

**BREAST CONSERVATION TREATMENT AT
GROOTE SCHUUR HOSPITAL:
TREATMENT OUTCOME**

By

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Dedication

This work is dedicated to the soul of my father

University of Cape Town

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Abstract

This study was conducted on information relating to breast cancer patients who attended the multidisciplinary Breast Clinic (known as the 'combined' Breast Clinic), in the Department of Radiation Oncology at Groote Schuur Hospital, in Cape Town, from January 1995 to December 2001. It is a retrospective study, analysing 69 out of 176 patients who presented with early breast cancer (T1/T2, N0-1).

Study Population

The 69 patients under analysis received breast conservation treatment.

Study Objectives

The objectives of the study were two-fold: 1) to evaluate the treatment outcome in terms of disease-free survival and overall survival; 2) to assess factors associated with early disease relapse or short overall survival.

Data Collection and Analysis

Data was collected from the Breast Clinic database and completed by reviewing patients' departmental folders. All data was checked and missing information sought by referring to the patients' general hospital folders, or by reviewing the histopathology specimens, wherever the slides were available. Analysis of data was performed using the Statistical Package for the Social Sciences (SPSS), which is a data management and analysis product of SPSS, Inc, Illinois.

Results and Discussion

The majority of the study population were older than 50 years, of coloured race, and presented with tumours that were of T1 size with moderate to poor tumour differentiation. 56.5% of these tumours were estrogen receptor positive. These tumours were completely excised in 81.2% of the patients. The resection margin status for 13% of patients was reported as positive. The verification of the status of the resection margin of the rest of the patients was not possible and hence reported as unknown.

The relapse rate reported in this study is 17.4%. The disease relapse was found to be relatively more frequent among patients who were young (≤ 40 years). It was also noticed from the data that the disease characteristics and disease outcomes improve

with advancing age. However, the effect of age on overall and disease-free survivals was found to be not significant statistically.

The disease relapse was also found to be relatively more frequent among patients with large tumours, and those with high grade tumours. Actually there was progressive increase of relapse rate as grade increased from G1 to G3.

The disease relapse was also reported to be twice as high among patients with nodal involvement than in patients with no nodal involvement. The study also showed that 32 patients out of the whole study population had inadequate axillary nodal dissection which affects their proper classification and management.

The study indicated a relatively high relapse rate associated with positive resection margins, negative estrogen receptor status, and among patients who had lymphovascular invasion.

Chi squared analysis was performed to determine the statistical significance of patient's and tumour's related variables on overall survival (OS) and disease free survival (DFS). Results of this analysis showed that most variables were not found to significantly affect outcome. However local disease recurrence was found to negatively affect OS with a high level of significance ($p = 0.0008$) and race had a marginally significant effect on DFS ($p = 0.051$).

Kaplan Meier's survival analysis of the Groote Schuur's study group was performed and showed that 88.4% of the study population might be expected to survive the period of 5 years and that the 5 years disease free survival calculated was more than 75%. Although the study covers only a short period of follow up for a small number of patients, these percentages give an indication of the high survival rate this group of patients could achieve.

Conclusion

The present study is a retrospective analysis and has all the shortcomings typical of such a study besides the short follow up duration and small population size, but in general and after considering these factors, the Groote Schuur population seems to have a similar outcome of breast conservation therapy to outcomes published in the literature from different study groups in different parts of the world. A lengthy follow up of a larger patient's number in a well design prospective study is recommended to clarify these findings.

Chapter 1

1.1 Introduction

1.1.1 Background

Breast cancer has a long-standing history. It was documented as far back as the time of the early Egyptians, when the popular treatment was cauterization of the diseased tissue. Surgery was practised, but it was an extremely radical treatment considering there was no anaesthesia or antiseptics available (1).

According to the doctrines of the Greek physician, Claudius Galen (130-200 AD), whose works on physiology and anatomy dominated medical thought until the Middle Ages, melancholia was the chief factor in the development of breast cancer. Special diets were the recommended treatment. However, other treatments included exorcism and the use of topical applications, which were seldom favoured by patients (1). During the Renaissance, Andreas Vesalius recommended mastectomy, as well as ligatures (sutures), to control the bleeding rather than cauterization (1).

That breast cancer could, and did, spread to the regional axillary nodes was first recognised by the physician, Le Dran (1685-1770). He, it seems, was also the first to associate poor prognosis with the spread of breast cancer to the lymph nodes. This observation was a major breakthrough in understanding breast cancer. Unfortunately, it is difficult to determine the level of success associated with archaic treatments (cauterization, mastectomy and ligature) (1).

Surgeons recorded the first detailed account of breast cancer during the mid-1800s. Those statistics indicate that even patients treated by mastectomy had a high rate of recurrence within eight years – especially when the axillary lymph nodes were affected. Nevertheless, the common treatment was to remove the breast and the axillary lymph nodes in an effort to stave off any further tumour development. This practice was highly significant, as it demonstrates that the common belief among the medical community was that breast cancer was a systemic disease that could spread

and affects other parts of the body (1), and that the cancerous breast and nodes to which the disease could have spread should be removed to try and prevent further spread.

By the late 1880s, with the advent of improved anaesthesia, radical mastectomies were commonly carried out, as well as the removal of the axillary lymph nodes in an effort to deter the spread or recurrence of breast cancer. However, most procedures performed were for locally advanced cancer rather than for small breast lumps, which are more commonly seen today, while what was believed, incorrectly, to be a “cure” was based on only three years’ survival rate. In fact, statistics kept at that time, at the John Hopkins Hospital, New York, indicate that a ten-year survival rate was only 12%, with a 30% local recurrence rate (1).

Between the 1930s and 1950s, improvement in treatment was noticeable. Research produced by many scientists, including George Hitchings and Gertrude Elion, (2) showed that cancer could be treated with chemical compounds. Cancer chemotherapy joined surgery and radiation as methods of treatment. The most important development in clinical methods was to classify the stage and progression of the disease: stages I and II represented operable or curable groups of cases; stage III indicated the locally advanced disease, where surgery was not a viable option; and stage IV described patients with distant metastases.

Survival rates improved dramatically during the 1900s. Ten-year survival rates following mastectomy improved from approximately 10% in the 1920s to roughly 50% in the 1950s. It is thought that the high recurrence rate was due to the advanced stage of disease at presentation, which could be attributed to factors such as poor early detection techniques (1).

In 1920s-1930s pioneering investigators, such as Dr. Geoffery Keynes (3), a surgeon at St Bartholomew’s Hospital in London, Peters in Canada, Baclesse in France and Musta Kallio in Finland (1), began to treat groups of women with breast conserving, partial mastectomies followed by irradiation to the remaining breast tissues, challenging the need for total mastectomy. Results from these early studies were quite

promising and a comparison of these with those of similarly staged patients who underwent mastectomy revealed no difference in survival.

The first trial of breast conserving therapy was performed at Guy's Hospital in London, in 1961. This demonstrated no difference in survival but a higher rate of local recurrence (a low dose of radiation had been given to the patients) (1). In the early 1970s, several European reports created a great deal of interest in non-mastectomy treatment world-wide, since excellent results were being seen in a series of several hundreds of patients (3). In 1975, a small clinical series was published by Pronitz and Goldenberg, from Yale University, and soon after the Joint Centre for Radiation Therapy in Boston, led by Hellman and colleagues, began to publish their results, which were also encouraging.

The randomised controlled studies by surgeons, Umberto Veronesi in Italy and Bernard Fisher in the USA, in the early 1980s, resulted in this treatment approach's being more widely accepted, as it showed in a selected patient population that mastectomy and breast conserving surgery yielded similar overall survival (4).

To date, six randomised trials of breast conserving therapy versus mastectomy have been published. More than 4 000 women have been included and randomised between the two therapies. The outcome, at 5, 10, 15 and 20 years, shows that survival in the two treatment groups is identical (5).

In 1990, the NCI held a Consensus Development Conference on Treatment of Early Breast Cancer (6) and declared that breast sparing therapy was not only equivalent to mastectomy, but was actually the "preferable" treatment, since it preserved the breast with all the attendant psychological and body image advantages associated with a less radical surgical procedure.

1.2.1 The multidisciplinary Breast Clinic

At Groote Schuur Hospital, Cape Town, patients have been treated with breast conserving treatment since 1963 (reference: Breast data-base). The multidisciplinary Breast Clinic (referred to generally as the 'combined' breast Clinic), which is based in the Department of Radiation Oncology, serves a good number of breast patients

through proper diagnosis and management. The clinic has all the required specialties: surgery, plastic surgery, radiology, pathology, clinical radiation oncology and a department of social work, all of which have the expertise necessary for the proper assessment and management of patients.

Breast conserving therapy is a well-established modality that has been used with a good number of patients, although the majority of those who presented with early stages of the disease at this clinic did undergo mastectomy.

No study had been conducted to evaluate the treatment outcome among these patients. Although it had long been proven that breast conserving treatment was equivalent to mastectomy, as is shown above, it occurred to me that it would be both interesting and of value to ascertain the treatment outcome in terms of survival and risk factors associated with local recurrence or metastases in those patients who presented at the Groote Schuur Hospital.

1.2 Objectives

The objectives of the present study were thus:

1. To evaluate the treatment outcome in terms of disease-free survival and overall survival.
2. To assess factors associated with early local recurrence or short overall survival.

Chapter 2

2.1 Patients and Methods

2.1.1 Study populations

Patients in this study were those who presented to the Department of Radiation Oncology at Groote Schuur Hospital with early breast cancer (T1/T2, N0-1), from January 1995 to December 2001, and who had been treated with breast conserving surgery, either at the Groote Schuur Hospital or in other hospitals (These hospitals included hospitals in the Western Cape and other provinces of South Africa.). Along with this, patients had to fit a number of criteria designated for breast conservation therapy. These criteria included axillary lymph nodes dissection and post-operative radiotherapy. Twenty patients did not undergo axillary node dissection and/or post-operative radiation after conservative surgery and they were thus excluded from analysis, from the start.

Patients referred from other hospitals after breast conserving surgery brought with them full details about their surgical management, and, for purposes of this study, the documentation of the treatment they received was easily found from their records.

Clinical assessment as to the stage of disease was considered, initially, in the process of gathering data about patients. The stage was then verified by reviewing the histopathology reports. If there was any missing information in these reports, the original histopathological specimens were sought for and reviewed, wherever the original slides were available.

There was no follow-up of the patients beyond the last one which reported in their hospital folders. The short follow-up time was considered a major weakness of the study because breast cancer is a disease that needs a lengthy follow-up to be able to determine properly disease free and overall survival and factors affect them.

2.1.2 Methods of treatment

In accordance with the protocol for breast cancer treatment of the Department of Radiation Oncology, Groote Schuur Hospital and the University of Cape Town, the

study population received adjuvant treatment. This protocol has changed over the years, according to international guidelines and research findings.

According to the protocol being used at the time, the CMF (Cyclophosphamide, Methotrexate and 5FU) schedule was either classic CMF or a similar regimen with intravenous Cyclophosphamide replacing oral Cyclophosphamide. According to the protocol, CMF, Tamoxifen or both in sequence have been used, in node positive and node negative, high-risk patients.

In special circumstances CAF (Cyclophosphamide, Adriamycin and 5FU) was used, e.g., more than three involved lymph nodes. An AC regimen (Adriamycin and Cyclophosphamide) was also sometimes used under this protocol.

Adjuvant radiation therapy, according to this protocol, was given as follows:

1. Indications: radiation was indicated for all patients with T1-2, node negative/node positive, M0 breast carcinoma after wide local excision and axillary clearance.

2. Prescription: Whole breast 2.15Gy/fraction, 4 fractions/week for 21 fractions to 45.15Gy total tumour dose at the ICRU point, which was defined as lying midway between the ribs and the skin, in the centre of the tumour volume was prescribed.

Electron boost: 2.50Gy/fraction, 4fractions/week for 5 fractions to 12.50Gy total given dose was the boost prescribed. A 90 % isodose was to cover tumour volume as far as possible.

3. Technique: Treatment usually was on Cobalt-60 or 6MV linear accelerator machines unless there was large separation (e.g. > 22 cm), in which case, an 8MV linear accelerator beam was used. An aim was to achieve homogeneity of at least 15%. Compensators and cast technique were used.

Treatment with a 6MV linear accelerator beam with cast off was considered standard for irradiating most breasts but a 6MV beam was not always available.

Before November 1996, the dose used was 43.05Gy to the isodose surrounding the target volume. After November 1996, the dose at the ICRU point as described above was used.

2.2 Disease Recurrence

Histology, cytology and radiology were used to confirm recurrence. The date of confirmation of recurrence, using the tools of investigation mentioned above, was then recorded as the date of recurrence. All the cases reported with disease recurrence were confirmed ones and none of them was suspicious only. “Loco-regional recurrence” means a failure occurring within the treated breast or its immediate lymph nodes including supraclavicular nodes.

2.2.1 Disease-free survival

The disease-free survival was calculated for all patients from the date of presentation to the multidisciplinary Breast Clinic until the date of confirmed local recurrence or distant metastases. In the patients who had no disease relapse, this duration was calculated to the date of the last follow-up or the date of death.

