical size ($n=51$, $r^2=0{\cdot}68$, $P<0{\cdot}0001$). Close correlation with pathological tumour size was observed for mammographic ($n=45$, $r^2=0{\cdot}84$, $P<0{\cdot}0001$) and ultrasonographic ($n=52$, $r^2=0{\cdot}89$, $P<0{\cdot}0001$) tumour size. Response was correctly evaluated by clinical assessment in 31 of 35 patients, by mammography in 20 of 35 and by ultrasonography in 31 of 35. Actual tumour size can be measured accurately by available imaging techniques but ultrasonography is the most practical and accurate method for monitoring response.

Tumour size is an important independent indicator of prognosis for patients with carcinoma of the breast[1–3]. Repeated size measurements during primary systemic therapy produce detailed information about response[4] that can be used to select the most effective treatment regimen[5,6] and to estimate better a patient's prognosis[7–11].

Tumour size can be measured clinically using engineers' callipers[4,12,13]; the estimate, however, is indirect, influenced by associated oedema and obesity[14], and observer dependent[15].

Mammography is well established as an objective technique of assessing breast tumours[16] but the frequency with which it may be performed is limited by the radiation dose. In some patients the mammographic tumour outline is so diffuse as to preclude estimation of small variations in size[17,18].

Ultrasonography is simple to perform, provides a permanent record of tumour size and may be carried out frequently[16,19–21]. This technique provides an alternative method of assessing response to primary systemic treatment, particularly in patients with dense breasts[22].

The aims of this study were to establish the degree with which estimates of tumour diameter determined by clinical, mammographic and ultrasonographic methods correlate with actual tumour size, and to compare the efficacy of the methods, used sequentially, to assess response to primary systemic treatment.

Patients and methods

A total of 77 patients with palpable operable tumours undergoing wide local excision or mastectomy were studied. Diagnosis of malignancy had been established by cytology and mammography. The study was conducted in two parts with two overlapping subsets of patients.

For the first part of the study, single measurements were obtained on 63 tumours in 62 patients, including 42 patients treated by initial surgery and 20 who had completed 12 weeks of primary systemic therapy. Tumours were measured clinically, mammographically and ultrasonographically in the week preceding surgery.

Presented to the Surgical Research Society in London, UK, January 1992 and published in abstract form as *Br J Surg* 1992; **79**: 455
Paper accepted 11 July 1993

For the second part of the study, sequential measurements were performed over a period of 2 years on 35 patients (including 20 from the first part) undergoing primary systemic treatment. Patients were seen once a week and lesions measured by calliper and ultrasonography. Single oblique mammography was performed once every 4 weeks. Primary systemic treatment was continued for 12 weeks when mastectomy was performed. The logarithm of tumour volume was plotted against time, and response defined as a significant negative correlation between time from the start of treatment and log [volume], as described previously[5,23].

Clinical, mammographic and ultrasonographic measurements were performed by single designated observers. Examination of resected specimens was performed, or directly supervised, by one pathologist. The following techniques were used.

Clinical assessment. Tumours were measured across four diameters at 45° to each other using engineers' callipers. Mean tumour diameter was recorded as the clinical tumour size. Tumour volume was calculated using the formula for the volume of a sphere.

Mammography. Single oblique views were used to measure tumour diameter. The largest diameter and that at 90° to this axis were measured. Mammographic size was recorded as the mean of the two measurements and tumour volume calculated using the formula for the volume of a sphere.

Ultrasonography. A Siemens SL1 machine (Siemens, Tokyo, Japan) with a 7·5-MHz linear-array probe was used. The probe was held orthogonal to the skin and moved over the tumour until maximum diameter was demonstrated. Four measurements were made at 45° intervals, and the mean diameter and thickness of the lesion recorded using the machine's electronic callipers. Tumour volume (V) was calculated with the formula for the volume of an ellipsoid:

$$V=\frac{D^2\times d\times\pi}{6}$$

where D is the mean diameter and d the mean thickness.

