FIVE-YEAR REVIEW OF BREAST-CONSERVING THERAPY FOR BREAST CARCINOMA: SURGICAL MARGINS, RE-EXCISION AND LOCAL RECURRENCE IN A SINGLE TERTIARY CENTER

by

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Dedication

To my beloved family ***Rahma, Fahri, Faheem and Fatimah***

Declaration

I, Pueya Mekondjo Nashidengo hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abbreviations

BCT	=	Breast-conserving therapy
DCIS	=	Ductal carcinoma in-situ
NSABP	=	National Surgical Adjuvant Breast and Bowel Project
EORTC	=	European Organization for Research and Treatment of Cancer
EIC	=	Extensive intraductal component
WLE	=	Wide local excision
NHLS	=	National health laboratory services
IDC	=	Infiltrative ductal carcinoma
ILC	=	Infiltrative lobular carcinoma

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Abstract

Background: Breast cancer burden is on the increase in the developing world. Breast-conserving therapy (BCT) is prescribed for early breast cancer. It is the wide local excision of the tumour usually followed by radiation treatment to the breast. It is the mainstay treatment for carefully selected patients with early breast cancer presenting to the Groote Schuur Hospital's Oncology and Endocrine Surgical unit, Cape Town South Africa. There has not been a formal audit to review the outcomes of BCT in the unit.

Objectives: The objective of this study is to determine and analyse the excision margins for all the wide local excisions and the re-excision and local recurrence rates during the study period.

Methods: This is a histopathological and oncology records review of the patients that have undergone BCT in the unit from the 1st of January 2006 until the 31st of December 2010. The University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee granted approval. Data points accrued included patient age, pathological tumour size and nodal status, histological tumour type, oestrogen receptor status, presence of lymphovascular invasion, volume of specimen excised, margin status, management of involved or close margins, completeness of radiotherapy, ipsilateral breast recurrence rate and total duration of follow up.

Results: A total of 192 patients had BCT during the study period. The mean age is 53 years (range 25 to 84 years). A median of 229.5 cm^3 volume of specimen was excised (range 4 cm^3 to 10530 cm^3). Infiltrating ductal carcinoma was the commonest histological type at 79.1%. 42.7% were pT1 tumours, 49.0% pT2 tumours and 2.6 % pT3. The resection margin status are: positive margins rate of 15.1%, 8.3 % close margin (≤ 1 mm), 35.9% 1 – 5 mm, 23.4% 6 – 10 mm and > 10 mm 17.2%. An overall of 26 (13.5%) patients underwent a repeat surgical procedure. 16 (8.3%) had re-excision

and 10 (5.2%) had a mastectomy. Residual tumour was present in 50% of the re-excisions and 63.6% of mastectomies. As per category of the resection margins, 68.9% of patients with positive margins had repeat surgery (48.3% re-excision and 20.6% mastectomy). 31.1% of patients with positive margins did not have repeat surgery despite the indication due to advanced age, loss to follow up or residual tumour on the deep chest wall margin. 80.8% patients completed radiotherapy treatment post breast-conserving surgery. At a median follow up of 60 months (range 1 to 108 months), a total of 11 (6.8%) patients had ipsilateral breast local recurrence. Median time to recurrence is 39 months (range 12 to 106 months).

Conclusion: Positive and close margin re-excision and local recurrence rates in our unit are acceptable and comparable to other units in South Africa and internationally.

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Chapter 1 - Introduction and Literature review

Breast cancer affects 1 million women in the developed world every year [1]. The burden of breast cancer is also on the rise in the developing world. According to Jones [2], it is estimated that 70% of new cancer cases will occur in the developing world by the year 2020.

Until the 1970s, the Halsted radical mastectomy had been the surgical procedure in the management of breast cancer irrespective of size. It was described and performed by William Stewart Halsted in 1882 [3]. It included the excision of the skin, the breast and underlying pectoralis muscles. Patients also underwent an axillary lymph node dissection. A skin graft was often used to close the wound defect. Patients were left with morbid disfiguring appearances.

Modified radical mastectomy was shown to be as effectual as radical mastectomy and less mutilating. Modified radical mastectomy remains to be applicable to certain patients. However, BCT has become the adopted procedure for the surgical management of early breast cancer. BCT refers to the surgical excision of the primary breast cancer tumour with a rim of normal breast tissue, followed by radiation therapy. It is also referred to in the literature as lumpectomy, partial mastectomy or segmental mastectomy [4].

Over the past forty years prospective large multicentre randomized controlled trials (RCTs) in Europe and United States have provided level 1 evidence that there is no statistically significant difference in the overall long-term survival between mastectomy and BCT in appropriately selected patients treated for early breast cancer [5]. Although the overall long-term survival is similar between

the two procedures, patients undergoing BCT are at a recognized risk of ipsilateral breast tumour recurrence [6]. The success rate of BCT relies upon appropriate patient selection, surgical technique, and postoperative radiotherapy to eliminate microscopic tumour cells in the ipsilateral breast. The goals of BCT are therefore to resect the tumour with clear microscopic margins and to achieve acceptable cosmetic outcomes without compromising patient survival.

The American College of Radiology and the American College of Surgeons provide a general framework for BCT [4]:

- Single focal cancer is most desirable
- Diffuse, malignant-appearing micro calcification on pre-operative mammogram contradicts BCT. This frequently correlates with diffuse ductal carcinoma-in-situ (DCIS), precluding the ability to achieve negative margins [7]
- Prior therapeutic chest radiation therapy is a contraindication
- Radiation treatment during pregnancy is a contraindication due to foetal safety concerns. Surgery can be done during pregnancy and radiation therapy completed after the delivery.
- Connective tissue disease is a relative contraindication due to enhanced radiation toxicity.
- Failure to clear margins after multiple repeated excisions is a contraindication to further BCT
- Large tumour to breast size ratio is contraindication
- Patient's choice should be respected

The following are not contraindications to BCT: Family history, age, histological subtypes other than infiltrative ductal carcinoma, extensive intraductal component, involved lymph nodes in the axillar, tumour location, high risk of systemic relapse and dense breast tissue [4].

BCT has become the standard of care in our surgical oncology/endocrine unit for patients meeting the above criteria diagnosed with early breast cancer at Groote Schuur Hospital. There has not been a formal audit to review the outcomes of BCT in the unit. In South Africa, there has been only one retrospective study on BCT. In 2005, Mannell, a part-time staff member at the University of Witwatersrand, published a retrospective review of 165 patients that underwent BCT at her private practice at Linksfield and Parklane Clinics over a period of 12 years. In her series 10 (6%) patients had close/involved margins, 7 patients had re-excision, 3 patients had mastectomy post the primary WLE. At a median of follow-up of 65 months, disease recurrence occurred in 9 (5.5%) patients [8].

The oncological safety of BCT in early breast cancer has been proven in many prospective randomized clinical trials (RCTs) that compared it to modified radical mastectomy [9-15].

Fisher *et al* randomized 1851 patients whose tumours sized less than 4 cm and clinically node-negative axillae in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial to receive modified radical mastectomy, lumpectomy alone, or lumpectomy with postoperative irradiation of the breast without extra boost to the lumpectomy site. All patients with histologically positive axillary lymph nodes received chemotherapy. The overall survival and disease-free survival at 20 years follow up were the same in all three-treatment arms. Local cumulative incidences of recurrence rate were 14.3% in women treated with lumpectomy and radiation therapy and 39.2% in women treated with lumpectomy alone (p value < 0.001) [9]. The patients with microscopically involved margins were managed with a mastectomy [9].