2.2.2 Overall survival

The overall survival was calculated from the date of presentation to the Breast Clinic to one of the following dates: the date of death or the date of the last follow-up, provided the patient was regular in attending the follow-up appointments.

2.3 Study Design

This was a retrospective study based on departmental and patients’ data.

2.3.1 Data collection

Collection of data was made from the breast clinic data base and completed from the patients’ radiotherapy folders. All data was checked and additional information

searched for, either from each patient's general hospital folder or by reviewing the histopathology specimens. Usually patients have two folders: a general hospital folder; and a dedicated radiation Oncology Department folder.

2.4 Variables Collected

Specific information analysed for each patient included the following variables: date of presentation, date of last follow-up, date of recurrence, site of recurrence, status of patient at last follow-up, date of death, age, race, tumour size, tumour grade, estrogen receptor status, surgical margin status, status of lymphovascular invasion, total number of excised lymph nodes and total number of lymph nodes involved with cancer.

2.5 Data Analysis

Data was analysed using SPSS (Statistical Package for the Social Sciences) software, which is a data management and analysis product produced by SPSS, Inc., Chicago, Illinois. Among its features are modules for statistical data analysis, including descriptive statistics such as plots, frequencies, charts and lists, as well as sophisticated inferential and multivariate statistical procedures, like analysis of variance (ANOVA), factor analysis, cluster analysis and categorical data analysis. SPSS is particularly well suited to survey research, though by no means limited to just this topic of exploration.

The data collected was analysed according to two sets of variables: patient-related variables and tumour-related variables. The patient-related variables were age and race. The tumour-related variables were tumour size, tumour grade, status of resection margins, status of vascular invasion, number of lymph nodes involved with cancer and estrogen receptor status.

Chi square (X^2) test was performed to assess the statistical significance of the effect of each variable on disease-free and overall survival. Two-tailed p-value (significance testing) was used, while the pre-selected value for considering the effect of a variable statistically significant was 0.05 or less (i.e., to reject null hypothesis).

Chi square is used most frequently to test the statistical significance of results reported in bivariate tables, and interpreting bivariate tables is integral to interpreting the results of a chi square test. It is an approximate test of the probability of getting the frequencies actually observed if the null hypothesis were true.

The t-test was used only on one occasion where the sample size was too small to be checked by X^2 .

The t-test gives the probability that the difference between the two means is caused by chance. It is customary to say that if this probability is less than 0.05, that the difference is 'significant' and is not caused by chance.

The overall survival curve for the study group was obtained with use of the Kaplan–Meier method. It was also used to determine the overall survival curves for three groups of patients. These were patients with tumour size of T1, T2, and patients who developed disease relapse.

The Kaplan-Meier method is a nonparametric (actuarial) technique for estimating time-related events (the survivorship function). Ordinarily it is used to analyze death as an outcome. It may be used effectively to analyze time to an endpoint, such as remission. The Kaplan Meier analysis allows estimation of survival over time, even when patients drop out or are studied for different lengths of time.

The methods of analysis outlined above were designed to examine the relevant information on the outcome of treatment of breast cancer at the multidisciplinary Breast Clinic from January 1995 to December 2001. The results of the analysis are given in the chapter below, which also includes a set of tables and figures detailing different aspects of the study.

Chapter 3

3.1 Results

From January 1995 to December 2001, 176 patients with early breast lesions (T1 & T2) presented to the Groote Schuur Multidisciplinary Breast Clinic. The initial information concerning these patients was collected for this study from the Breast Database.

A total of 89 patients from the group underwent breast conservation surgery (some of them didn't have axillary clearance). Sixty-nine of these patients underwent breast conservation therapy (lumpectomy, axillary clearance and radiotherapy). It is these 69 patients who form the population for this study. Characteristics of the study population are shown in table 1.

By December 2001, 12 patients from the study population had relapsed (17.4%), either loco-regionally (10.1%) or with distant metastases (7.3%). There was no patient who had both local and distant metastases. 4 had died (5.8%). The death in 3 of these patients was associated with relapsed disease (4.3%). Two of them had local relapse initially but there was no confirmation of the status of disease at the time of death, i.e. whether there was progression to distant metastasis. The third patient died with distant lung and liver metastases. The fourth patient died of a cause unrelated to breast cancer, being clear of disease when she died.

Of the 7 patients with loco-regional relapse (10.1%) only one had supraclavicular nodal relapse and was treated with chemotherapy. The remaining cohort of patients had local recurrences in the treated breast; however, all of these were salvaged surgically. Among this group there were 2 deaths reported (28.6%). The disease-free survival for this group of patients ranged between 10 and 62 months, within a mean duration of 33.3 months. The mean overall survival was 60.1 months (the range extends between 44 and 73 months).

In the category of distant metastases, there were 5 patients in the study population (7.3%). Of these, 4 had bone metastases and one, both liver and lung metastases.

The disease-free survival of these patients ranged from 17 to 48 months, with a mean duration of 34.4 months. The mean overall survival was 48.8 months, ranging from 21 to 71 months.

There were 31 patients in the study population who at the time of assessment had already lived for 4 years or more after the treatment (44.9% of the study population). Among these, there were relatively more patients from the group without disease relapse than there were from those who relapsed (49.1% versus 25%).

Mean follow-up duration for the whole population was 43.86 months (ranging from 1.9 months to 79.08 months). Median follow-up duration was 44.98 months.

Mean overall survival for the study population was 43.86 and mean disease-free survival was 40.84 months but it must be noted that follow-up ranged from 1.9 months to 79.08 months.

3.2 Detailed Results

The tables and figures set out below detail the study population characteristics, and the effect of each variable on disease relapse, overall survival and disease-free survival.

Overall study population

Table 1

Overall study population characteristics (n=69)

Patients' characteristics		Number of patients	Percentage
Age	<= 40	12	17.4
	> 40<50	17	24.6
	>= 50	40	58.0
Race	White	26	37.7
	Coloured	39	56.5
	Black	4	05.8
Tumour size	T1	47	68.1
	T2	22	31.9
Tumour grade	Grade 1	17	24.6
	Grade 2	25	37.7
	Grade 3	22	31.9
	Unknown	4	05.8
Lymph node involvement	Yes	9	13.0
	No	55	79.7
	Unknown	5	07.2
Resection margin involvement	Yes	9	13.0
	No	56	81.2
	Unknown	4	05.8
Estrogen receptor status	Positive	39	56.5
	Negative	23	33.4
	Unknown	7	10.1
Vascular invasion	Yes	10	14.5
	No	45	65.2
	Unknown	14	20.3
Disease relapse	Local*	7	10.1
	Distant*	5	07.3

*85.7% of the local recurrences occurred within the first five years after treatment, however the short follow-up period for both distant and local recurrences should be noted.

Table 1 indicates that the majority of the study population were older than 50 years, of coloured race, and presented with tumours that were of T1 size with moderate to poor tumour differentiation. 56.5% of these tumours were estrogen receptor positive. These tumours were completely excised in 81.2% of the patients. The resection margin status for 13% of patients was reported as positive. The verification of the status of the resection margin of the rest of the patients was not possible and hence reported as unknown. Also it should be noted that the different variables were not necessarily well balanced among the groups.

Age**Table 2****Patients' characteristics with relation to different age groups**

Characteristic		Age \leq 40 (n = 12)	Age >40<50 (n = 17)	Age \geq 50 (n = 40)	Total (n=69)
Race	White	4	7	15	26
	Coloured	6	10	23	39
	Black	2	0	2	4
Tumour size	T1	8	11	28	47
	T2	4	6	12	22
Tumour grade	Grade 1	2	4	12	18
	Grade 2	2	8	15	25
	Grade 3	8	4	10	22
	Unknown	0	1	3	4
Lymph node involvement	No	11	15	29	55
	Yes	1	0	7	8
	Unknown	0	2	4	6
Resection margin involvement	No	9	17	30	56
	Yes	3	0	6	9
	Unknown	0	0	4	4
Estrogen receptor status	Positive	6	9	25	40
	Negative	4	6	12	22
	Unknown	2	2	3	7
Lympho-vascular invasion status	No	9	12	24	45
	Yes	2	2	6	10
	Unknown	1	3	10	14
Disease relapse	Local	4	0	3	7
	Distant	1	2	2	5
Percentage relapse		41.6%	11.8%	12.5%	17.4%

A breakdown of the patient characteristics with age are shown in table 2. A strikingly high percentage of relapse (41.6%) was found among the younger patients (\leq 40) who also had relatively higher number of patients with grade 3 tumours than other groups. The small size of the sample and the short follow up duration should be noted.

Table 3
Age group distribution with relation to overall survival

SURVIVAL/MONTHS	Age \leq 40 (n = 12)	Age > 40<50 (n = 17)	Age \geq 50 (n = 40)	TOTAL
1-36	4	8	11	23
36.1-48	2	4	9	15
48.1-60	3	3	10	16
> 60	3	2	10	15
TOTAL	12	17	40	69

Table 4
Age group distribution with relation to disease-free survival (DFS)

DFS/MONTHS	Age \leq 40 (n = 12)	Age > 40<50 (n = 17)	Age \geq 50 (n = 40)	TOTAL
1-36	9	6	16	31
36.1-60	3	5	16	24
>60	0	6	8	14
TOTAL	12	17	40	69

Tables 3 and 4 indicate the effect of age on overall and disease free survival respectively. Overall survival was similar for the youngest (\leq 40) and oldest (\geq 50) groups which showed a 25% 5 years survival ($3/12 = 25\%$ and $10/40 = 25\%$ respectively). The intermediate group ($>40 <50$) had a lower 5 year survival close to 12% ($2/17 = 11.8\%$).

The youngest group showed the worst 5 year DFS ($0/12 = 0\%$) followed by the oldest group ($8/40 = 20\%$) while the intermediate group had the best DFS ($6/17 = 35.3\%$).

Race

Table 5
Race distribution with relation to disease relapse

(White n= 26, Coloured n= 39, Black n= 4)

Race	Number of patients	Relapse	percentage
White	26	6	23
Coloured	39	5	12.8
Black	4	1	25
Total	69	12	17.4

Table 5 indicates the effect of race on disease relapse. There were about twice the percentage of relapses in each of the white and black groups relative to the coloured group.

Table 6
Race distribution with relation to overall survival

(White n= 26, Coloured n= 39, Black n= 4)

SURVIVAL/MONTHS	WHITES	COLOUREDS	BLACKS	TOTAL
1-36	12	9	2	23
36.1-60	9	21	1	31
> 60	5	9	1	15

As shown in table 6, a similar proportion of patients from each race group survived more than 5 years (white $5/26 = 19.2\%$, coloured $9/39 = 23\%$, black $1/5 = 25\%$).

Table 7**Race distribution with relation to disease-free survival (DFS)**

(White n= 26, Coloured n= 39, Black n= 4)

DFS/MONTHS	WHITES	COLOURED	BLACKS	TOTAL
1-36	15	12	4	31
36.1-60	8	16	0	24
>60	3	11	0	14
TOTAL	26	39	4	69

Disease free survival for the different race groups is shown in table 7. Due to short follow-up only 14 patients from the study population could probably be reported to be disease free more than 5 years, and none of the black patients was disease free more than 3 years. The disease free survival (>60 months) for the coloured group was approximately 2.5 times that of the white group (white 3/26 =11.5%, coloured 11/39=28.2%)

Tumour size**Table 8****Tumour size distribution with relation to disease relapse**

Tumour size	Frequency	Relapse	percentage
T1	47	6*	12.7
T2	22	6#	27.3
Total	69	12	17.4

* 4 patients had local recurrence and 2 had distant metastases.

3 patients had local recurrence and 3 had distant metastases.

Table 9**Tumour size distribution with relation to overall survival**

SURVIVAL/MONTHS	T1	T2	TOTAL
1-36	14	9	23
36.1-60	24	7	31
> 60	9	6	15
TOTAL	47	22	69

The influence of tumour size on relapse rate is shown in table 8. The majority of the study population had small tumours (T1) (47/69) and the relapse rate among them was less than half that among patients with bigger tumour size (T2). However, as shown in table 9, there appears to be an overall survival advantage in the T2 group over T1 group with twice as many patients surviving > 5 years (T1: 9/47= 14.1%, T2: 6/22 = 27.3%)

This is illustrated in Fig.1 where survival curves represent the overall survival for the whole study population, in addition to overall survival for the patients with local disease relapse and the patients with T1 and T2 tumour size.