Fresh resected specimens were serially sectioned at 0·5–1-cm intervals and at right angles to the skin. Length, width and thickness of the tumour were recorded, and volume calculated using the formula for the volume of an ellipsoid.

Distribution of the data was assessed for normality with a probit plot and skewed measurements normalized by logarithmic transformation. Mean tumour diameter measured by the pathologist was designated 'actual size', and the relationship between this and size

assessed by other techniques was established using linear regression by the method of least squares. Mean pathological, clinical, mammographic and ultrasonographic diameters were compared using Friedman's two-way analysis of variance to determine overestimation and underestimation.

Response to primary systemic treatment assessed by sequential measurement of tumour volume was compared with 'actual response'. This was determined by estimating the pretreatment tumour volume and standard error (s.e.) from the initial mammographic and ultrasonographic measurements, using graphs presented in the results section. After primary systemic treatment, macroscopic size and microscopic extent of tumour were measured in the surgical specimen, and volume of residual tumour calculated. The disease was classified as static if this was within 2 s.e. of the estimated initial volume. Residual volumes less or greater than this were classified as indicating regression and progression respectively.

Results

Of the 63 surgical specimens examined on excision, five contained no macroscopically detectable residual tumour and in a further three the margins were too diffuse for accurate assessment. Fifty-five lesions (87 per cent) were assessable.

Two patients had clinically palpable lesions that did not correspond to tumours detected in resected specimens and two tumours presenting in one breast were clinically indistinguishable. Ten tumours had diffuse mammographic outlines and could not be measured by this method. Three lesions were larger than the maximum diameter of the ultrasonographic probe (6 cm) and were not assessable by ultrasonography. Fifty-one clinical, 45 mammographic and 52 ultrasonographic measurements were available for analysis.

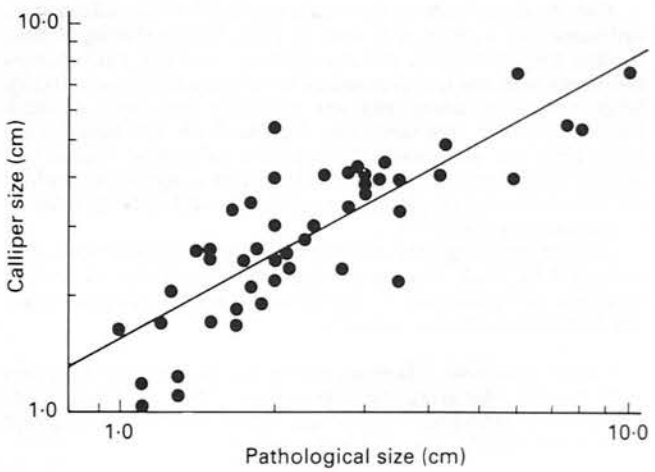

Fig. 1 Relationship between pathological and clinical tumour diameter ($n=51$). $y=1{\cdot}55x^{0{\cdot}73}$; $r^2=0{\cdot}68$, $P<0{\cdot}0001$

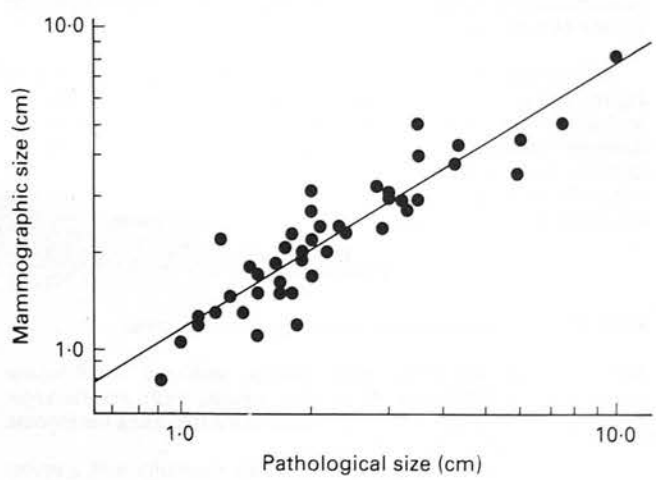

Fig. 2 Relationship between pathological and mammographic tumour diameter ($n=45$). $y=1{\cdot}15x^{0{\cdot}83}$; $r^2=0{\cdot}84$, $P<0{\cdot}0001$