In the Milan I Trial, Veronesi *et al* randomized 701 women with tumours of up 2 centimetres and clinically node-negative axillae to radical mastectomy and BCT in the form of quadrantectomy with axillary dissection and postoperative radiation from the year 1973 to 1980 [10]. Patients with pathologically involved nodes received chemotherapy. Similar to the above study (NASBP B-06), at 20 years follow up, the overall survival was the same between the two groups. There was a statistical difference in the crude cumulative recurrence incidence between the two surgical groups. Women who underwent quadrantectomy had a recurrence of 8.8% compared to 2.3% of women that had radical mastectomy (p value < 0.001) [10]. Recurrence was found to be high in younger females below the age of 45 years. The authors attributed this to the multifocality and multicentricity of breast cancers in the younger women. The authors further concluded that the survival is determined by metastases and not by the extend of surgery. Patients with intraductal non-invasive carcinoma were excluded from the trial [10].

In the European Organization for Research and Treatment of Cancer (EORTC) Trial 10801 conducted from May 1980 to May 1986, 868 patients with American Joint Committee on Cancer (AJCC) stage I and II breast cancer were randomized to BCT or modified radical mastectomy across 8 centres in the United Kingdom, Netherlands, Belgium, and South Africa [11]. In this trial, BCT constituted excision of the cancerous lump with a macroscopic margin of at least 1 cm and axillary dissection. This was followed by radiation dose of 50 Gy and 25 Gy boost to the tumour bed. In contrast to the NSABP B-06 and Milan I trials, the EORTC 10801 included larger tumours of up to 5 cm. At 10-year follow-up, van Dongen *et al* reported a difference in loco regional recurrence rate favouring the modified radical mastectomy group (11.8% versus 19.7% for patients assigned to

BCT; P=0.0097) [11]. The recurrence rate for complete excision and positive margin was 17.6% and 26.5% respectively. The median time to local recurrence was reported at 3.9 years after BCT. However, it is important to note that the excision margins were not routinely inked to assess the microscopic completeness of the lumpectomy, and that there were no instructions in their protocol for re-excision. Re-excision took place only when macroscopic disease was let behind [11].

Litière *et al* showed that at twenty-year follow-up of the EORTC 10801 trial, distant metastases-free survival and overall survival rates did not show any significant difference between BCT and mastectomy groups [12]. They further demonstrated on a multivariate that clinical tumour size >2 cm, lymph node metastasis and age greater than 50 were associated with increased rates of death, independent of treatment group, with hazard ratios of 1.35 (p value = 0.013), 1.88 (p value <0.0001) and 1.50 (p value <0.0001) respectively [12].

In the institute Gustave-Roussy Breast Cancer Group trial, 179 women with tumours less than 2 centimetres were randomized to modified radical mastectomy versus lumpectomy [13]. All of their patients had frozen section of the axillary lymph nodes. The patients with nodal metastases were further randomized to lymph node irradiation versus no further regional treatment. The results show that overall survival, distant metastasis, contralateral breast cancer, new primary malignancy, and loco regional recurrence rates were not significantly different between the two surgical groups, or between lymph node irradiation groups at fifteen years of follow up. Local recurrence rate at 15 years was 9% and 14% in the BCT and mastectomy groups respectively. This difference was not statistically significant [13].

The National Cancer Institute in the USA trial randomized 237 patients with AJCC clinical stages I and II breast cancer to modified radical mastectomy versus lumpectomy, axillary dissection, and radiation therapy between the year 1979 and 1987 [14]. At 10 years follow up, no statistical difference in survival and recurrence rates between the mastectomy and BCT patients [14].

The Danish Breast Cancer Group trial randomized 904 patients with invasive cancer to modified radical mastectomy versus quadrantectomy wide local excision from January 1983 until March 1989 [15]. At 6 years, survival was not statistically significant between the two groups [15].

Risk factors for ipsilateral breast tumour recurrence in BCT

A number of pathological, clinical and treatment-related factors have been studied to identify patients that are at risk of ipsilateral breast tumour recurrence. Identifying risk factors for recurrence after BCT will help to optimize the management of patients.

Pathological Features

1. Margin Status

The resection margin status is defined as the closest microscopic distance between the inked lumpectomy tissue edge and any cancerous tissue, be it invasive or carcinoma in-situ [7]. Therefore,

obtaining a negative excision margin is considered a basic prerequisite for standard-of-care BCT [16]. Pathologic margin status is the most established factor for predicting local recurrence after BCT [6]. There is a general agreement that if the surgical margins are positive, there is a very high risk of local recurrence. However, assessment of the final margin status is influenced by a number of factors such as the method of excision, the method of identifying specimen margins (orientation and inking of true margins), thoroughness of the pathologic assessment (number of histologic sections evaluated), and the definition of what constitutes a positive, negative, or close pathologic margin [6]. Local recurrence rate has been reported between 6 to 33% in positive margins, defined as tumour cells directly at the inked edge of the surgical specimen, compared with rates of 2-10% with tumour-free pathologic margins [17-19]. The definition of a negative margin has varied substantially in the literature. In an attempt to clarify what constitutes a negative margin, most studies report it as the absence of invasive or carcinoma in-situ at the inked margin.

Most studies define close margins as ≤ 1 mm or ≤ 2 mm with reported recurrence rates of 2 – 11% and 6 – 33% respectively [19,20]. In a survey conducted by Vallasiadou *et al* in the United Kingdom and USA, approximately 50% of surgeons aim for a margin of more than 2 mm, whereas 50% of surgeons are happy with a margin of 2 mm or less [21]. A systematic review by Singletary reported that some of the lowest rates of local recurrence were in centres that had used narrow margins of excision (1 or 2 mm) [22].

Perhaps the important question to address with regards to the margin status is, does increasing the size of resection decrease recurrence? In order to answer this question, the optimal extent for resection before radiation needs to be defined. Unfortunately there is no consensus on what

constitutes an adequate margin of excision for BCT in the reviewed literature. According to Vicini *et al* after analysing the relation of recurrence to the volume resected in 507 patients who had BCT between 1968 and 1982, patients with extensive intraductal component tumours who had the largest volume resections (defined as specimen volume more than 74 cm^3), were correlated to significantly lower risk of recurrence in the ipsilateral breast than the patients who had smallest volume resections (less than 13 cm^3) both for T1 and T2 tumours. For patients with absent extensive intraductal component tumours, recurrence rates were significantly lower than for extensive intraductal component positive tumours and were not influenced to the same degree by the volume of resection thus advocating that the extend of any in-situ carcinoma present to be the determinant of the extend of resection [23].

Moreover, the volume of the wide local excision specimen and extent of surgery affect the cosmetic outcome. A poor cosmetic result may negatively affect the quality of life. According to Olivotto *et al*, the resection of 70 cm^3 or more of breast tissue was more common among the patients that reported worse cosmetic outcome compared to those with good outcome (p value 0.03) [24]. This size should not be set as the limit because the volume of resected tissue depends on factors such as, the tumour size in relation to the breast and the patient's perception of a good outcome.

In contrast, in a meta-analysis by Housami *et al*, although positive and close margins significantly increase the odds of local recurrence (odds ration 2.02, P value < 0.001), the distance used to declare negative margins did not independently contribute to the risk of local recurrence (P value = 0.27) [5]. The evidence was weak to suggest that the odds of local recurrence decreased as the threshold distance for negative margins increase. In other words, there was no statistically significant

improvement in local control in using a wider threshold for negative margin relative to a narrower distance [5]. This meta-analysis concluded that a 1 mm margin is sufficient. Increasing the size of resection volume will inevitably impact on the cosmetic outcome of BCT.

There is a need to develop a reproducible and reliable technique to address the inherent problem of defining margins. Such inherent problems arise because the breast specimens are fatty and the cut specimen surface is irregular therefore making surface markings with ink difficult. Routine sectioning of specimens does not usually permit examination of the entire surface of the specimen and DCIS associated with the tumour may be non-continuous with the tumour [23].