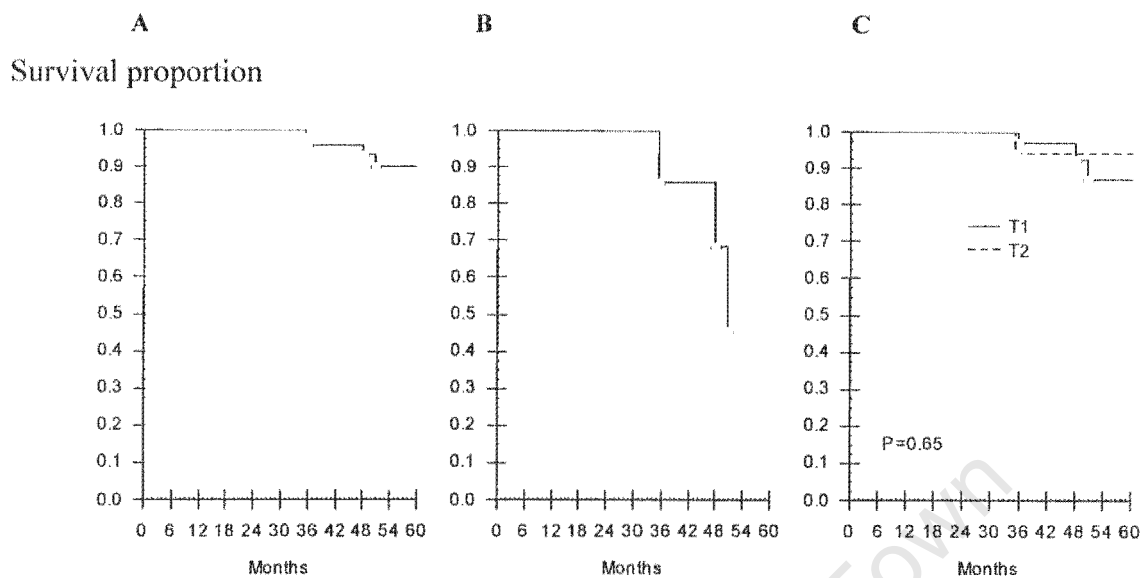


Fig 1: Kaplan-Meier survival probabilities for (A) the whole group, (B) for patients who developed disease relapse, and (C) when patients were stratified by tumour size.

It is not possible to calculate the median survival from the data (the survival curve is well above the 50% cumulative proportion surviving), however, here, by end of the study period the survival proportion is more than 90% at 5 year-follow up. We should note that breast cancer is a disease that needs a lengthy follow-up to be able to calculate the median survival for it. Nevertheless, treatment would appear to remain effective for both groups.

The effect of the disease relapse can be noticed from curve B, where it was not possible to calculate the 5-year survival for the patients with relapse because the curve did not reach this point. On the other hand the effect of the different tumour size did not show any significant difference during the first 4 years but the curves start to move apart after this point in time favouring the big tumour size (T2) in curve C.

Disease free survival curves representing the disease free survival for the whole study population are shown in Fig.2, in addition to disease free survival for the patients with T1 tumour size and the patients with T2 tumour size.

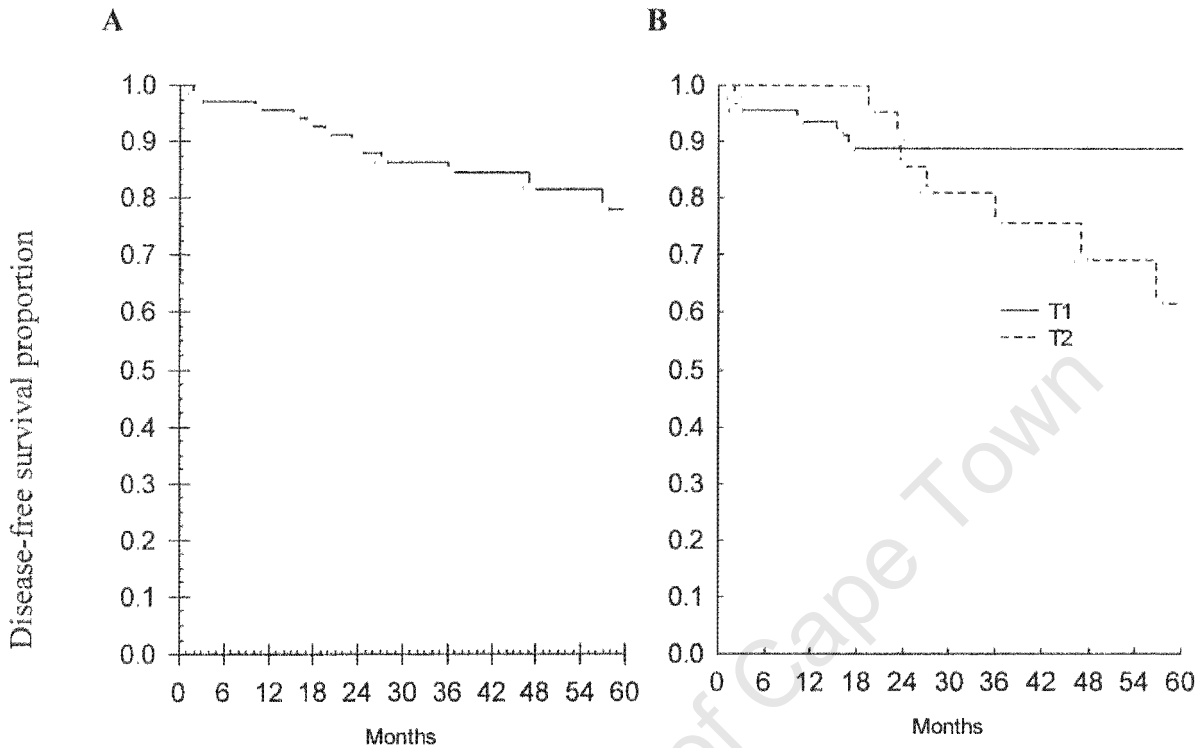


Fig 2: Kaplan-Meier survival disease-free probabilities for (A) the whole group, and (B) when patients were stratified by tumour size.

The 5 years disease free survival calculated from diagram 2 (A) was found to be more than 75% but the short duration of follow up and the small population sample should be noted.

The curves in diagram 2 (B) which represents different tumour sizes, started to show remarkable difference after 2 years of follow up favouring small tumour size (T1). Again the short duration of follow up and the small population sample should be noted.

Tumour grade

Fig.3

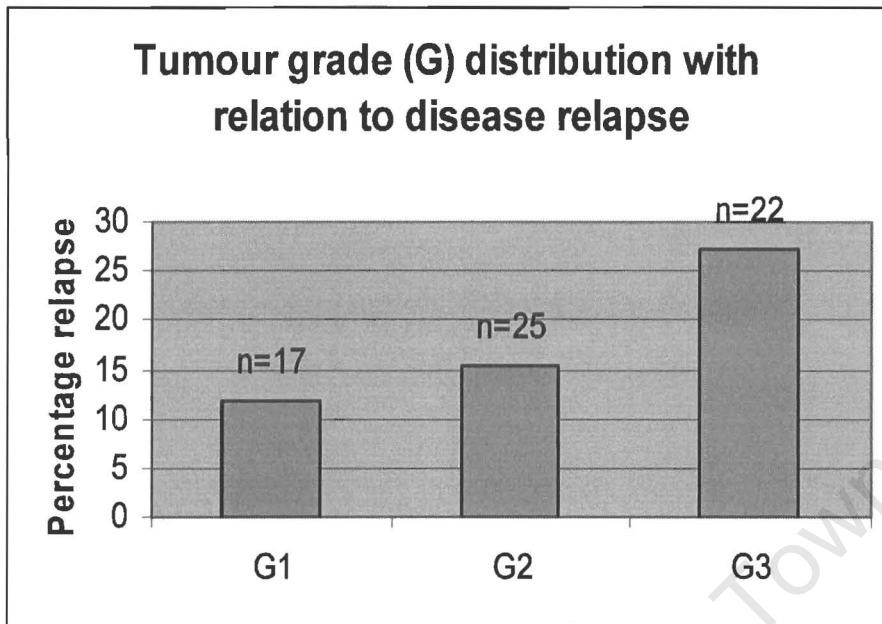


Figure 3 indicates that there is progressive increase in relapse rate as grade is increased from G1 to G3 (G1 =11.8%, G2=15.4% and G3=27.3%).

Table 10

Tumour grade (G) distribution with relation to overall survival

SURVIVAL/MONTHS	G1	G2	G3	TOTAL
1-48	9	15	12	36
> 48	8	11	10	29
TOTAL	17	26	22	65

Table 10 indicates that almost same percentage of patients with grades 1, 2 and 3 tumour differentiations survived for more than 4 years at the time of assessment for the study. (G1:8/17=47.1%, G2: 11/26= 42.3% and G3: 10/22 =45.6%).

Kaplan Meier survival analysis was not found to be meaningful when patients were stratified according to grade as all patients with grade 1 cancer were alive by end of the study.

Table 11
Tumour grade distribution with relation to
disease-free survival (DFS)

DFS/MONTHS	G1	G2	G3	TOTAL
1-36	5	11	14	31
36.1-60	7	8	7	22
>60	5	7	1	13
TOTAL	17	26	22	65

Table 11 indicates that only one patient with poorly differentiated (G3) tumour was followed up and survived for more than 5 years (1/22).

Fig. 4

Kaplan Meier disease free survival probability when patients were stratified according to tumour's grade

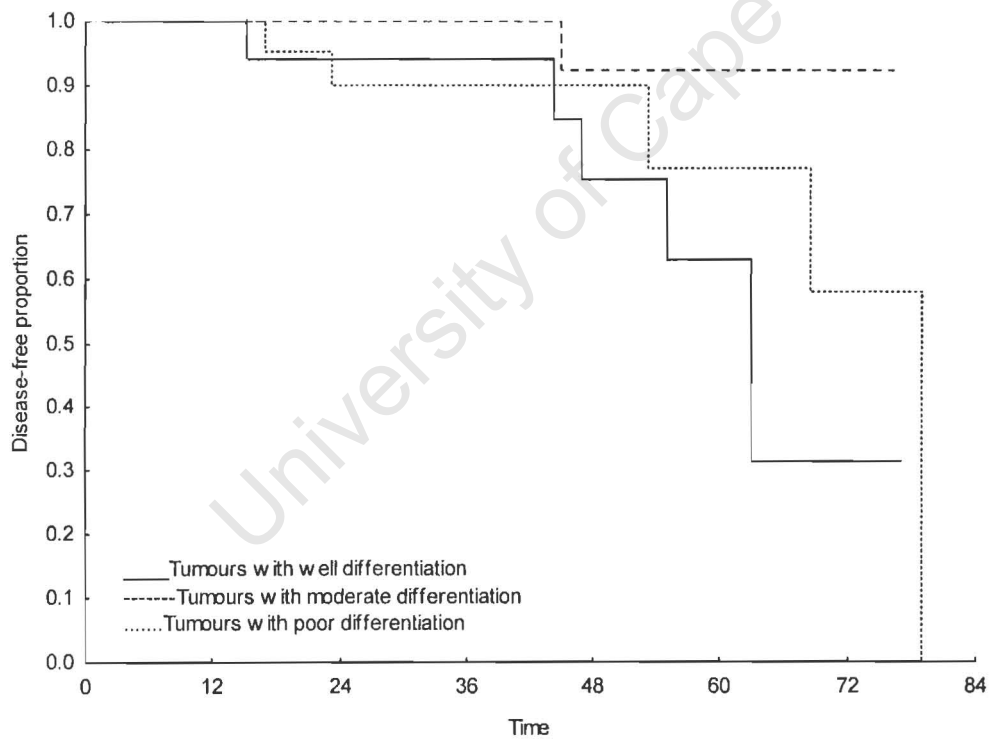


Fig.4 Shows Kaplan Meier analysis of disease free survival/ months when patients were stratified according to grade. The analysis showed differences in the disease free survival patterns which were become marked after the first 4 years favouring grade 1 and 2.

Lymph nodes

Among the population of the study, the total number of dissected lymph nodes ranges from 3 to 21. There were only 32 patients who had 10 or more lymph nodes dissected, while the remaining group had between 3 and 9 dissected.

Table 12

Involved lymph node distribution among the study population

INVOLVED LYMPH NODES	FREQUENCY	PERCENTAGE
0	55	79.7
1	4	5.8
2	3	4.3
6	2	2.9
TOTAL	64	92.8
MISSING	5	7.2
TOTAL	69	100.0

Table 12 indicates that the majority of the patients had no lymph node involvement (79.7%) and the number of lymph nodes involved ranged between 1 and 6.