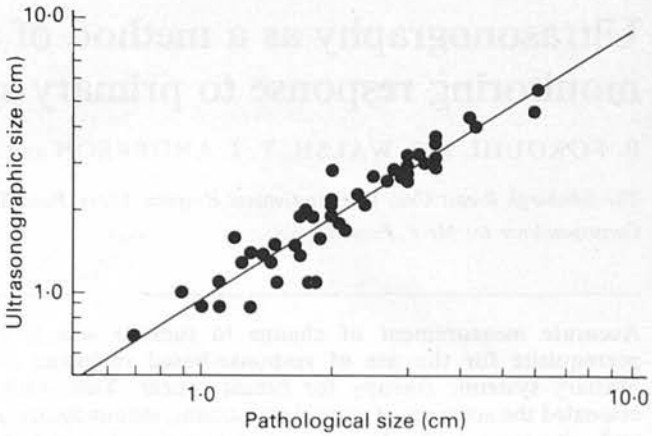

Fig. 3 Relationship between pathological and ultrasonographic tumour diameter ($n=52$). $y=0{\cdot}95x^{0{\cdot}99}$; $r^2=0{\cdot}89$, $P<0{\cdot}0001$

Table 1 Assessment of response to primary systemic treatment

Method	Not assessable	Incorrectly assessed	Correctly assessed
Clinical	0	4	31
Mammography	12	3	20
Ultrasonography	2	2	31

Response was measured clinically, mammographically and ultrasonographically, and compared with 'actual response' as defined in the text. Ultrasonography was able to detect response correctly in significantly higher numbers of patients compared with those identified using mammography ($P=0{\cdot}005$, McNemar's χ^2 test)

Diameter and volume values followed a positively skewed distribution curve and log-transformed data were used for linear regression. The relationship between actual size and mean clinical, mammographic and ultrasonographic tumour diameters is shown in *Figs 1–3*. Correlation was moderate for measurements using calipers (*Fig. 1*), but much closer for those assessed with mammography and ultrasonography (*Figs 2* and *3*).

For 45 cases in which measurements were available by all methods, Friedman's analysis of variance revealed no significant difference between pathological (mean 1·9 cm), mammographic (mean 1·9 cm) and ultrasonographic (mean 1·8 cm) diameters. Clinical diameter (mean 2·7 cm) was significantly larger than the others ($P=0{\cdot}0001$).

Tumour volume was used for sequential assessment of response. Correlation between pathological and clinical tumour volumes was moderate ($r^2=0{\cdot}63$, $P<0{\cdot}0001$) and those between pathological tumour volume and mammographic and ultrasonographic volumes were close ($r^2=0{\cdot}85$ and $r^2=0{\cdot}87$ respectively, $P<0{\cdot}0001$).

The results of sequential measurements of volume for assessment of response are presented in *Table 1*. Ultrasonography correctly evaluated ten of the 12 patients who could not be assessed using mammography. Four tumours were either not assessable or incorrectly assessed by all three techniques.

Histological examination revealed diffuse infiltration of the breast in two patients who were erroneously evaluated as responders. The two patients who were inaccurately assessed as non-responders had discrete residual breast masses consisting of hyalinized stroma, with only a small rim of residual malignant cells.

Discussion

Ultrasonography and mammography estimate actual tumour diameter and volume with greater accuracy than clinical measurement. The correlation between tumour diameter measured by ultrasonography or mammography and actual tumour diameter on excision was greater in the present study than in others[24–26]. In one series[24], ultrasonography was the most accurate technique of measuring tumour size but a recent report[26] described all three methods as having the same degree of inaccuracy. Pathological size is the standard against which other measurements are evaluated and the authors paid particular attention to its accurate assessment. Previous studies recorded this retrospectively, sometimes on fixed tissues. This may have been relatively inaccurate, as evidenced by the significant clustering of sizes around whole numbers[24,26].