2. Extent of Margin Involvement

The extend of margin involvement has been identified as a predictor for who would benefit from repeat excision of the biopsy site. DiBiase reported the specific number of margins involved by the tumour influenced the overall outcome. The 10-year local control rate for women with 1 positive surgical margin was 74%, compared with 63% with ≥ 2 positive margins. Furthermore, positive margins also significantly affected disease-free survival, with 10-year disease-free survival rates of 71% and 82% with positive and negative margins, respectively (P = 0.001) [19].

3. Interaction of Margins Status and Other Factors

The increased hazard of local recurrence associated with close or positive margin status is even more pronounced when additional risk factors such as delayed radiation, presence of extensive intraductal component (see below), lack of systemic therapy, or young age are present [20,25-27].

4. Extensive Intraductal Component (EIC)

EIC is defined as intraductal carcinoma composing > 25% of the tumour mass and extending into surrounding normal breast parenchyma, or predominantly intraductal carcinoma with areas of microinvasion [26]. Local recurrence rates after BCT range from 2% to 9% for EIC-negative tumours and from approximately 10 – 30% for EIC-positive tumours [26].

Clinical Features

1. Age

Studies have reported an increased risk of local recurrence in younger women undergoing BCT for invasive and carcinoma in-situ breast cancer. According to Boyages *et al*, patients with very young age, defined as 34 years or younger in their study had higher local recurrence compared to older patients (25% vs. 11%, p value 0.001) [28]. The corresponding 5-year actuarial rates of breast cancer recurrence were 21% and 9% (p value 0.005) [28]. According to Vicini *et al*, on a multivariate

analysis, young age, defined as less than 45 years of age, was independently associated with recurrence of the index lesion in patients treated with BCT for DCIS [23]. The 10-year rate of ipsilateral failure was 26.1% in younger patients versus 8.6% in older patients (p value 0.03) [23].

Several hypotheses to explain the increased risk in younger women have been postulated based on histopathology review such as, greater prevalence of EIC, greater prevalence of higher nuclear grade, more inherently aggressive biologic behaviour (triple negative tumours) or higher probability of residual disease after initial excisional biopsy in younger patients [6].

2. Family History

Family history of breast cancer has been considered a possible risk factor for BCT failure. This is due to genetic predisposition that can increase the likelihood of cancer in the ipsilateral breast. Some studies such as Haffty *et al* reported a significantly higher rate of ipsilateral breast recurrence at 12 years of follow-up after BCT in 22 patients with BRCA1 or BRCA2 mutations compared with 105 patients with sporadic breast cancer (49% vs. 21%; P = 0.007) [29]. Other series have not found elevated recurrence rates in patients with a family history of breast cancer [30-32].

Treatment-Related Features

1. Radiation Therapy

Excision of the primary tumour alone is inadequate treatment for early breast cancer. By targeting residual malignant cells, radiotherapy post wide local excision reduces local recurrence. This was clearly shown in the NSABP B-06 trial in which local recurrence was reduced from 39% to 14% with postoperative radiotherapy [9]. In the Milan I trial, the addition of whole-breast radiotherapy decreases the recurrence rates from 24% to 6% [10]. In the EORTC study, the risk of a local recurrence decreased from 7.3% to 4.3% ($P < 0.001$) with the additional dose of radiation therapy to the lumpectomy cavity [11]. The interval between surgery and radiation may be important and there are suggestions that the rates of local recurrence increase if radiotherapy is delayed [33].

2. Systemic Therapy

Prospective studies have proven a decline in local recurrence with the addition of tamoxifen, aromatase inhibitors and chemotherapy after BCT in invasive and intraductal breast cancer [34-36].

A meta-analysis of all tamoxifen trials shows that women with ER-positive tumours significantly benefit from 5 years of tamoxifen in reducing the likelihood of recurrence and death, whereas women with ER-negative tumours do not [37]. However, in the absence of radiotherapy, aromatase inhibitors, tamoxifen or chemotherapy alone do not produce satisfactory rates of local control apart from in low-grade, node-negative cancers [38].

The management of the unsatisfactory margin in BCT

The goal of BCT is to adequately remove the disease with preservation of satisfactory cosmesis. The presence of microscopically clear surgical margin is the most important indicator in ensuring the completeness of a surgical excision [39]. On the other hand as mentioned above, a positive margin is a major predictor of local recurrence and it generally leads to further resource utilization, patient anxiety and leads to the delay in postoperative radiation therapy.

When an unsatisfactory margin is attained after the primary wide local excision, a second procedure is usually required in the form of either a re-excision or mastectomy depending on the patient's fitness for surgery or which margin is involved in order to clear the breast of tumour [40].

A number of factors have been correlated with positive margins. Of particular interest are the technical ones influenced by a surgeon. The NSABP has developed recommendations for BCT that include preoperative diagnosis by needle aspiration biopsy, surgeon orientation of the specimen with marking sutures, and intraoperative gross pathologic evaluation of tumour margins [41]. In one study, such recommendations resulted in achieving clear margins in 73% of patients compared with 17% when a more traditional excisional biopsy was done [42].

Positive margins are significantly associated with large tumour size and the presence of lymphovascular invasion and EIC [22, 43]. Others have demonstrated that lobular histology, higher grade, and positive axillary nodes are associated with positive margins [40].

A number of studies have evaluated the use of cavity shavings and bed biopsies, but few have compared these with standard assessment of margins [33]. A minority of surgeons continue to take cavity shavings and bed biopsies routinely for frozen sections in an attempt to clear resection margins. Neither has been shown to be reliable indicators of local recurrence. A major concern of taking cavity shavings routinely is that significant amounts of extra breast tissue can be removed resulting in poor cosmetic outcome. Centres that do not use these method report excellent local control rates [5, 22]. If any role at all, bed biopsies or cavity shavings are only of value and warranted where there is a concern at operation that one particular margin is involved and should not be done routinely.

Re-excision of positive or close margins is done on the premise that a second procedure (i.e. re-excision or mastectomy) will completely excise the cancer with resulting negative margins and hence reduce local recurrence. Local re-excision rate alone ranges between 24% and 57% [44-46]. Smitt *et al* [47] have shown that re-excision of inadequate margins can achieve local control rates similar to those achieved when the initial excision has been adequate. However, whether in fact re-excision helps to decrease local recurrence remains an unanswered question [48]. Few small studies that have studied re-excision of positive margins or have assessed local recurrence after re-excision compared to no further surgery have not shown a significant difference in local recurrence rate over a short follow-up period [45,49-53]. The study by Wiley *et al* suggested that the host response to injury might destroy residual infiltrating ductal cancer in some instances in which the tumour was incompletely resected [49]. Solin *et al* have suggested that, in some instances, close or focally positive margins can be compensated for by adjuvant radiotherapy [53]. Surgeons have to balance the

extent of surgical margin clearance and against cosmetic outcome. Most surgeons are unwilling to sacrifice the former for the latter, which would leave the responsibility for local control with the radiotherapist [40]. Furthermore, it has been shown that, with proper selection criteria, it may be safe to omit adjuvant radiotherapy in patients with adequate margins for example in DCIS [54,55].

In numerous reported series, residual cancer is detected in approximately 50% of re-excisions after partial mastectomy or lumpectomy with positive margins [22,50,56,57]. In other studies, residual cancer following re-excision for close but clear margins has been noted to be in the range of 22% to 43% [57-59].

In one of the large randomized controlled trials on BCT by Fisher *et al*, lumpectomy-treated women whose resected specimen margins were found on histologic examination to contain tumour underwent total mastectomy rather then re-excision [9].