Fig. 5

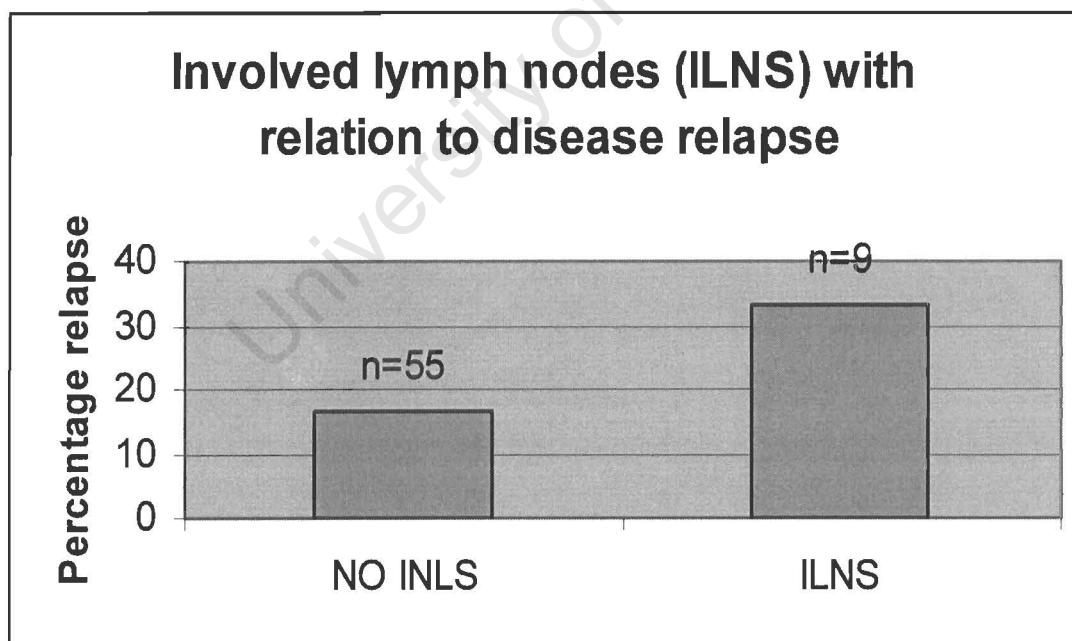


Fig.5 illustrates the influence of lymph node involvement on disease relapse. Disease relapse was twice as much among patients with nodal involvement. (33.3% versus 16.4%)

Resection margin

Of the 9 patients with positive surgical margins, 3 had disease relapse: two of them had local recurrence and one, distant metastases. Among patients with negative surgical margins (56 patients), 9 had relapsed. The percentage relapse is twice as much among patients with positive resection margin (33.3% versus 16.1%). .

Fig.6

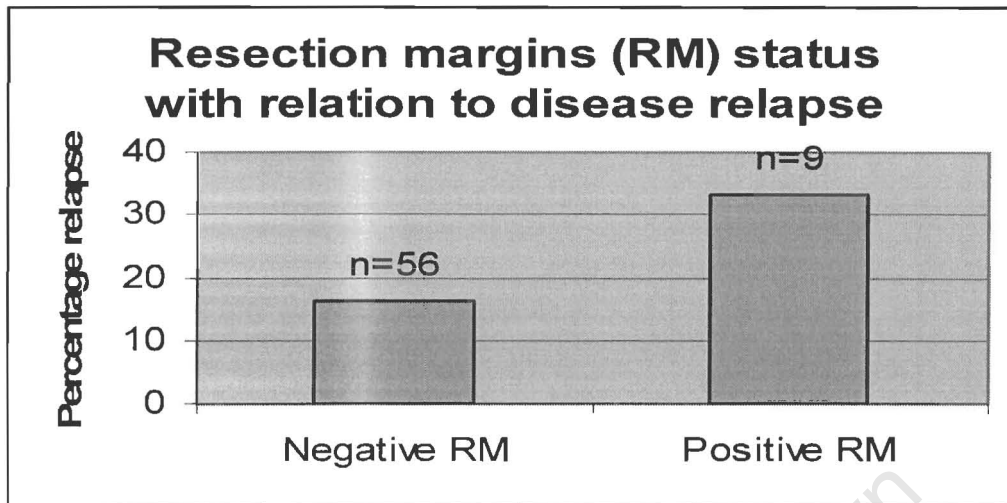


Fig.6 illustrates the influence of the status of resection margin on disease relapse. This result has been reflected in the patterns of the disease free survival curves in fig.7 when Kaplan Meier analysis was performed according to RM.

Fig.7

Kaplan Meier disease free survival probability when patients were stratified according to RM.

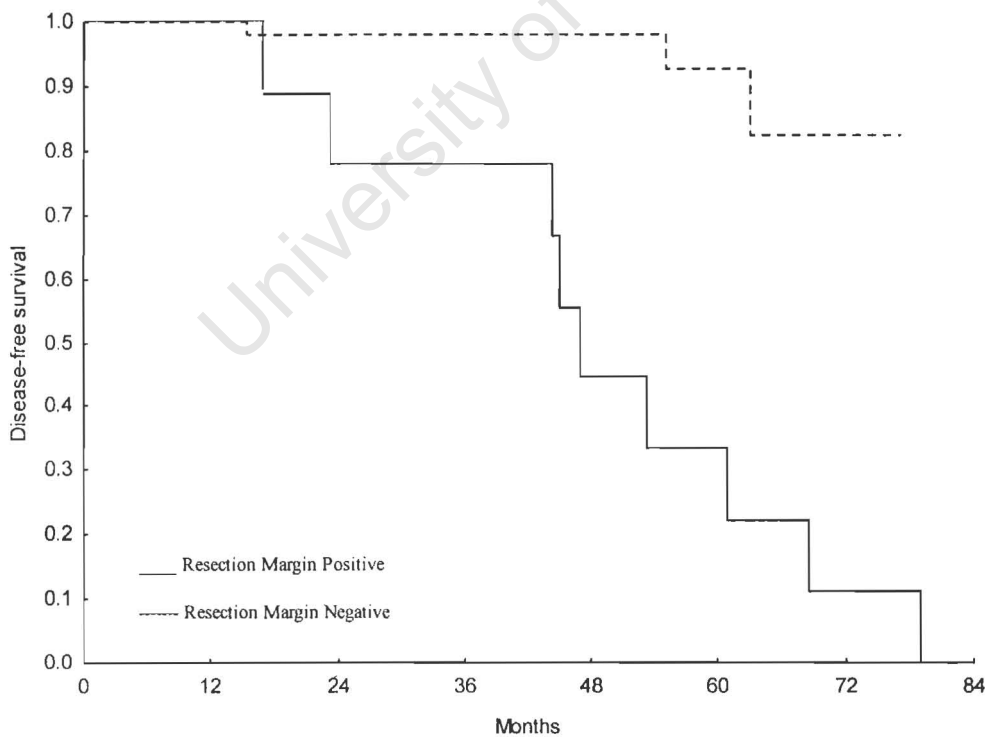
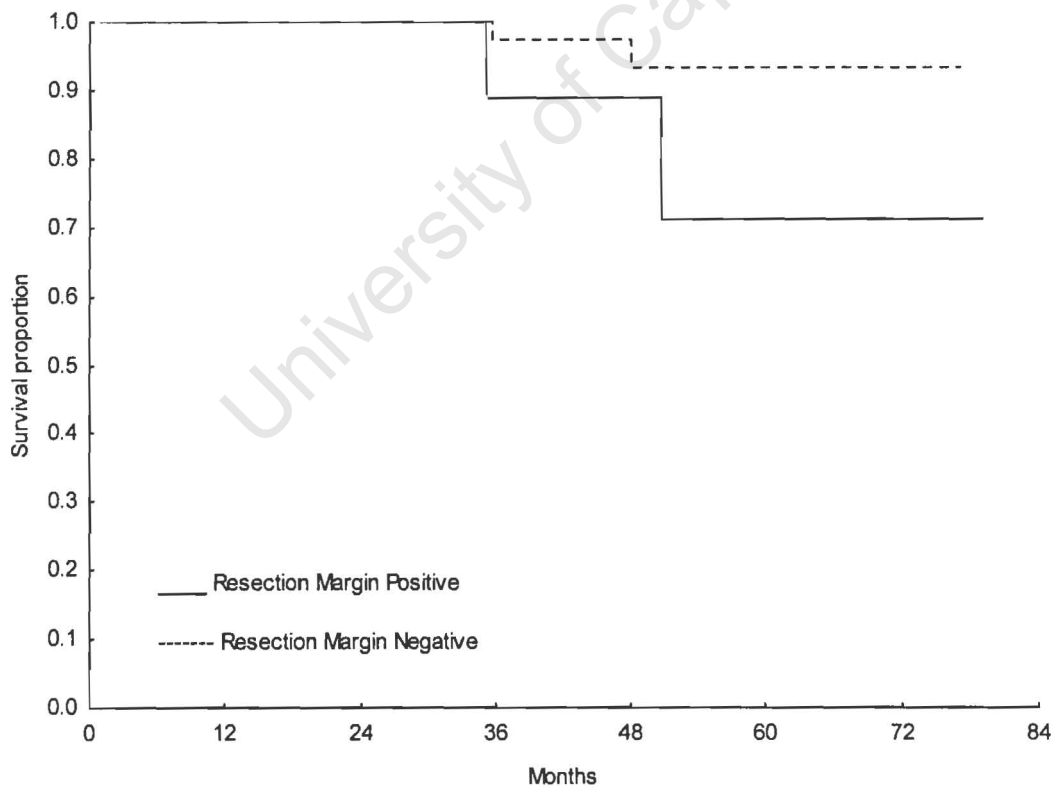


Table 13
Resection margin (RM) status distribution with relation
to overall survival

SURVIVAL/MONTHS	POSITIVE RM	NEGATIVE RM	TOTAL
< 48	4	33	37
> or = 48	5	23	28
TOTAL	9	56	65

Table 13 indicates that only 5 patients with positive RM were followed up and survived the period of 4 years or more ($5/9 = 55.5\%$) while 23 from those with negative RM survived the same period ($23/56 = 41.1\%$). The difference (55.5% versus 41.1%) has been reflected again in the overall survival patterns when Kaplan Meier analysis was performed according to RM.

Fig 8
Kaplan Meier overall survival probability when patients were
stratified according to RM.



Estrogen receptor status

Among patients with positive ER status, there were 5 (out of 39) diagnosed with disease relapse. The same number of relapses was observed in patients who had negative ER status (5/23).

Fig.9

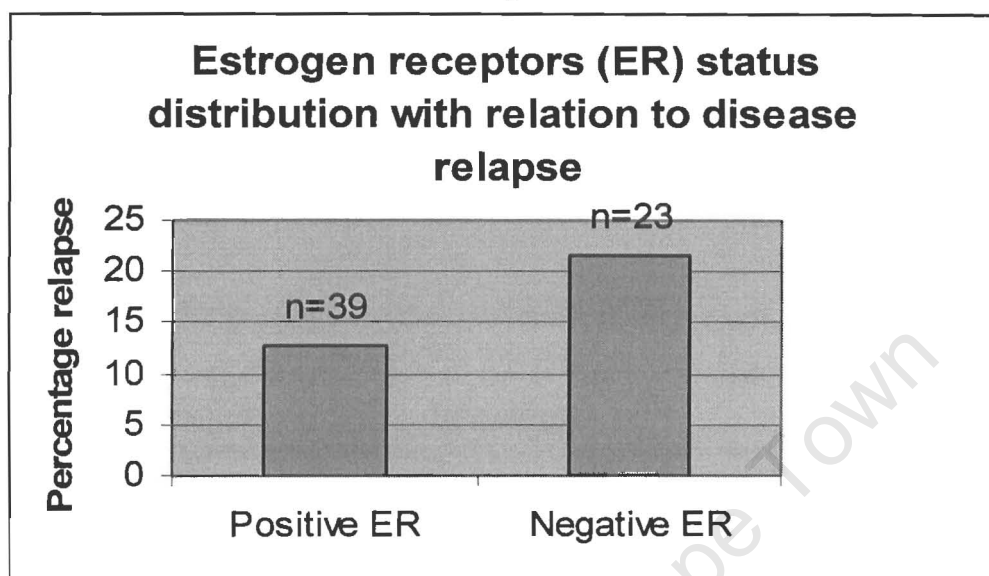


Fig. 9 indicates the high relapse rate associated with negative estrogen receptor status (21.7% versus 12.8%).

Table 14

Estrogen receptors (ER) status distribution with relation to overall survival

SURVIVAL/MONTHS	ER POSITIVE	ER NEGATIVE	TOTAL
< 48	18	15	33
> or = 48	21	8	29
TOTAL	39	23	62

Table 14 indicates that there was a relatively high percentage of patients with ER positive tumour who had been followed up and survived the period of 4 years or more (21/39 =53.8% versus 8/23 =34.8%) but the Kaplan Meier analysis for overall survival according to ER in fig. 10 shows very little difference possibly due to small number of the patients and short follow up duration.

Fig. 10

Kaplan Meier overall survival probability when patients were stratified according to ER.