Sequential calliper measurements performed by the same person were confirmed as an accurate method of monitoring response to primary systemic treatment. Imaging techniques are nevertheless important in providing independent and objective verification of clinically observed responses. Mammography and ultrasonography were equally good in assessing response in mammographically discrete tumours, but ultrasonography could also be used in diffuse lesions, and was therefore successful in significantly more patients. Failure to assess response correctly appeared to be a function of the tumour architecture rather than the technique. It is likely that this can be avoided only by monitoring parameters other than tumour dimensions.

Mammographic or ultrasonographic tumour diameter, rather than clinical size, should be used in clinical staging of breast cancer and in planning future clinical trials. Ultrasonography is the method of choice for monitoring the response of breast tumours to primary systemic treatment.

Acknowledgements

The authors are grateful to Professor D. C. Carter for reviewing the manuscript and thank Helen Dirom, Carol Lindsay and Linda McGregor for taking on the additional radiographic work. This study was supported by a grant from the Scottish Hospitals Endowments Research Trust.

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British Journal of Surgery 1994, **81**, 226–228

Recurrent laryngeal nerve palsy after thyroid gland surgery

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Risk factors for recurrent laryngeal nerve (RLN) lesions after thyroid gland surgery were evaluated retrospectively in 1026 patients. RLN palsy occurred in 5·9 per cent; the incidence of permanent palsy was 2·4 per cent as 59 per cent of paralyses were transient. For euthyroid nodular goitre, Graves' disease, chronic lymphocytic thryoiditis, recurrent goitre and thyroid carcinoma, permanent nerve damage occurred in 1·7, 4, 5, 3·8 and 8 per cent of patients respectively. In relation to the number of nerves at risk, the incidence of permanent RLN palsy was 1·1 per cent for subtotal lobectomy and 4·0 per cent for total lobectomy. The overall incidence of permanent RLN palsy was 1·8 per cent of nerves at risk. There was no statistically significant difference between the number of RLN paralyses occurring after nerve exposure and that occurring after non-exposure in subtotal lobectomy, but in total lobectomy the permanent palsy rate increased from 3·8 to 7 per cent when the nerve was not exposed or identified ($P<0·01$). Underlying thyroid disease, the extent of resection and exposure of the nerve in total lobectomy are risk factors for both transient and permanent RLN palsy.

The major concern in modern thyroid gland surgery is morbidity[1–5]. Besides haemorrhage and hypoparathyroidism, damage to the recurrent laryngeal nerve (RLN) is the complication most feared by both patient and surgeon[1,6]. There is an expected risk of nerve damage during surgery for Graves' disease, thyroid carcinoma and recurrent goitre[4,6–9], despite anatomical variations of the RLN[10–14] and appropriate techniques for performing safe thyroid gland resection being well documented[15–18]. Whether or not the RLN should be exposed during every thyroid operation is still debated, although recent publications favour exposure[15,16,19–22].

To define the risk factors for RLN injury in thyroid gland surgery, 1026 patients who had 1474 nerves at risk were evaluated retrospectively.

Patients and methods

Between January 1983 and December 1991, 1026 patients underwent thyroid surgery at this institution. They comprised 770 women (75·0 per cent) and 256 men (25·0 per cent) of age 16–84 (mean 54) years. Details of operative procedures, histopathological reports and postoperative course obtained from patients' records were evaluated retrospectively. All patients underwent preoperative and postoperative laryngoscopy by an otorhinolaryngologist to examine vocal cord function. Those with RLN paralysis after operation received voice therapy until recovery of the nerve or voice. Of the 1026 patients, 896 underwent primary and 130 secondary neck exploration, and 52 had pre-existing RLN palsy from either the underlying disease or previous operation. Two patients had nerve involvement at operation requiring resection. Therefore, 54 nerves were excluded from the study, which left 1474 at risk.