Therefore the management of unsatisfactory margin post primary WLE depends on patient factors, surgeon factors and institutional guidelines.

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Chapter 2 - Publication-ready Manuscript

(See **appendix E** for the **South African Journal of Surgery (SAJS) author guidelines**)

Five-year review of breast-conserving therapy for breast carcinoma (BCT): surgical margins, re-excision and local recurrence in a single tertiary centre

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Abstract

Background: BCT is the wide local excision of the tumour usually followed by radiation treatment to the breast. It is the mainstay treatment for carefully selected patients with early breast cancer. There has not been a formal audit to review the outcomes of BCT in our unit.

Objectives: To determine the excision margins, re-excision and local recurrence rates.

Methods: A histopathological and oncology records review of BCT patients from 1st January 2006 to 31st December 2010. The health faculty's ethics committee granted approval. Data points accrued included age, pathological tumour size and nodal status, tumour histology, oestrogen receptor status, presence of lymphovascular invasion, volume of specimen excised, margin status, management of involved or close margins, radiotherapy, ipsilateral breast recurrence rate and duration of follow up.

Results: A total of 192 patients had BCT. The mean age is 53 years. A median of 229.5 cm^3 volume of specimen was excised. Infiltrating ductal carcinoma was the commonest histological type at 79.1%. The resection margin status: positive margins rate of 15.1%, 8.3 % close margin (≤ 1 mm), 35.9% 1 – 5 mm, 23.4% 6 – 10 mm and > 10 mm 17.2%. An overall of 27 (14.0%) patients underwent a second procedure. 16 (8.3%) had re-excision and 10 (5.2%) had a mastectomy. At a median follow up of 60 months, a total of 11 (6.8%) patients had recurrence. Median time to recurrence is 39 month.

Conclusion: Positive and close margin re-excision and local recurrence rates in our unit are acceptable and comparable to other units in South Africa and internationally.

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Introduction

Breast cancer affects 1 million women in the developed world every year [1]. The burden of breast cancer is also on the rise in the developing world. According to Jones [2], it is estimated that 70% of new cancer cases will occur in the developing world by the year 2020.

Until the 1970s, the Halsted radical mastectomy had been the surgical procedure in the management of breast cancer irrespective of size. It was described and performed by William Stewart Halsted in 1882 [3]. It included the excision of the skin, the breast and underlying pectoralis muscles. Patients also underwent an axillary lymph node dissection. A skin graft was often used to close the wound defect. Patients were left with morbid disfiguring appearances.

Modified radical mastectomy was shown to be as effectual as radical mastectomy and less mutilating. Modified radical mastectomy remains to be applicable to certain patients. However, BCT has become the adopted procedure for the surgical management of early breast cancer. BCT refers to the surgical excision of the primary breast cancer tumour with a rim of normal breast tissue, followed by radiation therapy. It is also referred to in the literature as lumpectomy, partial mastectomy or segmental mastectomy [4].

Over the past forty years prospective large multicentre randomized controlled trials (RCTs) in Europe and United States have provided level 1 evidence that there is no statistically significant difference in the overall long-term survival between mastectomy and BCT in appropriately selected patients treated for early breast cancer [5]. Although the overall long-term survival is similar between the two procedures, patients undergoing BCT are at a recognized risk of ipsilateral breast tumour recurrence [6]. The success rate of BCT relies upon appropriate patient selection, surgical technique, and postoperative radiotherapy to eliminate microscopic tumour cells in the ipsilateral breast. The goals of BCT are therefore to resect the tumour with clear microscopic margins and to achieve acceptable cosmetic outcomes without compromising patient survival.

BCT has become the standard of care in our oncology and endocrine surgical unit for patients meeting the above criteria diagnosed with early breast cancer at Groote Schuur Hospital. There has not been a formal audit to review the outcomes of BCT in the unit. In South Africa, there has been only one retrospective study on BCT. In 2005, Mannell, a part-time staff member at the University of Witwatersrand, published a retrospective review of 165 patients that underwent BCT at her private practice at Linksfield and Parklane Clinics over a period of 12 years. In her series 7 out of 165 patients had re-excision and recurrence rate of 5.5%[7].

Materials and Methods

This is a 5 years review of a series of consecutive patients who underwent BCT in a specialized unit at Groote Schuur Hospital from the 1st January 2006 until the 31st December 2010. It is based on histo-pathology and oncology records. Approval for the study was obtained from the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee. Inclusion criteria are all the histologically confirmed invasive or in situ breast carcinoma patients. Exclusion criteria are the patients with benign pathological diagnoses, incomplete histo-pathological reports, patient with missing folder numbers, patients' whose folders could not be found at records and patients lost to follow up during the study period. Primary endpoints were margin status, rate and type of re-operation and recurrence rate. Secondary outcomes are to identify factors associated with margin status, re-excision and recurrence. Data was retrieved from the unit's prospectively collected patient surgical breast cancer Microsoft Access 2010 database by identifying all the patients that had wide local excisions (WLEs). Additional data was retrieved from patients' folders, National Health Laboratory Service (NHLS) pathology reports and the radiation oncology records.

Data from identified patients was captured using an online password-protected forms designed with Google Forms and subsequently transferred onto a spreadsheet. Limiting access and using proxy patient identifiers maintained patient confidentiality.

The following variables captured: age, pathological tumour size (pT), pathological node status (pN), tumour grade (low, intermediate or high), histological type of tumour, volume of resected specimen in cm^3, oestrogen receptor (ER) status, presence of lymphovascular invasion, margin status, type of tumour at margin, management of positive margins (re-excision vs. mastectomy), type of residual tumour in the resection or mastectomy specimen), radiation therapy post WLE – if completed or not, local recurrence and time to recurrence, type of tumour and management of recurrence, duration of follow up at oncology outpatients' department. Extensive intraductal component was not recorded as it did not feature in the NHLS pathology reports.

Positive margin is interpreted as the presence of breast cancer, invasive and/or non-invasive at the inked surgical margin. The absence of tumour within a specified distance of more than 1 mm or 2 mm from the resection margin was regarded as a negative margin. A close margin is the presence of tumour within that distance (1 mm) but not at the resection margin. Volume of specimen is the gross volume of excised cancer with surrounding breast tissue calculated by multiplying height by width by length using the dimensions as described in the pathology report.

The wide local excision procedure in the unit is performed as per standards for BCT [4]. An elliptical skin incision followed by excision of the tumour together with circumferential normal breast tissue of 1 cm to ensure that the resected specimen margins are free of the tumour with tactile perception. The axilla was managed as indicated by clinical or sentinel lymph node biopsy. Lymph node clearance was limited to Level II dissection. Local recurrence refers to the first site histologically proven relapse of invasive or intraductal carcinoma post WLE in the ipsilateral breast.

Statistical analysis was performed using the IBM SPSS Statistics version 22 for Macintosh software. Continuous variables were expressed as means and median as measures of central tendencies and categorical variables as frequencies and percentages. The Chi-Square test was used to determine the associations between categorical data variables to recurrence.

Results

Patients and disease characteristics (Table 1)

The query design for the unit's Microsoft Access database retrieved 242 patients that had procedures recorded as WLEs. Fifty patients were excluded from the study for the following reasons: lost to follow up (31), incomplete histo-pathology report (8), benign pathology (3) (benign phylloides 2 and juvenile fibroadenoma 1), diagnostic radio guided occult lesion localization (2), incomplete database entry (3) (no name and folder number) and unable to retrieve pathology or oncology records (3).