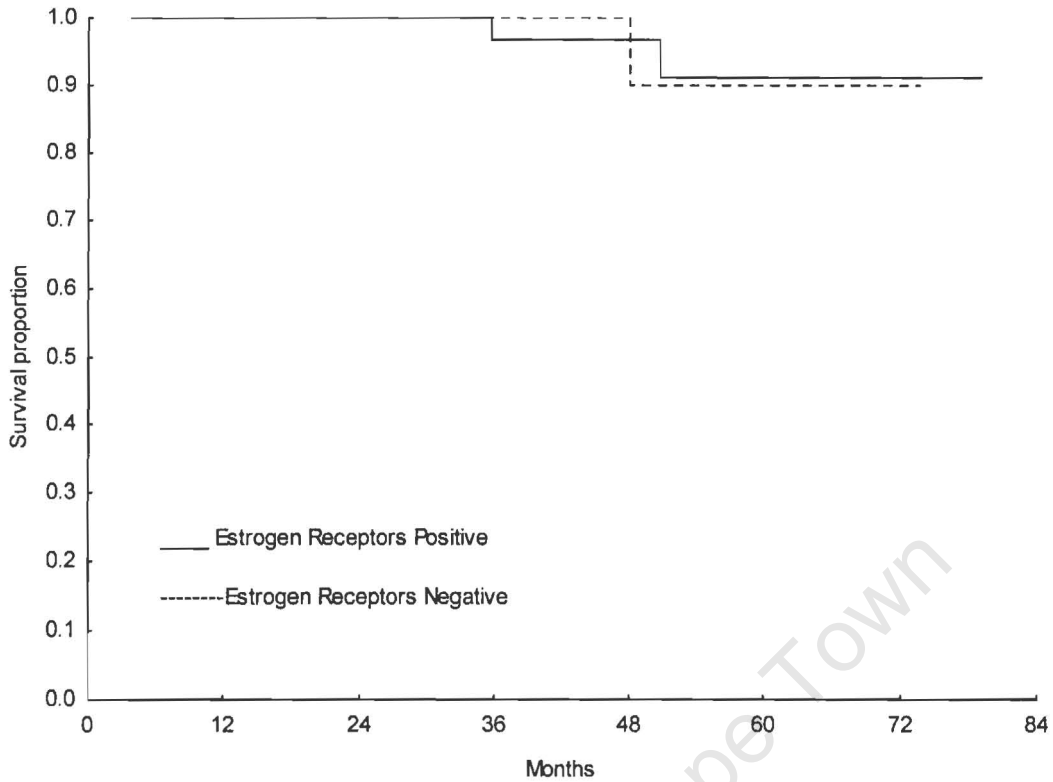
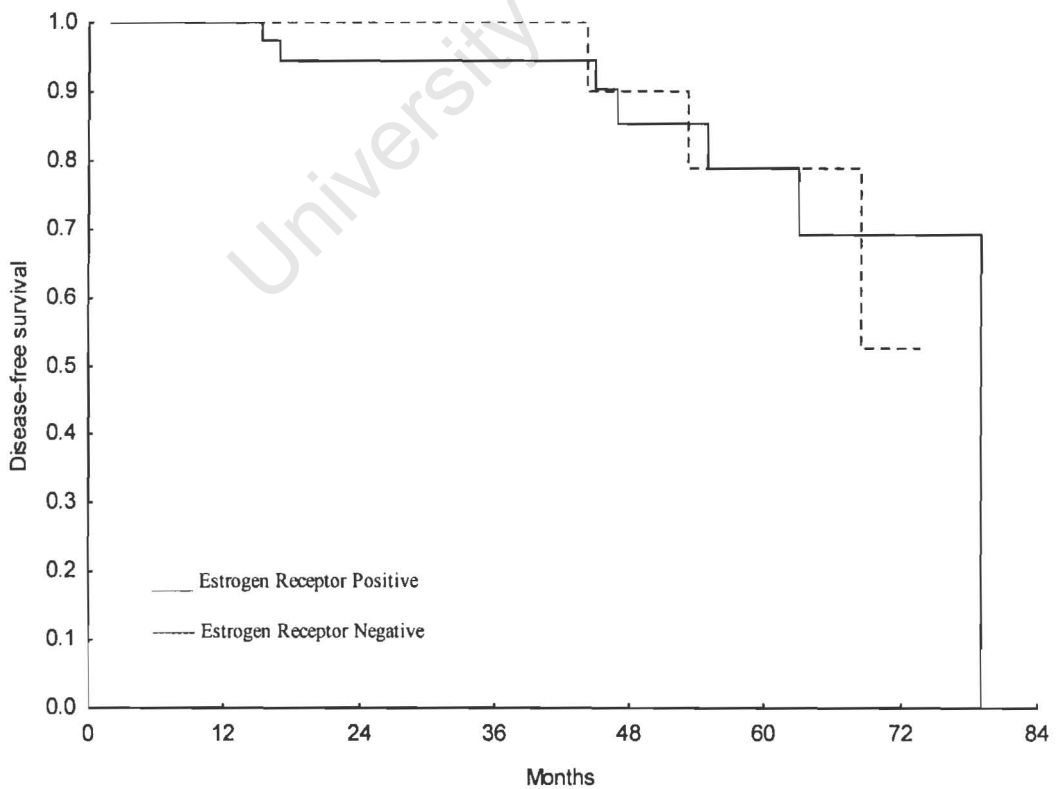


Fig. 11

Kaplan Meier disease free survival probability when patients were stratified according to ER.



Among the study population there was a relatively high percentage of patients with ER positive tumour who were disease free for 3 years or more at the time

of assessment for the study (26/39 =66.6 % versus 10/23=43.5% for ER negative) but the Kaplan Meier graph on Fig. 11 for the disease free survival according to ER did not reflect this result possibly due to small number of the patients and short follow up duration.

Lympho-vascular invasion (VI) status

Table 15

Lympho-vascular invasion (VI) status distribution with relation to disease relapse

VI STATUS	FREQUENCY OF RELAPSE	PERCENTAGE
POSITIVE (n=10)	3	30%
NEGATIVE (n=45)	8	17.8%
MISSING (n=14)	1	7.1%
TOTAL	12	17.4%

Table 15 shows the influence of vascular invasion on disease relapse. Of the patients with positive VI 30% relapsed versus 17.8% for patients with negative VI. The total relapse rate for the patients with negative VI was similar to overall relapse rate for the study population and contributed the largest portion of them.

The results presented thus far describe the effect of individual variables on the chance of relapse, overall survival and disease free survival. In addition Chi squared analysis was performed to determine the statistical significance of each variable on OS and DFS. Results of this analysis are summarized in Table 17. Most variables were not found to significantly affect outcome. However local disease recurrence was found to negatively affect OS with a high level of significance (p = 0.0008). Race had a marginally significant effect on DFS (p = 0.051).

Table 16

Statistical significance of the effect of individual variables on overall (OS) and disease-free (DFS) survivals (X² Test)

Variable	Effect on DFS	Effect on OS
Age	*N.S (0.063)	N.S (0.663)
Race	::M.S (0.051)	N.S (0.151)
Tumour size	N.S (0.132)	N.S (0.417)
Tumour grade	N.S (0.114)	N.S (0.138)
Lymph node involvement	N.S (0.765)	N.S (0.598)
Total number of lymph nodes dissected	N.S (0.498)	N.S (0.231)
Resection margin involvement	N.S (0.817)	N.S (0.781)
Estrogen receptors status	N.S (0.151)	N.S (0.717)
Vascular invasion status	N.S (0.600)	N.S (0.273)
Local disease recurrence		S (0.0008)

* N.S: not significant. :: M S: Marginal significance. S: Significant. Numbers between brackets indicate p- value

Chapter 4

4.1 Introduction to discussion

In South Africa there is no official (governmental) national cancer registry, nor is there an accurate one. None the less, via a voluntary countrywide network of all private and public histology, haematology and cytology laboratories, the National Cancer Registry (NCR) has collected information on histologically diagnosed cancer. It has compiled a summary of the minimal incidence of cancer for 1993, 1994 and 1995 and lately has published more recent summaries for 1996 and 1997. Together these act as a source for cancer control programmes and related activities (7, 8).

In the report on 1996-97 (8), the minimal lifetime risk (LR) for breast cancer was 1 in 57 in black females, 1 in 13 in Asian, and 1 in 16 in white and coloured females. The overall LR was 1 in 31 (it was 1 in 36 in the 1995 report). The most common cancer in Asian females is breast cancer, while it is the second-most occurring cancer in white, black and coloured females. The recently published data of 1997 indicated that breast cancer was the second leading cancer in females although it was the most common of all cancers when all racial groups were viewed together (16.6%) in the 1995 report (7, 8).

Between 1993 and 1995, an annual average of 3,785 new cases of breast cancer was reported to the NCR, the crude incidence rate being 18.5%. In 1996-97, the annual average became 4,624 new cases, which constitutes an average of 17% of all female cancers per year.

Breast cancer is less common in black females than in white and coloured (7, 8). The age-standardised rate (ASR) of 11.3/100,000 in 1995 or 15.8/100,000 in 1997 in South Africa is similar to rates from central Africa (Harare ASR= 20.4/100,000 and Kampala 16.4/100,000). Breast cancer is even rarer in Gambia (3.4/100,000). Rates for black females in the USA are, however, high (65/100,000) in comparison to those among black females in African countries (7, 8).

Among whites, the incidence rate in South Africa of 70/100,000 is comparable to those from developed countries, like the UK (56/100,000) or the USA (89/100,000). This rate dropped somewhat in the 1997 data to 55.5/100,000, as a result of coloured and white females being combined in one group (7, 8).

There is no agreed policy in South Africa with regards to screening for breast cancer, by using regular mammograms, as in the USA and Britain. (7) Lack of resources, existence of more pressing health problems, like AIDS, and the need to expand primary health care facilities could be possible factors for the lack of a systematic breast screening programme. This could partially explain, beside other factors, such as cultural, religious and economic ones, the high rate of advanced cancer of the breast existing among South African women with this type of cancer. Moreover, this could perhaps have been the cause for late referrals, necessitating more extensive surgery rather than the breast conservation therapy suitable for early-detected cancers.

It is well-established that breast conservation therapy is a safe and effective treatment for early invasive breast cancer (9, 10, 11). Prospective randomised trials have demonstrated no statistical difference in overall survival between patients treated with modified radical mastectomy or with breast conservation treatment (9, 10, 11). Several factors, however, have been associated with high loco-regional failure after breast conservation treatment. These include large tumour size, multi-centricity, extensive intra-ductal component, lymphovascular invasion and the young age of a patient (12).

Breast conservation therapy has been defined as local excision of the mass (lumpectomy), axillary nodal dissection and post-operative radiotherapy (12). Sentinel lymph node biopsy would now be considered as possible replacement for axillary node dissection provided the sentinel nodes are negative. According to this definition, 69 of the breast cancer patients who attended Groote Schuur Hospital were found eligible for further analysis (Table 1).

The present study, as previously outlined in the methods, is a retrospective analysis and has all the shortcomings and problems typical of such a study. These problems are due to the fact that data are retrieved rather than recorded as they occur. The data might be obtained from folder review or survey and this can lead to the problem of unrecognized

group differences and bias but the study remains relevant, however, since it deals with a group of patients who presented early in the course of their disease. Careful study of these patients will further our understanding of several prognostic factors that may be associated with the disease at this stage, in this area, in comparison with the rest of the world. The other important aspect of this study is that it is, as was stated above, the first to be conducted among those patients who have attended the 'Combined' (multidisciplinary) Breast Clinic at Groote Schuur Hospital in South Africa.

In the following sections, the results of this study are discussed and compared to international data on the same subject. The discussion then deals with the main objectives of the study which are to assess the treatment outcome in terms of disease and overall survival and to find factors affecting them, taking into consideration the two sets of variables previously mentioned, namely, patient- and tumour-related variables.

4.2 Patient-Related variables

4.2.1 Age

Age is one of the most important factors that affects the incidence rate of breast cancer. It has been noted for many years that the incidence of breast cancer increases steadily with increasing age. It is exceedingly rare before 20. The incidence increases between 25 and 50 years of age, after which it continues to increase at a somewhat slower rate. The median age at diagnosis in the USA is 64 years. In other parts of the world, where life expectancy may be shorter, the median age at which breast cancer develops is 10 to 15 years younger (13). This is supported by the median age in this study of 51 years, but as the patients were not necessarily representative of the whole population and the group was very small this is not definite proof that the median age in South Africa is younger than in the USA.

In this study, the patients were divided into 3 groups by age (Table 1). It was noted from analysing these groups of patients (Table 2) that the majority of them were in the third group (Age ≥ 50) and that this disease is rare before the age of 40, which reflects the natural history of the disease that peaks during the post-menopausal period in females. A

higher proportion of black patients was expected to be young because of the population (age distribution) curves but this has not been found, possibly because of the small number of black patients in the study. In addition, the data suggests that the disease characteristics and disease outcomes (Table 2) improve with advancing age. This is evident from reviewing the younger age group which showed the worst outcome of treatment among the study population. Five patients had failed the treatment, which is a high rate among such a small population group. This correlates with the traditionally held views that older postmenopausal women with breast cancer have a more indolent course of disease, by contrast with young patients who have a more aggressive one. However, the extensive literature on this issue is inconsistent, and the cumulative recent data suggests that this particular patient variable is not a very important prognostic factor, particularly when other, more significant, tumour characteristics are taken into account (13). Yet, on considering the results of many studies which have demonstrated a higher rate of local and regional relapse in pre-menopausal women treated with breast conservation treatment, particularly those under 35 years of age (9,12, 14, 15,16), and surveying the large trial conducted by the European Organization for Research and Treatment of Cancer (EORTC), which demonstrated an increased local recurrence rate in young patients (17), it appears that, although several factors, including patient characteristics, tumour, treatment factors and age, were found which might explain the high local recurrence rate in the younger patients, age itself – together with the boost radiation dose in the EORTC trial – was the only factor that was independently related to local control. In the case of the Groote Schuur study, the majority of the patients received similar radiation doses to the whole breast, with electron boost to the tumour bed, which excluded the effect of radiation boost.