Clinically, 820 patients (79·9 per cent) were euthyroid, 21 (2·0 per cent) hypothyroid and 185 (18·0 per cent) hyperthyroid (which was the indication for operation). Other indications included symptomatic multinodular goitre (35·1 per cent) and cold nodules (20·0 per cent). A group of 205 patients (20·0 per cent) had findings suggesting malignancy on fine-needle aspiration cytology. Chronic lymphocytic thyroiditis with cold or enlarging nodules (2·0 per cent) and recurrent thyroid cancer (4·9 per cent) completed the case distribution.

Surgical technique

The procedure used for thyroid gland resection was similar to that described previously[15–18,20]. The neck was explored through a transverse cervical incision and the thyroid gland exposed. The superior thyroid vessels and the lateral and lower pole veins were ligated and divided. After dissecting out the inferior thyroid artery, the RLN was usually identified and completely visualized in total but not subtotal resection. At least one parathyroid gland was preserved on each side. Parathyroid autografting was rarely performed. In bilateral subtotal resection the inferior thyroid artery was not routinely ligated, to prevent ischaemic damage to the parathyroid glands. The isthmus and pyramidal lobe were always resected. Subtotal lobectomy corresponded to resection leaving a remnant of about $4 \times 1 \times 1$ cm. Overall, 606 patients in this study (59·1 per cent) underwent unilateral and 420 (40·9 per cent) bilateral resection.

RLN palsy rates were calculated in relation to the number of patients and nerves at risk, the underlying disease, and extent of resection and exposure (*versus* non-exposure) of the nerve. Permanent RLN palsy was defined as persisting paralysis of the vocal cord 1 year after surgery. Differences were assessed using the χ^2 test with Yates' correction[23,24].

Results

Pathological findings are shown in *Table 1*. Euthyroid, uninodular or multinodular goitre, hyperthyroid goitre, follicular adenoma, thyroid carcinoma and recurrent goitre were found in 51·0, 18·0, 7·2, 9·1 and 12·7 per cent of patients respectively. There were no deaths. Three patients suffering postoperative haemorrhage required re-exploration. Five patients had symptoms of hypocalcaemia after total thyroidectomy, one of which progressed to permanent hypoparathyroidism. The duration of hospital stay ranged from 3 to 5 (mean 3·5) days.

RLN injury occurred in 61 patients (5·9 per cent); it was transient in 36 and permanent in 25 (*Tables 1* and *2*). One patient with pre-existing palsy needed a tracheostomy for contralateral transient paralysis.

Patients with Graves' disease or chronic lymphocytic thryoiditis had a permanent RLN palsy rate of 4 and 5 per cent respectively; in euthyroid nodular goitre, hyperthyroid goitre, thyroid carcinoma and recurrent goitre, permanent nerve damage occurred in 1·7, 1·6, 8 and 3·8 per cent respectively. No permanent paralysis was seen after lobectomy for follicular adenoma (*Table 1*).

Table 2 shows results according to the extent of resection and related to the number of nerves at risk. Postoperative nerve injury affected 4·1 per cent of nerves at risk and 1·8 per cent

Paper accepted 11 May 1993

British Journal of Surgery 1995, **82**, 79–82

Prospective randomized study of surgical morbidity following primary systemic therapy for breast cancer

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The influence of primary systemic therapy in treating operable breast cancer on postmastectomy morbidity rates was investigated. The contribution of other risk factors was assessed by multiple logistic regression. Seventy-nine eligible patients were randomly allocated, 39 to undergo immediate modified radical mastectomy, and 40 to receive initial cytotoxic or endocrine treatment followed by mastectomy. Postoperative wound seroma, infection and necrosis were recorded prospectively. Fourteen minor and six major complications occurred in 17 patients treated conventionally, while 14 patients developed 11 minor and six major complications after systemic therapy ($P > 0{\cdot}4$). Median hospital stay was 8 days for both groups. Age, smoking, immediate breast reconstruction and the type of primary systemic treatment given were not independent predictors of complication risk. Obesity emerged as a significant risk factor for postmastectomy complications ($P = 0{\cdot}015$). Primary systemic therapy does not increase the rate of morbidity after mastectomy.