Therefore a total of 192 patients underwent BCT in the surgical oncology unit within the period of 1st of January 2006 to 31st December 2010 as per inclusion criteria. The patients' age ranged from 25 years to 84 years with a mean age of 53.4 years. More than half of the patients (54.7%) were above 51 years. 5.2% of patients were young women who were less than 35 years. The majority of patients (91.7%) had breast cancers with a maximal diameter of 5 cm. A total of 5 and 4 patients had tumours categorized as T3 and T4 by pathology respectively. Seven patients had WLE post neoadjuvant chemotherapy.

115 patients (59.9%) had no pathological nodal involvement (pN0) and 61 (29.8%) had involved nodes (pN1 to pN3). 16 patients (8.3%) had unknown pathological nodal status (pNx). Low grade cancer was present in 62 patients (32.3%), intermediate grade in 77 patients (40.1%) and high grade in 53 patients (27.6%). 145 patients (75.5%) had absence of lymphovascular invasion and 47 patients (24.5%) had presence of lymphovascular invasion.

Two-thirds of patients had oestrogen receptor (ER) positive cancers (67.7%), 14.1% had negative oestrogen receptors. ER receptor status was not recorded in 35 patients (18.2%) in the histopathology reports.

The commonest histological tumour type was infiltrative ductal carcinoma (IDC) at 79.1%. It was associated with DCIS in 40.6%. Infiltrative lobular carcinoma (ILC) was present in 5.3% followed by DCIS in 3.6% of the patients.

The median volume of the specimens was 229.50 cm^3 with a range of 4 cm^3 to 10 530 cm^3.

Table 1. Patient and tumour characteristics

Variable	Number of patients (frequency)	Percentage (%)
Age Category (in years):		
≤ 35	10	5.2
36 – 50	77	40.1
≥ 51	105	54.7
Pathological Tumour Size:		
Tis	7	3.6
T1	82	42.7
T2	94	49.0
T3	5	2.6
T4	4	2.1
Pathological Lymph Node Status:		
Nx	16	8.3
N0	115	59.9
N1	47	24.5
N2	9	2.7
N3	5	2.6
Tumour Grade:		
Low	62	32.3
Intermediate	77	40.1
High	53	27.6
Lymphovascular Invasion:		
No Lymphovascular Invasion	145	75.5
Lymphovascular Invasion	47	24.5
ER Receptor Status:		
ER Positive	130	67.7
ER Negative	27	14.1
Unknown	35	18.2
Excision Margins (mm):		
Positive	29	15.1
Close (≤ 1)	16	8.3
1 – 5	69	35.9
6 – 10	45	23.4
> 10	33	17.2

Margin status and management

Of the 192 women who were treated with BCT, 29 had an involved or positive margin after the initial excision (15.1%). The commonest pathology at the involved margin was carcinoma in-situ at (15 patients) 51.7%. Sixteen patients (8.3%) had a close margin of less than 1 mm. Sixty-nine patients (35.9%) had a margin between 1 mm to 5 mm. Seventy-eight patients (40.6%) had a margin of more than 6 mm (Figure 1). Of the patients that had carcinoma in-situ at the margins, 8 had repeated WLE, one had a mastectomy and 6 had no further surgical intervention. In the infiltrative carcinoma group (14 patients), 6 had a repeated WLE, 2 had mastectomy and 6 had no further surgical intervention (Table 2).

A total of ten patients had no further surgery for involved margins, six and four in the DCIS and infiltrative carcinoma groups respectively. The reasons for no further surgery in the DICS group were, one patient developed severe pancreatitis and lost to follow up, 4 patients had involved deep margins and one transferred to another province. In the infiltrative carcinoma group, one was deemed surgical unfit due to advanced age, 2 had tumour at deep margins infiltrating the major pectoralis muscle and we could not determine the reason in the records for one patient.

For the women that had a close margin (<1 mm), 5 and 11 patients had DCIS and infiltrative carcinoma respectively. In the DCIS group 3 patients had a subsequent mastectomy and one patient each had a repeat WLE and no further surgery due to deep close margins. In the infiltrative close margin group, no patient had a repeat WLE, 2 had mastectomy and 9 had no further surgery mostly due to deep close margins.

In the group of women who had excision margin 1 to 5 mm, one (6.3%) had a re-excision for infiltrative carcinoma and none had a mastectomy. Neither re-excision nor mastectomy was performed in the women with excision margins of more than 6 mm.

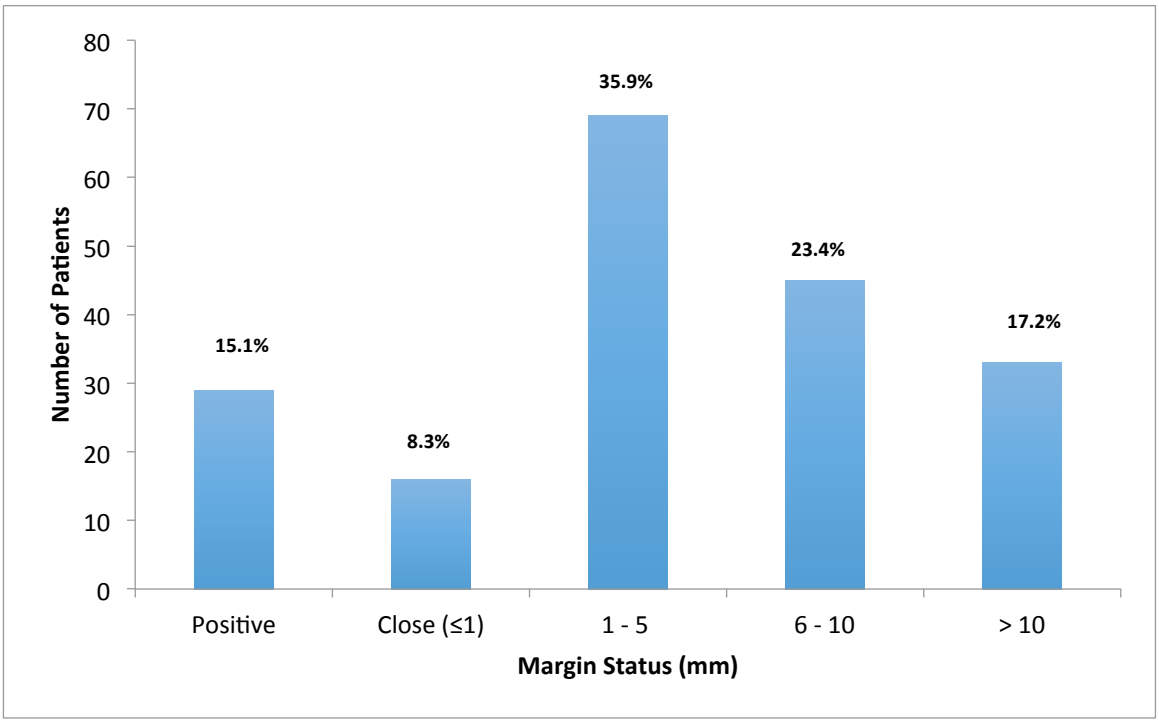

Figure 1. Bar chart showing the percentages of the excision margins

Table 2. Summary of management of positive and close margins after initial wide local excision according to histo-pathology

		Positive Margin		Close Margin	
		DCIS	Infiltrative Carcinoma	DCIS	Infiltrative Carcinoma
Management of Margin	Re-WLE	8	6	1	0
	Mastectomy	1	4	3	2
	No Surgery	6	4	1	9

A total of twenty-six patients had subsequent repeat WLE or mastectomy for involved (19), close (6) and 1-5 mm (1) margins, giving an overall re-excision rate of 13.5%. Re-excision rate according to margin status is 9.9% for positive and 3.1% for close margins. The rate was similar for DCIS and invasive carcinoma in positive margin group.

A total of ten patients had mastectomy for involved or close margins giving an overall mastectomy rate to 5.2% for this study (Table 2).