A review of the literature reveals, by contrast, that there are authors who have reported no difference in local and regional relapse-free survival and overall survival for young patients with cancer of the breast (12, 18). Certain authors even report that old age is noted to be a negative prognostic factor (19). This indicates clearly the inconsistency of the literature about the effect of age. In addition to the above-mentioned controversy, there is still no general consensus about the definition of ‘young age’, which varies from <30 to < 50 years.

As well as demonstrating that the median age at which breast cancer develops in Groote Schuur's state hospital population is about 15 years younger than the published age for the western population, the study also demonstrates that age plays an important role in determining the outcome of the breast conservation therapy. This is evident from the failure rate (Table 2) reported in the young age group (41.6%). This point will be further examined in association with other risk factors.

The present study includes few black females of all age groups (Table 2), despite the fact that they represent the majority of the population in South Africa, a fact also reflected in the NCR reports (the rate was 13.4% in the 1995 report and 11.02% in the 1997 report (7, 8)). These rates among the black community were the lowest of all race groups. Although a conclusion on this issue could not be reached, due to the nature of this study, this may reflect the socio-economic standards, local traditional beliefs, population distribution and lack of health awareness, all of which could mean that black females with breast cancer present late, or refuse treatment.

Tables 3 and 4 indicate the effect of age on overall and disease free survival respectively. Overall survival was similar for both the youngest (≤ 40) and oldest (≥ 50) groups which showed a 50% 4 years survival. The intermediate group ($>40 <50$) had a lower 4 year survival close to 30%. The youngest group showed the worst 5 year DFS followed by the oldest group while the intermediate group had the best DFS. However, patients in groups 2 and 3 (Age $>40 <50$ and ≥ 50 respectively) did considerably better having DFS of 35 % and 20% respectively. This reflects the importance of age on the DFS of the patients in question and compares favourably with the studies that showed good prognosis among older patients (12, 14, 15). However, the effect of age on overall and disease-free survivals was found to be not significant statistically in this study (Table 16).

4.2.2 Race

Categorising populations and comparing patterns of disease between different racial groups can be a useful technique for identifying potential causes of disease. In this context, ethnicity is a valid social concept that may be used to investigate the consequences of self-ascribed identity on health. However, it is often used as a euphemism for race, even though there are no genetically distinct human subspecies that can be identified and categorised as discrete races. Indeed, race as a biological concept

has no validity in human biology. Despite this, categories based on ethnicity and population group continue to be used in health research, reinforcing the perception that differences in disease patterns between different racial, ethnic and population groups are the results of inherent biological characteristics (20).

The rates of developing and dying from breast cancer differ among ethnic groups. Some of the reasons documented for these divergences include possible differences in specific risk factors (21, 22, 23, 24).

A study conducted by Kotwall et al (2003) (25) among African-American women, demonstrated that they have a higher mortality rate from breast cancer than Caucasians. It was concluded that prognostic factors are related to race among African-American women who presented at an earlier age and more often with palpable disease. More importantly, the author indicated that those patients presented significantly more often with tumours which were of a higher-grade, hormone receptor-negative, with higher proliferation indices and with node positive disease. He concluded, moreover, that these findings might explain the higher breast cancer mortality rate in African-American women (25).

Another effect of race concerns the difference in breast cancer awareness and screening rates that exists among the different races. The latter could be due to lack of awareness about mammography, cost of health insurance and lack of access to screening facilities, all of which are applicable to the disadvantaged groups in South Africa (26). As previously mentioned, no screening programme for South African women, generally, exists.

The study population in this section has been divided into 3 groups. These accord with the ethnic groups that were previously adopted by health authorities in South Africa, since they were thought to be of use for this study. The three ethnic groups that occur among the study population are: white, coloured (mixed race), and black ethnic groups. No Asian patients were found among the population of this study. Of the patients reviewed, the majority of this group of breast cancer patients was found to belong to the coloured community (56.5%), followed by the white community (37.7%). The black community (5.8%) was found to be the least represented group among the study

population (Table 1). These findings may reflect the composition of the population serviced by Groote Schuur, and pertain to the period covered by the study. The Hospital provides for part of the population of the Western Cape Province. At the time of the study, the population served by the hospital was composed mainly of coloured and white communities. A few patients from other areas of South Africa were also seen. This population composition, it should be noted in passing, is changing rapidly, because of a constant influx of black people from other provinces and the African countries to the North, a factor that could impact not only on the Groote Schuur population, but also on future treatment of, and research into, breast cancer in South Africa.

Findings in the present study may also reflect other factors, both social and economic, but mainly highlight that of the differing levels of awareness regarding breast cancer among the different racial groups (26). In this regard, the black community may be at a disadvantage and the low number of patients who underwent breast conservation could be explained by the fact that most of the black patients presented with advanced stages of disease, where only total mastectomy, if any surgery, could be offered (21, 27).

Among the twelve patients who failed treatment, 6 were white (23.1% of all white patients), 5 were coloured (12.8% of all coloured patients) and only one was black (25% of all black patients) (Table 5). The sample size in the black group was too small to draw any relevant conclusions as to why the highest rate of recurrence existed among them. Recurrence rate of the other two groups seems to fall within the international reported rates of recurrence and there is no obvious effect of race in that instance although the recurrence rate among white patients was nearly twice that among coloured patients (9, 10). The effect of race on overall survival (Table 6) was found to be not statistically significant (Table 16).

The disease free survival (>60 months) for the coloured group was approximately 2.5 times that of the white group (white $3/26 = 11.5\%$, coloured $11/39 = 28.2\%$) and none of the black patients was disease free more than 3 years (Table 7). The effect of race on DFS was marginal (Table 16). Although the short follow up duration of Groote Schuur's study population may not allow the effect of race on the disease free and overall survival to be properly assessed, this could indicate some effect of race on disease-free survival and correlates with the results of the Kotwall et al study previously mentioned. These

investigators studied the prognostic indices in relation to race and found that African-American women have a higher mortality rate from breast cancer than Caucasians and they concluded that prognostic factors are related to race (25). In addition, this is in agreement with the review by Murray (2004) (28), on the same subject. This indicates that the difference in survival noted between race groups may be associated with many other factors among each group and that race is very unlikely to have an independent effect on survival.

From this point, the discussion deals with tumour-related variables.

4.3 Tumour Characteristics

The clinical advances that have occurred during the last twenty years, both in the diagnosis of the ever-increasing numbers of early breast cancer in patients and in their management, have emphasised the need for an acknowledgement of the prognostic and predictive factors used in selecting the most appropriate management for patients. (Prognostic factors are measurements available at diagnosis or time of surgery that, in the absence of adjuvant therapy, are associated with recurrence rate, death rate, or other clinical outcomes; predictive factors are measurements associated with the degree of response to a specific therapy.)

Such factors may be used to identify those patients most likely to have recurrences after removal of their primary tumour from those at low risk of recurrence. Moreover, they may be used to differentiate between those likely to benefit from adjuvant therapy and those whose form of the disease is likely to be resistant to treatment.

In the past, the one factor most consistently used in the majority of centers world-wide as a guide to therapy was that of loco-regional lymph-node status, which was also the case for patient stratification in clinical trials (29). Great store has been placed in the development of more accurate and rapid methods of immuno-histochemical and fluorescent insitu methodologies for the characterisation of oncogenes, suppressor genes and related proteins.

Serum and plasma assays for growth factors are also of interest, in addition to the more traditional tumour markers of CA 15-3 and CEA (carcino-embryonic antigen) for determining prognosis and response to therapy. Obviously, detection of estrogen and progesterone receptors (ER and PR) in tumours has led the way for the integration of molecular markers into clinical decisions regarding prognosis and response to therapy (30).

Certain tumour characteristics now assessed routinely before treatment recommendations are made in managing breast cancer patients are derived from studying the morphological patterns of the excised tumour and axillary nodes. These characteristics are used as prognostic or predictive factors. The standard factors here are lymph node status, tumour size, histological grade, histological type, nuclear grade, and estrogen and progesterone receptor status (31). Her 2neu is now considered by many as a standard factor but it was not available at Groote Schuur Hospital at the time of conducting this study.

These tests of the standard factors are performed and accepted internationally and most centers are using them routinely in selecting appropriate management for breast cancer patients. Other tests and more sophisticated studies (e.g., characterisation of oncogenes, suppressor genes and related proteins) are still not widely available in most centers, due to the financial expense involved and lack of experience. Gene microarrays are being tested and may become very important in prognosis and prediction of response to treatment. In South Africa, although some centers have acquired and utilised sophisticated tests, the majority still depend entirely on the traditional prognostic and predictive factors.

At the Multidisciplinary Breast Clinic at Groote Schuur, the adjuvant treatment decision is usually made after reviewing the histopathology report, in addition to other relevant clinical factors concerning the patient (e.g., biological age). Besides this, consideration is given to the patient's preference. The usual prognostic and predictive factors that have been used extensively are tumour size, tumour grade, status of the resection margins, status of axillary lymph nodes, lymphovascular invasion and estrogen receptor status.

A brief outline of the importance of the available prognostic and predictive factors for patients attending the Multidisciplinary Breast Clinic has been set out above. This is

followed by an analysis of these factors and their effects on the treatment outcome of the study population. Comparison to international published data on the same subject forms part of the discussion.

4.3.1 Traditional prognostic and predictive factors

4.3.1.1 TUMOUR SIZE

In addition to being a determinant for optimal local therapy, tumour size has prognostic significance and affects adjuvant treatment decisions. As the size of the tumour increases, the risk of recurrence or metastasis does as well, for both lymph node-negative and node-positive tumours (32).

In the TNM system of breast cancer staging, where T refers to tumour size, it refers to maximal size of the invasive component as measured on microscopic sections. Size correlates with the number of histologically involved nodes, but has independent prognostic significance. That is to say, within each nodal status, tumour size remains an important prognostic determinant. In a study done by Dimitrakakis et al (1999), tumour size was found to be the only statistically significant and independent prognostic factor for T1 breast cancer patients (33). Michaelson et al (2002) (34) have gone so far as to note the correlation between tumour size and lethality using a simple equation that describes breast carcinoma death as a result of discrete events of cellular spread, which occur with small but definable probabilities.

Most of the patients (68.1%) of the present study population had T1 tumour size, according to the TNM, UICC classification. (Table 1) This may reflect the preference shown by surgeons for operating on small, rather than relatively large tumours, when it comes to breast conservation. Of this group, 12.7% failed treatment, either locally (4 patients) or distantly (2 patients). The patients who had T2 tumours showed a 27.3% relapse rate (3 patients had a local relapse and 3, distant metastases) (Table 8).

It is obvious from the above that there were relatively more treatment failures among patients with larger tumour sizes with a relapse rate as high as twice that occurring among patients with T1 tumour size. This result reflects the importance of tumour size as

a prognostic indicator of treatment outcome; however, as shown in Table 9 and Fig.1(C), there appears to be an overall survival advantage in the T2 group over the T1 group with almost 50% as many patients surviving > 5 years. This could be due to the effect of small population size and short follow up duration because patients with T2 do not generally fare as well as those with T1 tumours.

Although there were relatively more patients with T1 tumour size who enjoyed longer disease-free survival with a low relapse rate (Fig.2 (B)), which serves to corroborate the previously mentioned studies which indicated the importance of tumour size (28, 33, 31, 32), the effect of tumour size as a prognostic indicator for disease-free and overall survivals was found to be statistically not significant (Table 16).

4.3.1.2 TUMOUR GRADE

Tumour grade was generally provided on the relevant pathology reports. Several investigators have demonstrated in individual series that grade is an important prognostic factor (18, 15).

The use of tumour grade, however, has been limited by difficulties with reproducibility. The most widely utilised grading systems are the Scarff-Bloom-Richardson classification and Fisher's nuclear grade, although both systems are used frequently in modified versions (18).

Using these systems, breast cancers have been categorised into three histological grades of malignancy, depending upon the degree of tubular formation, size of cells, size of nuclei, degree of hyperchromatism and number of mitoses. Histological grade 1 breast cancers are recognised as well-differentiated tumours, grade 2 as moderately differentiated, and grade 3 as the most poorly differentiated. A converse classification has become associated with tumour nuclear grade: i.e., nuclear grade 1 is indicative of the most poorly differentiated tumour (29).

The grades of tumours, both histological and nuclear, have been reported to have important prognostic significance, especially in node negative patients. Less than 20% of

such patients having tumours of histological grades 1 or 2 (well to moderately well differentiated) experienced a recurrence by 5 years, as compared with more than 30% of patients with grade 3 tumours (29).

The majority of the patients of the Groote Schuur study population had grades 1 and 2 tumour differentiation (62.3%), (Table 1). Fig.3 indicates that there was a progressive increase in relapse rate as grade was increased from G1 to G3. The difference between these three groups of patients supports the idea of the prognostic importance of tumour grades after breast conservation treatment.