Systemic treatment, when used as an adjunct to surgery, increases the length of survival for patients with operable breast cancer[1]. Investigations examining systemic therapy as primary treatment are currently in progress[2–5], but surgery continues to form an important component of many protocols[4,6–9].

There is justifiable anxiety regarding the use of drugs before surgery. Cytotoxic agents compromise immune function and interfere with the normal healing of surgical wounds in animal models[10–12]. Initial systemic treatment has been associated with more wound infections and wound dehiscence following surgical excision of childhood abdominal tumours[13], greater risk of prosthetic infection and limb loss after surgical reconstruction for bone malignancy[14], and increased mortality from pneumonectomy for lung cancer[15].

Modified radical mastectomy[16] is the operation of choice for local treatment of larger breast cancers[17]. Increased surgical morbidity and unexpected mortality have been reported following mastectomy with perioperative chemotherapy[18]. Limited uncontrolled data on the effect of preoperative chemotherapy have failed to show an increase[19,20].

This study investigated in a prospective randomized trial whether primary systemic treatment increased the rate of morbidity associated with modified radical mastectomy. The contribution of other patient and tumour factors was coincidentally examined.

Patients and methods

Patients

Women aged less than 70 years with operable breast cancer larger than 4 cm in maximum diameter, diagnosed by fine needle aspiration cytology and mammography, were eligible for the study. Inoperability was defined according to the criteria of Haagensen[21], and patients with metastatic disease were excluded by applying guidelines issued from the Union Internacional Contra la Cancrum[22]. Informed written consent was required from each patient before entry into the study.

Study design

Patients were randomly allocated to one of the study options by the Scottish Cancer Trials Office and data were recorded prospectively, with foreknowledge of the patient's treatment option.

Surgery

Mastectomy with level III axillary clearance was carried out, removing a 3-cm skin margin around the tumour. Where a tumour had regressed with therapy, its pretreatment size was used to plan skin margins. For larger tumours skin closure was achieved using a latissimus dorsi myocutaneous flap (LD flap)[23,24]. Other patients were offered primary breast reconstruction with a subpectoral tissue expander[25,26]. Closed suction drainage of the axilla was maintained until less than 30 ml of fluid was drained in 24 h. Shoulder physiotherapy was started on the second day after operation. Patients with breast implants were given prophylactic flucloxacillin and penicillin (or erythromycin in cases of penicillin allergy) for 7 days, or until removal of all surgical drains, whichever was later. All patients received subcutaneous heparin until fully mobile.

Primary systemic treatment

Primary systemic ('preop') treatment was administered according to a modification of the protocol reported previously[27]. An incisional tumour biopsy was performed to determine oestrogen receptor (ER) levels and treatment was started within 10 days of the biopsy. Patients with ER less than 20 *f*mol/mg cytosol protein were defined as ER-negative[28] and treated with four cycles of cyclophosphamide 1 g/m^2, doxorubicin 50 mg/m^2 and prednisolone 40 mg for 5 days (CAP), administered at 3-weekly intervals. Surgery took place 3 weeks after the final cycle of chemotherapy or, in neutropenic patients, was delayed until the white cell count was greater than 3×10^9/litre. Two further cycles of CAP were administered after operation.

ER-positive patients received tamoxifen 20 mg daily if postmenopausal and goserelin, one injection every 4 weeks, if premenopausal. Endocrine treatment was continued for 12 weeks. Patients responding to goserelin treatment underwent surgical oöphorectomy at the same time as mastectomy. Patients with a preoperative response to tamoxifen continued with this therapy.

Tumour response was assessed weekly by ultrasonography as described previously[29]. Patients failing to respond to endocrine

Presented to the 76th meeting of the Surgical Research Society, Edinburgh, UK, July 1992 and published in abstract form as *Br J Surg* 1992; **79**: 1235–1236
Paper accepted 7 June 1994

therapy were switched to chemotherapy and if tumour progression occurred on chemotherapy mastectomy was performed early.