Residual tumour rate in the re-excision and mastectomy was 50.0% and 63.6% respectively. The most common residual histology in both groups was DCIS. One patient that had involved margins in the re-excision specimen had a subsequent mastectomy for persistent margin involved. The histology in this patient was IDC in association with DCIS.

The most significant predictors for re-excision were a positive margin (p value 0.000) and the pathological tumour size (p value 0.009). The following did not predict re-excision: age (p value 0.825), volume of the primary resected specimen (p value 0.148), tumour histological grade (p value 0.434), tumour oestrogen receptor status (p value 0.786) and lymphovascular invasion (p value 0.77).

Recurrence

Local recurrence (LR) is hereby defined as the first recurrence of a tumour in the chest wall or in the operative scar in the ipsilateral breast after the initial WLE. During the median follow-up period of 60 months, a total of eleven patients had histologically confirmed recurrence. A total of 31 patients lost to follow during the observational period, giving the relative observed rate of local recurrence of 6.8%. The median time to recurrence was 39 months. All the cases of recurrences were confirmed by histology. Infiltrative ductal carcinoma was the most common histological type of breast cancer at 63.6% followed by DCIS at 18.2%.

LR was 6.9% in patients with histologically positive margins, 5.8% in patients with 1 -5 mm margins, 6.7% in patients with 6 – 10 mm margins, 6.1% in patients with > 10 mm margins. No recurrence was noted in the close margin group. There was no statistical difference between the resection margins (Pearson Chi-square 0.890).

The total follow up duration period was calculated from the date of diagnosis to the discharge date or the date the patient was last seen at the oncology clinic at the time of data collection.
Cross tabulation analysis of the rest of variables such as the age of the patient, tumour pathological size, tumour grade, oestrogen receptor status, presence of lymphovascular invasion, completion of radiotherapy post breast conserving surgery, did not show a correlation with local recurrence (Table 3).
Table 3. Effect of different variables on local recurrence

	Pearson Chi-square statistic
Age (years):	**0.436**
</= 35	
35 – 50	
>/= 51	
Pathological T Stage:	**0.684**
Tis	
T1	
T2	
T3	
T4	
Tumour Grade:	**0.347**
Low	
Intermediate	
High	
Receptor Status:	**0.173**
ER Positive	
ER Negative	
ER Unknown	
Lymphovascular Invasion:	**0.617**
LVI	
No LVI	
Radiotherapy Completion:	**0.960**
Completed	
Not Completed	
Margin:	**0.890**
Positive	
< 1 mm	
1 – 5 mm	
6 – 10 mm	
> 10 mm	

Radiation treatment

A total of 157 patients (81.8%) were referred to the radiation oncology unit for radiotherapy post surgery, of which 152 (96.8%) completed the radiotherapy course.

Discussion

This study was conducted to review breast-conserving therapy for breast carcinoma in a single tertiary centre. It is the largest study to date conducted in South Africa. The rate of margin positivity was 15.1%. This rate is comparable to and lower than international studies that vary widely from 3% to 52% [7-17] (Table 4). The wide range in margin positive margin rates internationally is due to a number of factors. These include: inconsistent definitions of a positive margin, differences in the use of intraoperative pathological assessment of margins, variations in the handling of surgical specimens and in pathological sampling of margins. The type of surgery also affected these numbers, specifically whether surgery was diagnostic or therapeutic in intent. Also, different studies had a wide range of actual number of surgical resections that were performed to generate the published positive margin rates [18].

Table 4. Studies on positive margins and local recurrence by margin status

			Local Recurrence by Margin Status (%)		
Author(s)	Number of Patients	Positive Margins (%)	Negative	Positive	Follow-Up
Mannell [7]	165	6		5.5*	65 months median
Veronesi et al (Milan I) [8]	1973		9	17	6.5-year median
Van Dongen et al (EORTC) [9]	431		9	20	8-year actuarial
DiBiase et al [10]	453	19	13	33	120 months
Peterson et al [11]	120	16	8	10	5-year actuarial
Leborgne et al [12]	817	6	9	6	9-year actuarial
Cowen et al [13]	152	48.3[a] 51.7[b]	-	14[a] 31*	5-year crude
Dewar et al [14]	663	19.9	6	14	10-year actuarial
Kini et al [15]	400	8	6	17	10-year actuarial
Mansfield et al [16]	704	15	8	16	120 months
Pierce et al [17]	396	3	3	10	5-year actuarial
Nashidengo (current study)	**192**	**15.1**		**6.1[c]** **5.7[d]**	**60 months median**

Key: [a] = Focally positive margin

[b] = Extensively (Multiple) positive margin

[c] = Positive margin

[d] = Overall

In the current study, patients who had tumours with lymphovascular invasion were more likely to have a positive margin (Pearson Chi-square 0.002). Singletary reported that positive margin was significantly associated with large tumour size, young age, axillary node positive status, presence of lymphovascular invasion, and an extensive intraductal component [19]. Aziz et al reported that patients who were younger or had tumours with lymphovascular invasion or a DCIS component were more likely to have a positive margin on a univariate analysis [20]. In the current study, the following variables did not predict positive margins: age, pathological tumour size, pathological axillary nodal status, histological diagnosis, grade and oestrogen receptor status.

Nearly all the tumours in our study are pT1 and pT2 sized (91.7%). This is in keeping with international standards and guidelines for BCT for early breast cancer. However, the current trend internationally is that the eligibility of BCT has been expanded to locally advanced breast cancers post neoadjuvant chemotherapy. Primary tumour response rates of approximately 80% have been observed post neoadjuvant [21]. Several RCTs have demonstrated the oncologic safety of neoadjuvant chemotherapy locally advanced breast cancer. The NSABP B-18 trial demonstrated that there was no statistically significant difference in the local recurrence rate following BCT in the preoperative and postoperative chemotherapy arms [22].

This practice is not yet adopted in our surgical oncology unit. Although a total of six patients had WLE post neoadjuvant chemotherapy, we postulate that these patients either had large breast to tumour ratio or their tumours were located high on the chest wall or in the inframamary fold that would have rendered a mastectomy difficult.

Positive resection margins have been associated with a higher local recurrence rate [5,10,19,23,24]. It is a standard practice in our unit to re-excise a positive margin with the intent of achieving clear margin prior to radiation therapy. The decision for re-excision is discussed in a multi-disciplinary team comprising of surgeons with special interests in breast cancer, medical and radiation oncologists, histopathologists and radiologists. A variety of factors are taken into consideration before proceeding with re-excision, such as, patient age, co-morbidities, life expectancy, extent of excision, extent of margin involvement, tumour characteristics, and whether the patient will receive adjuvant treatment. Involved or close margins deep down to fascia are not re-excised due to the morbidity that results from partial muscle excision on the chest wall. Such patients usually receive boost radiation doses.

Our unit's overall re-excision rate of 13.5% is lower than most international studies. An observational study of 2206 women reported an overall re-excision rate of 22.9%. It is notable that within this study, there were wide substantial variations between surgeons and institutions following BCT [25]. The most consistent and reliable risk factors for re-excision appear to be the presence of micro-calcifications, EIC or DCIS, and lobular histological type [26]. A palpable tumour is more likely to facilitate complete excision while the existence of insensible DCIS outside the sensible part of the tumour can result in involved resection margin and the subsequent need for a second procedure.

Globally, indications for re-excision for involved or close margins are under constant review. A meta-analysis that included 33 studies and 28 162 patients with ipsilateral recurrences supports the use of no ink on the tumour as an adequate negative margin of resection for invasive breast cancer. The authors concluded that there was no evidence that a wider margin of normal breast tissue than no ink on the tumour decreased the rate of recurrence in the clinical setting of multimodality treatment [27]. Re-excision is therefore not mandatory for close margins < 1mm and each case should be individualised.