Almost the same percentage of patients with grade 1, 2 and 3 survived for 4 years or more (Table 10) and the statistical significance of tumour grades on overall survival thus was found to be not significant (Table 16).

The effect on disease-free survival was also regarded as not significant (Table 16) although there was only one patient with a poorly differentiated tumour who enjoyed disease free survival of more than 5 years (1/22 (Table 11)). Kaplan Meier' analysis of disease free survival when patients were stratified according to grade showed differences in the disease free survival patterns which became marked after the first 4 years favouring grade 1 and 2 (Fig.4).

These findings, while statistically not significant – a fact which could be attributed to the small population size of this study – supported the previously mentioned studies in indicating the importance of tumour grade as a prognostic factor (18, 15, 29).

4.3.1.3 LYMPH NODE STATUS

The most well established prognostic factor in breast cancer is the number of involved axillary lymph nodes harvested, based on at least a level I and level II axillary dissection, together with a detailed histological evaluation of these nodes (30). (Level I is the inferior level, below the lower edge of the pectoralis major muscle. Level II lies beneath the pectoralis major muscle.)

For the first three-quarters of the 20th century, complete axillary dissection, as part of radical mastectomy, was the standard of care. Long-term follow-up of these patients reveals a substantial cure rate for positive-node patients, before systemic therapy was available, indicating a possible therapeutic value to nodal dissection. This approach also provided good control of the axilla, axillary recurrence after removal of positive nodes being quite low. Even today, in patients with positive nodes, complete axillary clearance as part of a modified radical mastectomy or breast conservation approach with lumpectomy leads to control of the axilla, with complete axillary staging, allowing medical oncologists to tailor their systemic treatment to the total number of nodes involved (35).

An adequate axillary dissection usually contains at least ten lymph nodes. Recovery of a limited number of lymph nodes at axillary dissection could place the patients incorrectly, according to stage, and lead to inadequate treatment. This may result in an increased regional relapse rate and poorer survival (36). As the number of involved lymph nodes increases, so does the relapse rate, while the survival rate decreases. Patients are often grouped according to the number of nodes involved: negative nodes; 1-3 positive nodes; 4-9 positive nodes; and 10 or more positive nodes (12).

Given both the morbidity rate following axillary dissection and controversies about its therapeutic value, many patients are now undergoing either sentinel lymph node biopsy or no axillary surgery whatsoever (30). Several study groups are at present testing the hypothesis that, if the sentinel lymph nodes draining a primary invasive breast cancer are tumour-free, axillary lymph node dissection is contra-indicated for management of this disease process (37, 38). Among these groups are several single- and multi-institution validation studies world-wide that have confirmed that the procedure is 97% to 99% accurate in predicting the status of the axilla, and that it has a low false negative rate (<8%) when performed by surgeons who have had adequate experience with the technique (39).

The majority (55 patients) of the present study population had no lymph node involvement (Table 12). Only 9 patients had involved lymph nodes (range between 1 to 6 lymph nodes). Disease relapse was found to be twice as high among patients with nodal involvement than patients with no nodal involvement (33.3% versus 16.4 %, (Fig.5)). The relative difference between these two groups of patients supports the idea of the

importance of lymph node involvement as a prognostic indicator, following breast conservation treatment, as indicated in many studies (12, 30), but so few patients with nodal involvement were included in this study that this finding cannot be regarded as a definite confirmation.

Among the population of the study, the total number of dissected lymph nodes ranges from 3 to 21. There were only 32 patients who had 10 or more lymph nodes dissected, while the remaining group had between 3 and 9 dissected. These patients could be classified as having received inadequate axillary nodal dissection.

A study by Somner et al (2004) (40) in which the investigators showed that there is a direct correlation between the number of nodes collected and the presence of node metastasis ($p = 0.0005$). Another study, by Voordeckers et al (2004) (41), in which the investigators indicated that the percentage of positive lymph nodes in an axillary lymph node dissection appears to be an important prognostic factor for survival, showed the importance of the total number of lymph nodes.

Despite the fact that some authors have stated that lymph node status is considered the single-most important and reliable correlate of survival (42), neither the total number of dissected lymph nodes nor the presence of involved lymph nodes, among the present study population, revealed any statistical significance in relation to overall and disease-free survival (Table 16).

The total number of lymph nodes dissected from each one of 32 individual patients out of the 69 in this study was not adequate (Total number of dissected lymph nodes < 10). This could be one reason besides the small sample size and short follow up duration that there was no effect on survival. Another outcome of the small number of lymph nodes dissected from patients was that in this group of patients the number of nodes reported as being involved have been incorrect resulting in inadequate adjuvant therapy and prognostication.

4.3.1.4 STATUS OF SURGICAL MARGINS

Patients receiving breast conservation therapy, like mastectomy patients, face a life-long risk of local recurrence due to various factors. To minimise this risk, surgeons have

explored various approaches for examining the surgical margins of the resection specimen. If tumour cells are found at the margin, there is a high probability that residual tumour remains within the surgical cavity (37). Histological examinations are necessary for diagnosis and exact evaluation of the tumour extension. Microscopic evaluation of the resection margin is important for prognostication, as there is a direct correlation between local recurrence and tumour infiltration of the resection margin (43, 44).

A study conducted by Gary Freedman et al (1999) (45) at the Fox Chase Cancer Center, Philadelphia, confirmed that a negative margin identified patients with a very low risk of ipsilateral breast tumour recurrence after conservative surgery and radiation (7% at 10 years). Patients with a close margin were equally at risk of ipsilateral breast tumour recurrence compared with those who had a positive margin, especially if the margin was still positive following a re-excision. However, the association between a positive resection margin and the risk of ipsilateral breast tumour recurrence after conservative surgery and radiation is still controversial (46).

A clear surgical margin is defined in different ways by different authors: for example, in one report, a surgical margin was categorised as negative if all tumour foci are >2mm from the surgical margin. Margins are considered focally close if one or two foci of the tumour are 2mm or less from the post-surgically applied inked margin, and focally positive if one or two foci of the tumour are present at the surgical margin (46). Greater involvement of the margin than this is considered a positive resection margin.

The Multidisciplinary Breast Clinic at Groote Schuur Hospital adopted similar definitions for resection margins to those applied above. The existence of tumour cells at the margin was considered a positive margin. That of cells 3mm or less was considered a close margin. Surgical margins of the study population are consequently evaluated according to these criteria.

The majority (56 patients) of the study population had negative surgical margins; only 9 patients had positive surgical margins; and none was identified as having a close margin (Table 1). Of the 9 patients with positive surgical margins, 3 had disease relapse: two of them had local recurrence and one, distant metastases. This resulted in a 33.3% relapse

rate in this group. In the other group with negative surgical margins (56 patients), only 9 had relapsed, the relapse rate being 16.1%. A simple comparison between these two groups of patients indicates that there is relatively more relapse of disease in patients who had positive surgical margins (Fig.6), a finding consistent with the Freedman study (45) that indicates the effect of the status of surgical margins on the disease outcome. It is also in agreement with the studies mentioned above (37, 44, and 45).

This finding has also been reflected in the patterns of the disease free survival curves in Fig.7 when Kaplan Meier's analysis was performed according to RM. The curves indicate a favorable effect of negative surgical margin on disease free survival.

Table 13 indicates that only 5 patients with positive RM survived the period of 4 years or more ($5/9 = 55.5\%$) while 23 from those with negative resection margins survived the same period ($23/56 = 41.1\%$). The difference (55.5% versus 41.1%) has been reflected again in the overall survival patterns when Kaplan Meier's analysis was performed according to RM. The negative surgical margin status is associated with a favorable outcome in terms of overall survival (Fig.8).

No statistically significant effect could be registered for the significance of the resection margin as a risk factor affecting disease-free and overall survival among the study population (Table 16). The lack of statistical significance may be due to the small sample size and the short follow up duration.

4.3.1.5 ESTROGEN RECEPTOR STATUS

Estrogen is one of the most important factors influencing the development and proliferation of breast cancer cells. Estrogen functions through reaction with estrogen receptors (ER). These receptors act as a ligand-inducible transcription factor and regulate many genes related to cell proliferation. ER status is a useful predictive factor (47). About 60% of ER positive cancers respond well to anti-estrogen therapy (48). Some studies have shown that lack of ER expression is a strong independent factor associated with a higher rate of loco-regional recurrence and have even indicated that this may be of value in selecting a group of patients less suitable for breast conservation surgery (48).

The International Consensus Panel of the eighth St Gallen meeting (2003) modified the risk categories and indicated that the endocrine receptor-absent status was sufficient for the reclassification of an otherwise low risk, node negative, early disease to the category of average risk (49). On the other hand, a number of studies have reported only a weak correlation (30). Furthermore, several investigators have reported that ER status is a prognostic factor for 5-year disease-free survival although, with longer follow-up, the survival curves tend to merge. This suggests that ER status is a measure of proliferative capacity, rather than metastatic potential. Despite this possibility, hormone receptor determination is of critical importance as a predictive factor for hormonal therapy (30).

Other authors have reported worse prognoses associated with ER positivity in certain groups of patients. The International Breast Cancer Study Group (IBCSG), which conducted a study to examine the impact of age and ER status on the prognosis of young patients with breast cancer, divided patients into two groups: Young (<35 years) and Old (>35 years) (50). They reported that in younger patients with ER positive tumours the disease-free survival was significantly worse than in those with ER negative. By contrast, among older patients the disease-free survival was similar, irrespective of ER status (50).

Among the Groote Schuur study population, the majority had ER positive status (39 patients (Table 1)). Among patients with positive ER status, there were 5 (out of 39) diagnosed with disease relapse. The same number of relapses was observed in patients who had negative ER status (out of 23). Fig. 9 indicates that a high relapse rate is associated with negative estrogen receptor status (21.7% versus 12.8%) although the small sample size and short follow up duration may not permit drawing a conclusion on this observation. This finding is corroborated by the previously mentioned studies (47, 48) in so far as it indicates a worse prognostic effect for, and increased risk of disease relapse in those who lack ER expression.

Among the study population, the effect of the different levels of ER status on overall survival was not statistically significant (Table 16) although table 14 indicates that there was a relatively high percentage of patients with ER positive tumour who had survived 4 years or more than those with negative ER status (21/39 =53.8% versus 8/23 =34.8% respectively) at the time of assessment for the study. Also Kaplan Meier's analysis for overall survival according to ER on Fig. 10 shows very little difference between the

curves which could be due again to small number of the patients and short follow up duration.

The effect of ER status on disease free survival was not found to be statistically significant (Table 16) although among study population there was relatively high percentage of patients with ER positive tumours who were disease free for 3 years or more at the time of assessment for the study (26/39 =66.6 % versus 10/23=43.5%). Also Kaplan Meier' analysis on Fig. 11 for the disease free survival according to ER did not reflect this result. This could be explained by the small number of the patients and short follow up duration.

The above-mentioned findings seem to indicate that the expression of ER was a favorable prognostic factor in this study but the small patients numbers and short follow up duration weaken this conclusion. This effect of ER expression supports the findings of the studies (48, 49) that showed a strong correlation between ER expression and good prognosis. The apparent lack of significant effect statistically could be due again to the small study population.

4.3.1.6 LYMPHOVASCULAR INVASION

The use of peritumoural lymphovascular invasion as a prognostic indicator is not well established although the presence of such invasion has been found to be an important prognostic factor in a series of individual studies. This prognostic importance is limited by a lack of consistency in the reporting of vascular invasion. Some authors have shown that knowledge of both lymph node status and the presence or absence of lymphovascular invasion can be used to predict which subset of patients will do extremely well (node negative, with absent lymphovascular invasion) or extremely poorly (node positive, with presence of lymphovascular invasion). They indicate that this combination is most meaningful in patients with 1 to 3 positive lymph nodes (42). Others have noted a strong association between lymphovascular invasion and lymph node metastases (51).

Another study demonstrated that lymphovascular invasion and tumour size were independent predictors of the presence of positive nodes. Thus the decision to perform axillary dissection in T1 breast cancer could be based on the presence of lymphovascular invasion and the size of the primary tumour (52). There is evidence that histological

grade and the presence of lymphovascular invasion may be of little importance in the choice between breast conservation therapy and mastectomy (53).

In the Groote Schuur study population, the majority (45 patients) had no lymphovascular invasion (Table 1). Eight patients from the total of those without invasion, 3 from those with invasion and 1 patient with unknown status had disease relapse (Table 15). The difference in relapse rates reflects the importance of lymphovascular invasion as a prognostic factor for the population of this study. Moreover, it agrees with the studies indicating that lymphovascular invasion correlates with the worst prognosis and an increased rate of loco-regional recurrence (42, 54). However no statistical significance for the effect of lymphovascular invasion on overall and disease-free survival among the study population is recorded (Table 16).

From this point onwards, a discussion of disease relapse and the factors that affect overall and disease-free survival in general is presented.