Conventional treatment

Mastectomy was performed within 3 weeks of entry and appropriate adjuvant therapy[1] was started a minimum of 3 weeks after surgery.

Surgical follow-up

Inpatients were examined daily and were reviewed at 1 week and 6 weeks after discharge. Patients with complications requiring outpatient treatment were seen weekly until recovery.

Complications

The incidence of early mastectomy-related wound complications has previously been reported as 10–50 per cent, with seroma, wound infection and wound necrosis being the most frequent[30–33]. Complications were defined as shown in *Table 1*.

Analysis of risk factors

The risk of complications after mastectomy may be influenced by patient-related factors such as age, obesity and smoking[32,34,35], and by the use of breast reconstruction[32]. These four risk factors were chosen for analysis. Obesity was defined in terms of body mass index (weight in kilograms divided by the square of height in metres). Those who had smoked in the year preceding surgery were considered to be smokers. LD flaps and tissue expanders were considered in a single 'breast reconstruction' category. The trial option was treated as an additional, fifth risk factor.

To assess whether the choice of preoperative endocrine or cytotoxic therapy influenced complications, a further analysis was performed for patients in the primary systemic treatment arm of the study, but in this case 'trial option' was replaced with 'adjuvant therapy', categorized as any cytotoxic therapy or no cytotoxic therapy.

Statistical analysis

Results were analysed on the basis of intention to treat. The numbers of events in each arm of the trial were compared using a two-tailed Fisher's exact probability test, and duration of treatments compared using the log rank test.

The technique of multiple logistic regression was used to assess the relative contribution of each risk factor to the probability of a patient developing complications. Five risk factors were entered into the regression equation as independent variables. Major and minor complications were combined to yield four dependent variables: seroma, infection, necrosis and any complications.

Results

Seventy-nine patients were randomized over a period of 2 years, 39 received conventional treatment and 40 underwent primary systemic therapy. There were four major protocol violations: three patients in the primary systemic treatment arm were treated conventionally and one patient randomized to conventional treatment was given primary systemic therapy. None of these four patients developed any complication. Patient characteristics, including type of breast reconstruction, are detailed in *Table 2*.

Recorded complications are detailed in *Table 3*. Patients who developed complications required an additional 3–4 weeks of treatment.

Analysis of risk factors

Body mass index was the only significant independent predictor of developing a complication ($P = 0{\cdot}015$), and, when each complication was considered independently, was a highly significant predictor of wound necrosis ($P = 0{\cdot}006$).

Of the 40 patients in the primary systemic treatment arm, 23 had received cytotoxic chemotherapy, 18 from the start and five after failing to respond to endocrine treatment. Fourteen patients received endocrine treatment only, and three had no systemic therapy. Six minor and four major complications occurred in eight endocrine-treated patients compared with five minor and two major complications in six patients given chemotherapy. In the multivariate analysis, adjuvant therapy was not a significant independent predictor of complications following mastectomy.

Table 1 Definition of early complications

Minor	Seroma	Fluid collection requiring outpatient aspiration
	Infection	Clinically diagnosed, requiring oral antibiotics
	Necrosis	Superficial sloughing or edge necrosis under 1 cm in diameter
Major	Seroma	Fluid collection requiring surgical drainage
	Infection	Culture proven, requiring intravenous antibiotics or surgery
	Necrosis	Full thickness, requiring surgery

Table 2 Patient and tumour characteristics (no significant differences)

	Conventional	Preoperative
Total number	39	40
Mean age (years)	51	51
Mean BMI (kg/m^2)	25·8	26·6
Mean initial tumour diameter (mm)	50	48
No. of pN_1 patients	23	20
No. of ER+ patients	19	20
Immediate breast reconstruction	25	27
LD flaps	15	11
Tissue expanders	10	16

BMI, body mass index (normal range: 18·7–23·8 kg/m^2); pN_1, histologically proven involved axillary nodes; ER+, oestrogen receptor levels ≥ 20 fmol/mg cytosol protein