In our study, the mastectomy rate post the initial WLE for positive margin is 0.5% and 2.1% for DCIS and invasive cancer respectively. For close margins, it is 1.6% and 1.0% for DCIS and invasive cancer respectively. The surgical decision to a re-excision versus a mastectomy is made at a combined breast clinic. Tumour factors and patient preferences are taken into consideration. Patients with diffuse rather than focally involved margins are offered a mastectomy. A mastectomy is the preferred surgical treatment for multicentric DCIS or persistent positive margin after repeated WLE.

The residual tumour rate in re-excisions and mastectomy groups is 50% and 63.6% respectively. These rates are comparable to international studies [19,28,29]. In our study, the final margin status measurements were not captured and therefore we are not able to report the final close margin rate. However we noted one patient (0.52%) who had undergone more than one surgical procedure, a re-excision followed by a mastectomy for persistent positive margin.

The median volume of the excised specimen is 229.5 cm^3 in our study. This seems to be larger than the sizes of 60 cm^3 and 70 cm^3 quoted by Vicini et al [30] and Olivotto et al [31]. The volume of resected breast tissue has a direct impact on cosmesis in breast conserving surgery. According to Olivotto et al, tumours greater than 70 cm^3 resulted in a significant increase in the number of cosmetic failures [31]. We postulate that the larger volume reflects the likelihood that our patients presented with slightly larger sized-tumours and larger breasts. The cosmetic effects of BCT were not part of the current study. A different study in our unit looking into this aspect will provide more insight.

Our study shows a relative observed recurrence of 6.8% at a median follow-up of 60 months. The recurrence rate in the involved or positive margin patient group is 6.8%. Our local recurrence rate is comparable, if not lower, to international studies that show a local recurrence that varies between 2% to 13% for negative margins and 5.5% to 33% for positive margins [7,9-17,23,24] (Table 4). Our data was not sufficient to demonstrate any statistically significant difference between local recurrence and the variables studied.

A total of 156 (81.3%) of the 192 patients that had WLE were referred for radiotherapy. It is standard that patients over the age of 80 years of age or with significant comorbidities are not referred for radiation therapy. There were patients that lost to follow-up after their surgery due to defaulting, some followed up with private radiation oncologists, and some moved to other provinces, some declined further treatment. Of the referred patients, 151 (96.8%) completed radiation treatment.

Our study has a number of limitations. First, this was a retrospective study based on the local hospital sample. The database may not have included all the patients that had WLE and incomplete histological reports. We could not access information on non-retrieved folders. This lack of records may have influenced the final outcomes of the study and it reflects the general challenges public health sector with regards to poor record keeping. Therefore the analysis is subject to selection bias. The recurrence rate was calculated taking into consideration the patients that are lost to follow up

during the observational period.

Conclusion

Our study reviews the outcomes of BCT women with early breast cancer in a single tertiary centre. It represents the largest cohort of patients managed at a single institution in South Africa. Apart from the inherent limitation to this retrospective review, the median follow up period of 60 months is reasonable and provides valuable information regarding our unit's surgical margins in BCT, re-excision and ipsilateral breast tumour recurrence rate. The analysis of 192 patients demonstrates outcomes that appear well in keeping with those reported in the international literature in what regards the local recurrence rate.

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Appendix A: Data Capture Form

Patient Data Capture Sheet: BCT at GSH 2006 to 2010

MMed Research by Dr. Pueya M. Nashidengo

* Required

Hospital Number: *

Your answer

Oncology Number: *

Your answer

Age *

(Years)

- [ ] ≤ 35
- [ ] 36 - 50
- [ ] ≥ 51

Pathological Breast Cancer Clinical Size *

(American Joint Committee on Cancer Staging)

- [ ] pTis
- [ ] pT1
- [ ] pT2
- [ ] pT3
- [ ] pT4
- [ ] pTx
- [ ] Not specified

Pathological Breast Cancer Clinical Stage *

- [ ] pN0
- [ ] pN1
- [ ] pN2
- [ ] pN3
- [ ] pNx
- [ ] Not specified

Volume of Resected Specimen (mm3) *

Your answer

Histology Of The Tumor: Subtype *

- [ ] Invasive Ductal
- [ ] Invasive Lobular
- [ ] Ductal Carcinoma In-Situ
- [ ] Lobular Carcinoma In-Situ
- [ ] Other: _____

Histology Of The Tumor: Biomarkers/Receptor Status *

- [ ] ER
- [ ] PR
- [ ] HER-2
- [ ] None

Histology Of The Tumor: Grade *

- [ ] Low
- [ ] Intermediate
- [ ] High
- [ ] Not Specified

Histology Of The Tumor: Lymphovascular Invasion *

- [ ] Lymphovascular invasion
- [ ] Extensive Intravascular Component
- [ ] None

Size Of The Tumor (Greatest Diameter in centimeters) *

Left or Right

- [ ] ≤ 1.0
- [ ] 1.1 - 2.0
- [ ] 2.1 - 3.0
- [ ] 3.1 - 4.0
- [ ] 4.1 - 5.0
- [ ] >5.1
- [ ] Not Specified

Closest Resection Margin *

(Distance)

- [ ] Tumour at inked margin
- [ ] >0 - < 1mm
- [ ] 1 - 5mm
- [ ] 6 -10mm
- [ ] > 10mm
- [ ] Not Specified

Closest Margin Pathology *

- [ ] DCIS
- [ ] Invasive
- [ ] Both
- [ ] Clear
- [ ] Not Specified

Re-excision Before Local Recurrence? *

After the first WLE

- [ ] YES
- [ ] NO
- [ ] Not Applicable
- [ ] Not Specified

Re-excision Before Local Recurrence *

(If Yes, What was the second operation?)

- [ ] Repeated Wide Local Excision
- [ ] Mastectomy
- [ ] Not Specified
- [ ] Not Applicable

Recurrence? *

(At Two Years)

- [ ] Yes
- [ ] No
- [ ] Not specified

Histology of Recurrence *

- [ ] DCIS
- [ ] Invasive
- [ ] Not Specified
- [ ] Not Applicable

If Recurrence, Time To Recurrence *
(Months)

Your answer

Surgery For Local Recurrence? *

- [ ] Yes
- [ ] No
- [ ] Not Applicable
- [ ] Not Specified

Management of Local Recurrence *

- [ ] Mastectomy
- [ ] Hormonal Treatment
- [ ] Radiation
- [ ] Chemotherapy
- [ ] Not Specified
- [ ] Not Applicable

Chemotherapy *

- ( ) Complete
- ( ) Not Complete
- ( ) Not Specified
- ( ) Not Applicable

Page 1 of 1

SUBMIT

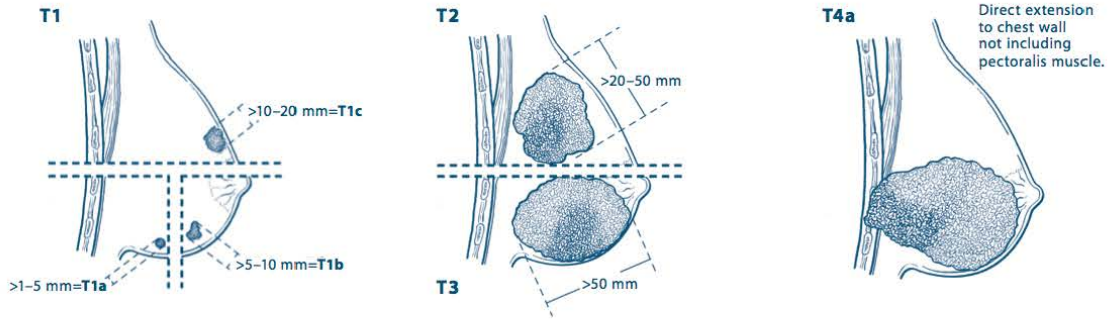
Never submit passwords through Google Forms.