4.4 Overview of disease relapse and survival in major studies

In 1985, results gathered from 1,843 women entered into NSABP B-06 (32) were reported. Life-table estimates through 5 years of follow-up indicated that treatment by lumpectomy, with or without breast irradiation, resulted in disease-free survival, distant disease-free survival, or overall survival which was no worse than that achieved after total mastectomy. It was concluded that lumpectomy, followed by breast irradiation in all patients, in association with adjuvant chemotherapy in women with positive nodes, is appropriate therapy for patients with tumours less than 4 cm, provided that margins of resected specimens are tumour-free. An update of the findings and conclusion did not change in a published 12 year update of the study (32).

In the same NSABP study, a Cox Regression Model indicated that, regardless of nodal status, three co-variables were significant predictors of the time before breast recurrence: treatment ($p < 0.001$); tumours with poor histological type ($p = 0.02$); and tumours with a maximum pathologic size greater than 2.0 cm ($p = 0.007$). When examined according to nodal status, the same three variables were significant in patients with negative nodes: treatment ($p < 0.001$); histological type ($p = 0.02$); and size ($p < 0.01$). Only two variables, treatment ($p < 0.001$) and tumour nuclear grade ($p = 0.03$), were predictors of breast tumour recurrence in node positive patients (32).

A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG, 1995) (11), in which the investigators reviewed 36 trials of mastectomy versus breast conservation surgery plus radiotherapy, found that the addition of radiotherapy to surgery resulted in a rate of local recurrence that was three times lower than the rate with surgery alone, but there was no significant difference in 10-year survival. Among a total of 17,273 women enrolled in such trials, mortality was 40.3% with radiotherapy and 41.4% without radiotherapy ($p = 0.3$). Radiotherapy was associated with a reduced risk of death due to breast cancer (odds ratio, 0.94; 95% confidence interval, 0.88 to 1.00; $p = 0.03$), which indicates that, after 10 years, there would be about 0 to 5 fewer deaths due to breast cancer per 100 women. However, there was an increased risk of death from other causes (odds ratio, 1.24; 95% confidence interval, 1.09 to 1.42; $p = 0.002$). This, together with the age-specific death rates, implies, after 10 years, a few extra deaths not due to

breast cancer per 100 older women or per 1000 younger women. During the first two decades after diagnosis, the excess in the rate of such deaths that was associated with radiotherapy was much greater among women who were over 60 years of age at randomization (15.3% vs. 11.1% [339 vs. 249 deaths]) than among those under 50 (2.5% vs. 2.0% [62 vs. 49 deaths]).

Breast-conserving surgery involved some risk of recurrence in the remaining tissue, but no significant differences in overall survival at 10 years were found in the studies of mastectomy versus breast-conserving surgery plus radiotherapy (4891 women). More-extensive surgery versus less-extensive surgery (4818 women), or axillary clearance versus radiotherapy as adjuncts to mastectomy (4370 women) revealed no apparent difference in total mortality (22.9 % versus 22.9 %). In 6 studies (involving 3,107 women), in which data on recurrence was available, there were fewer recurrences with mastectomy. The difference, however, was not significant (odds ratio, 0.9 \pm 0.08). (11)

This meta-analysis appeared to confirm the general postulate that local and regional therapies have little impact on overall survival; it did show that breast irradiation, after lumpectomy, significantly decreases the likelihood of a tumour recurrence ($p < 0.000005$). More recent studies have shown a survival benefit for post mastectomy radiotherapy in certain groups of patients (58).

A recent up-date of the study by Bernard Fisher et al (2002) (10), also indicates that breast irradiation decreased the likelihood of a recurrence in the ipsilateral breast in a group of 1,137 post-lumpectomy women, whose surgical specimens had tumour-free margins. The cumulative incidence of a recurrence in the ipsilateral breast 20 years after surgery was 14.3% among the women who underwent irradiation after lumpectomy; and, among those who underwent lumpectomy without irradiation, 39.2% (10).

Recently another 20-year update of their study comparing breast conservation therapy with mastectomy for early breast cancer has been published by Veronesi et al (9). These authors concluded that the long-term survival rate among women who undergo breast-conserving surgery is the same as that among women who undergo radical mastectomy. In this study, the crude cumulative incidence of recurrence between the two groups of patients was 8.8% and 2.3%, respectively, after 20 years of follow up. The probability of recurrent tumour was significantly higher in the group that received breast conserving therapy than in the radical mastectomy group ($P = 0.001$). The study also reported that the

rate of recurrence is highest among women who were 45 years or younger at the time of surgery (9).

4.4.1 Overall Survival

The clinical course of breast cancer is of a more chronic nature than the course of other curable malignancies, such as testicular cancer. Therefore, 5 year and ten year relapse free survival is not equivalent to cure. Statistical cure has been defined on the basis of population survival figures (59, 60, and 61). Thus, it is considered that a group of patients with breast cancer has achieved cure in statistical terms if its survival curve becomes parallel to the survival curve of the general population. For additional precision, these comparisons are made on age-matched populations. The mortality rate of breast cancer increases with clinical and pathological stage (62, 63). In fact, correlations of clinical characteristics with mortality after treatment defined clinical stages in the first place (64). Hazard rates of mortality show that there is an initial peak of several years in hazard rates, followed by a gradual decline over subsequent years (65, 60). The initial peak is higher and narrower for more advanced stages (stages III and IV); most relapses and deaths occur within the first 3–5 years in these groups. In contrast, patients diagnosed with stages I and II evidence a lower peak that tends to occur later. Thus, the survival curves of patients with more advanced or higher-risk breast cancer start to parallel the survival curves of the general population earlier than the survival curves of the earlier breast cancers. Stated in a different way, although high risk patients i.e. those with stage III and IV disease are very likely to die from breast cancer, the outcome of those who survive the early years parallel those of the general population so that this group achieves statistical cure earlier (10–15 years after diagnosis) than lower-risk groups (20–25 years after diagnosis). Because such lengthy follow-up is necessary for complete evaluation of treatment results, some have stated that breast cancer is, in essence, incurable. This argument states that, if follow up is long enough, relapses will occur. The systematic application of combined modality therapies and mammography screening has shown this position to be mistaken (66). Clearly, mammographically diagnosed early breast cancer (stages 0 and I) is associated with excellent survival rates, exceeding 90% at 20 years following surgical resection alone or breast conserving therapies (57). Twenty five years after diagnosis, the survival curves of patients with stages II, III and even IV breast

cancer suggest relapse-free survival plateaux that parallel the survival curves of the general population.

Kaplan Meier's survival analysis of the Groote Schuur study group showed that 88.4% of the study population could achieve the period of 5 years overall survival. Although the study covers only a short period of follow up for a small number of patients, this percentage gives an indication of the high survival rate this group of patients could achieve. This appears to confirm the statements given above about the favorable long term survival rate reported for patients with early breast cancer Fig.1 (A).

4.4.2 Effect of local Recurrence or Distant Metastases on survival

Regardless of the ultimate success or failure of salvage treatment, local failures are often highly traumatic for patients. A large majority of recurrences in the treated breast, following conservative surgery and radiation, are at or near the site of the primary tumour. The risk of this type of recurrence is relatively constant from 2 to 7 years after treatment and then declines (30). It occurs in approximately 8% to 20% of women within 10 years of breast conservation therapy (55). Tumour recrudescence after a breast-preserving surgical procedure can present as the result of residual tumour in the breast or as a completely new lesion (56). Ill-advised selection of patients for breast conservation can lead to high local failure rates.

In order to determine accurately the correct selection of patients for breast conservation therapy, Voogd et al (1999) (53) studied the risk factors for local recurrence and distant disease after breast conserving treatment and mastectomy, by pooling the data of two randomised clinical trials for stage I and II breast cancer patients, trial 10801 of the EORTC and trial 82TM of the Danish Breast Cancer Cooperative Group (DBCCG). These findings indicate that, from the viewpoint of local control, mastectomy may be preferred both for patients ≤ 35 years and for those with extensive intraductal component (EIC). Certainly, if these factors are combined, the high risk of local recurrence, after breast conservation therapy, for patients ≤ 35 years warrants further study to rule out any negative impact of breast conservation on individual patients.

The local recurrence rate of the Groote Schuur study was 10.1%. Fisher et al reported that the local recurrence rate for the NSABP B-06 study was 14.3% but in protocol B-06, 2163 patients underwent randomization at 89 institutions. The patients were accrued between 1976 and 1984 and the initial results were reported in 1985 and updated in 1989. The eligibility assessment included many criteria deemed critical to the outcome of the study. Unfortunately many of these criteria were not found by reviewing the folders of Groote Schuur's patients. Also it should be noted that the Groote Schuur study has much shorter follow up and a very small number of patients so that the local recurrence rate of 10.1% reported and the result that showed 85.7% of the recurrences occurred within the first 5 years after treatment should be read within the context of the study.

In the Groote Schuur study, the association between local recurrence and overall survival may indicate a direct effect of recurrence on overall survival (Table 16).

To detect if there was any effect of local disease relapse on overall survival, Kaplan Meier's survival analysis was performed (Fig.1 (B)). The difference between the survival rates among the group with disease relapse and the whole study population reflects the importance of disease relapse in determining the long term outcome of the breast conservative treatment.

Recurrences at a distance from the primary tumour are more common after longer follow-up (30). A patient's risk of developing distant disease increases with the diagnosis of a breast tumour recurrence. Analysis of the NSABP lumpectomy study (NSABP-B6), using innovative biostatistical approaches to ascertain whether a relationship exists between an ipsilateral breast tumour recurrence and metastases, indicated that such a recurrence is a highly significant predictor of distant metastases (32).

The majority of patients in fact develop distant metastases without a prior local recurrence. This is probably due to the presence of micrometastases undetected at the time of diagnosis, which developed to overt metastases in the course of follow up.

The occurrence of distant metastases in patients who had not had local recurrence in the Groote Schuur study was probably due to the presence of micrometastases undetected at the time of diagnosis.

It is noteworthy that there are relatively more patients without disease relapse who lived for 4 years or more, than patients with disease relapse (49.1% versus 25%). This reinforces the previously mentioned observation concerning the effect of disease relapse on overall survival.

It can also be noted from the comparison between the group with local recurrences and the group with distant metastases, the disease-free survival for both groups is almost similar (33.3 versus 34.4 months), but the former group enjoyed a longer overall survival (60.1 months versus 48.8 months). In addition patients with distant metastases as well as those with local recurrence had relatively more deaths than those with no disease relapse (20%, 28.6% and 1.8% respectively).

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Chapter 5

5.1 Conclusions and Recommendations

5.1.1 Conclusions

Relapse rate reported in this study is 17.4%. The disease relapse was found to be relatively more frequent among patients who were young (≤ 40 years). It was also noticed from the data that the disease characteristics and disease outcomes improve with advancing age. However, the effect of age on overall and disease-free survivals was found to be not significant statistically.

Disease relapse was also found to be relatively more frequent among patients with large tumours, and those with high grade tumours. Actually there was progressive increase of relapse rate as the grade increased from G1 to G3.

Disease relapse was also reported to be twice as high among patients with nodal involvement than in patients with no nodal involvement. Also the study showed that 32 patients out of the whole study population had inadequate axillary nodal dissection which affects their proper classification and management.

The study indicated a relatively high relapse rate associated with positive resection margins, negative estrogen receptor status, and among patients who had lymphovascular invasion.

Chi squared analysis was performed to determine the statistical significance of patient-and tumour- related variables on OS and DFS. Results of this analysis showed that most variables were not found to significantly affect outcome. However local disease recurrence was found to negatively affect OS with a high level of significance and race had a marginally significant effect on DFS.

Kaplan Meier's survival analysis of the Groote Schuur study group was performed and showed that 88.4% of the study population might be expected to survive the

period of 5 years and that the 5 years disease free survival calculated was more than 75%. Although the study covers only a short period of follow up for a small number of patients, these percentages give an indication of the high survival rates this group of patients could achieve.

The present study is a retrospective analysis and has all the shortcomings typical of such a study beside the short follow up duration and small population size, but in general and after considering these factors, the Groote Schuur population seems to differ little from other populations in terms of disease-free survival, overall survival and factors affecting these parameters. The breast conservation therapy outcome, therefore, is similar to outcomes published in the literature, from different study groups in different parts of the world.

5.1.2 Recommendations

A prospective study with a long follow up duration and a large number of patients is recommended.

Findings in the present study may reflect the differing levels of awareness regarding breast cancer among different racial groups as well as differing access to health care. In this regard, the black community may be at a disadvantage and the low number of patients who underwent breast conservation could be explained by the fact that most of the black patients presented with advanced stages of disease, where only total mastectomy could be offered. Research to detect factors behind this low rate and suggest solutions is recommended.

The effect of race in patients with short disease-free survival is marginal. It should not be used as contra-indication for breast conservation treatment among South African women.

Breast conservation treatment, it may be concluded, is a suitable treatment for South African women who present with early breast cancer. Availability of radiation therapy facilities is obviously a major issue that is to be considered before deciding about breast conservation therapy especially in a country with more pressing health and economic problems.

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