Table 3 Details of all complications

	Conventional	Preoperative	*P*
Total number	39	40	
Any complications	17	14	0·45*
Total minor complications	14	11	0·43*
Minor seroma	11	7	0·27*
Minor infection	1	4	0·36*
Minor necrosis	3	1	0·36*
Total major complications	6	6	0·88*
Major seroma	2	1	0·62*
Major infection	3	4	0·67*
Major necrosis	2	2	0·94*
Median (range) hospital stay (days)	8 (3–27)	8 (4–23)	<0·6†
Median (range) outpatient treatment for complications (days)	25 (4–91)	20 (6–92)	<0·5‡

*Fisher's exact test. †Log rank test, $\chi^2 = 0{\cdot}03$. ‡Log rank test, $\chi^2 = 0{\cdot}42$

Discussion

This randomized trial found no increase in morbidity rate following mastectomy when this follows a period of systemic treatment. These results are consistent with those from previous uncontrolled series, which found no excess in complications following chemotherapy for locally advanced[19] or large operable[20] breast tumours. The same observations have been made following breast conservation where primary chemotherapy does not appear to be an independent predictor of wound complications[36] or cosmetic outcome[37].

The overall incidence of surgical complications in this group of patients was 39 per cent. Most complications were minor and self-limiting. Clinically important complications occurred in 15 per cent of patients, a finding similar to other observations[30–33,38].

Obese patients were at significantly increased risk of postmastectomy wound complications, and in particular wound necrosis. This should be taken into consideration when making a choice between mastectomy and breast conservation.

Breast cancer surgery can be performed after primary systemic treatment without an adverse effect on surgical outcome.

Acknowledgements

The authors are grateful to the Department of Medical Statistics, University of Edinburgh for performing the statistical analysis for this paper. This work was supported by a grant from the Scottish Hospitals Endowments Research Trust.

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Short note

Scintigraphic detection of biliary fistula after removal of a T tube

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After removal of a T tube there is always a temporary biliocutaneous fistula, which normally closes within 48–72 h[1]. The irritant properties of the T tube stimulate a reactive granulation track[2] over 7–10 days.

In this study technetium-99m dimethyliminodiacetic acid (^{99m}Tc-HIDA) scintigraphy was used to diagnose biliary fistulas and leaks after T tube removal.

Patients and methods

Between October 1990 and April 1993, 46 patients underwent surgery for benign common bile duct (CBD) pathology (lithiasis, cholangitis). After CBD exploration a latex and silicone T tube of size 14–18 was left in the duct.

T tube cholangiography was performed after operation to confirm patency and the absence of bile duct pathology.

Scintigraphy was performed 24 h after T tube removal. A dose of 4 mCi ^{99m}Tc linked to trimethyl-HIDA was given intravenously. The patient was placed under a γ camera detection field and one image was obtained every 10 min for 1 h, using computer-based acquisition every minute starting 10 min after injection.

Results

The mean age of patients was 70·4 (range 42–91) years; 74 per cent were women.

Paper accepted 31 May 1994

The T tube was in place for a mean of 13·9 (range 6–24) days. In some cases the T tube was used for a longer period as a result of cholangiographic findings (fistula, stenosis, residual lithiasis) or postoperative pancreatitis. The cholangiogram was normal in 74 per cent of cases.

Scintigraphy provided normal findings in 35 of the 46 patients. Clinically significant findings were asymptomatic stenosis in five patients, asymptomatic abdominal fistula in three, cutaneous fistula in two and symptomatic intra-abdominal leakage in one.

Discussion

Intraperitoneal biliary leakage after removal of a T tube is not a common problem (0·5–0·8 per cent) but is a potentially fatal complication[1–3]. In the present series this complication occurred in one patient, fortunately without grave consequences although reoperation was necessary.

When such leakage occurs ultrasonography and computed tomography cannot determine accurately whether the fluid collection represents a biliary fistula or blood, or whether there is good biliary flow to the duodenum[4].

The importance of HIDA scintigraphy following T tube removal lies in the possibility of evaluating the presence and amount of peritoneal bile leakage. Correlation of these data with clinical findings helps to determine whether surgical treatment is necessary.

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