Appendix B: American Joint Committee on Cancer Staging for Breast Cancer

American Joint Committee on Cancer

Breast Cancer Staging

7th EDITION



Primary Tumor (T)

- **TX** Primary tumor cannot be assessed
- **T0** No evidence of primary tumor
- **Tis** Carcinoma in situ
- **Tis (DCIS)** Ductal carcinoma in situ
- **Tis (LCIS)** Lobular carcinoma in situ
- **Tis (Paget's)** Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted

- **T1** Tumor ≤ 20 mm in greatest dimension
- **T1mi** Tumor ≤ 1 mm in greatest dimension
- **T1a** Tumor > 1 mm but ≤ 5 mm in greatest dimension
- **T1b** Tumor > 5 mm but ≤ 10 mm in greatest dimension
- **T1c** Tumor > 10 mm but ≤ 20 mm in greatest dimension
- **T2** Tumor > 20 mm but ≤ 50 mm in greatest dimension
- **T3** Tumor > 50 mm in greatest dimension

- **T4** Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)

  Note: Invasion of the dermis alone does not qualify as T4
- **T4a** Extension to the chest wall, not including only pectoralis muscle adherence/invasion
- **T4b** Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
- **T4c** Both T4a and T4b
- **T4d** Inflammatory carcinoma (see "Rules for Classification")

Distant Metastases (M)

- **M0** No clinical or radiographic evidence of distant metastases
- **cM0(i+)** No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
- **M1** Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1*	N1mi	M0
Stage IIA	T0	N1**	M0
	T1*	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Notes

* T1 includes T1mi.

** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid; any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

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American Joint Committee on Cancer

Breast Cancer Staging

7th EDITION

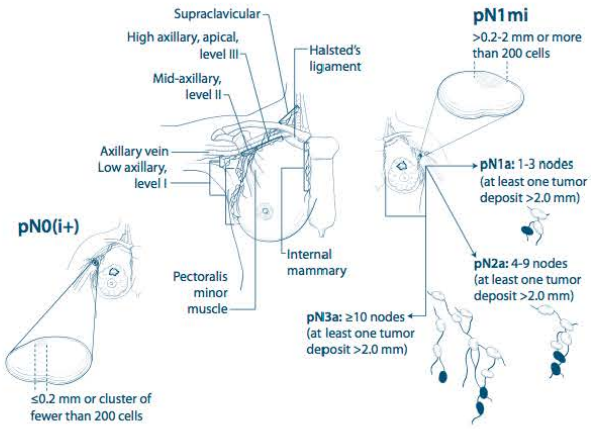
Regional Lymph Nodes (N)

CLINICAL

- **NX** Regional lymph nodes cannot be assessed (for example, previously removed)
- **N0** No regional lymph node metastases
- **N1** Metastases to movable ipsilateral level I, II axillary lymph node(s)
- **N2** Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases
- **N2a** Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
- **N2b** Metastases only in clinically detected* ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
- **N3** Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected* ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
- **N3a** Metastases in ipsilateral infraclavicular lymph node(s)
- **N3b** Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
- **N3c** Metastases in ipsilateral supraclavicular lymph node(s)

Notes

* "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.



PATHOLOGIC (PN)*

- **pNX** Regional lymph nodes cannot be assessed (for example, previously removed, or not removed for pathologic study)
- **pN0** No regional lymph node metastasis identified histologically

  Note: Isolated tumor cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumor cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.
- **pN0(i–)** No regional lymph node metastases histologically, negative IHC
- **pN0(i+)** Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
- **pN0(mol–)** No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
- **pN0(mol+)** Positive molecular findings (RT-PCR)**, but no regional lymph node metastases detected by histology or IHC
- **pN1** Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***
- **pN1mi** Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
- **pN1a** Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
- **pN1b** Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
- **pN1c** Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
- **pN2** Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
- **pN2a** Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
- **pN2b** Metastases in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases
- **pN3** Metastases in 10 or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes
- **pN3a** Metastases in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
- **pN3b** Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***
- **pN3c** Metastases in ipsilateral supraclavicular lymph nodes

Notes

* Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).

** RT-PCR: reverse transcriptase/polymerase chain reaction.

*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

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Appendix C: Department of Surgery Research Committee Approval

UNIVERSITY OF CAPE TOWN

Department of Surgery

Departmental Research Committee
Professor Anwar Suleman Mall
J-45 Room Old Main Building, Groote Schuur Hospital,
Observatory 7925, South Africa
Tel (021) 406 6168/6232/6227 **Fax** (021) 448 6461
Email: Anwar.Mall@uct.ac.za

23rd October 2013

Dr P Nashidengo
Department of Surgery
Division of General Surgery
Groote Schuur Hospital
University of Cape Town

Dear Dr Nashidengo,

RE: PROJECT 2013/119

PROJECT TITLE: Five year review of breast-conserving therapy (BCT) for breast carcinoma: Surgical margins, re-excision and local recurrence in a single tertiary centre

-

The above proposal was reviewed by the Department of Surgery Research Committee and I am pleased to inform you that the committee approved the study.

Please use the above project number in all future correspondence.

Yours sincerely

Signed by candidate

PROFESSOR ANWAR S MALL
CHAIRMAN: RESEARCH COMMITTEE

"OUR MISSION is to be an outstanding teaching and research university, educating for life and addressing the challenges facing our society."

Appendix D: Faculty of Health Sciences Ethics Committee Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
Email: lamees.emiedi@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

16 April 2014

HREC REF: 141/2014

Dr L Cairncross
Surgery/Endocrine Oncology
J Floor
OMB

Dear Dr Cairncross

PROJECT TITLE: FIVE YEAR REVIEW OF BREAST-CONSERVING THERAPY (BCT) FOR BREAST CARCINOMA: SURGICAL MARGINS, RE-EXCISION AND LOCAL RECURRENCE IN A SINGLE TERTIARY CENTRE (MMed - Dr Pueya Nashidengo)

Thank you for your response letter to the Faculty of Health Sciences Human Research Ethics Committee dated 23 March 2014.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th April 2015.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

We acknowledge that the MMed student Dr Pueya Nashidengo will also be involved in this study.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

141/2014

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

141/2014

Appendix E: The South African Journal of Surgery Author Guidelines

SAJS The South African Journal of Surgery

Submissions

Online Submissions

Already have a Username/Password for South African Journal of Surgery?
GO TO LOGIN

Need a Username/Password?
GO TO REGISTRATION

Registration and login are required to submit items online and to check the status of current submissions.

Author Guidelines

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, and will delay publication.

AUTHORSHIP
Named authors must consent to publication. Authorship should be based on substantial contribution to: (i) conception, design, analysis and interpretation of data; (ii) drafting or critical revision for important intellectual content; and (iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**).

CONFLICT OF INTEREST
Authors must declare all sources of support for the research and any association with a product or subject that may constitute conflict of interest.

RESEARCH ETHICS COMMITTEE APPROVAL
Provide evidence of Research Ethics Committee approval of the research where relevant.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY
Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION
References to ethnic classification must indicate the rationale for this.

MANUSCRIPTS
Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles not exceeding 3 000 words, with up to 6 tables or illustrations, are usually observations or research of relevance to surgery. References should preferably be limited to no more than 15. Please provide a structured abstract not exceeding 250 words, with the following recommended headings: *Background, Objectives, Methods, Results,* and *Conclusion.*

Scientific letters/short reports, which include case reports, side effects of drugs and brief or negative research findings should preferably be 1500 words or less, with 1 table or illustration and no more than 6 references. Please provide an accompanying abstract not exceeding 150 words.

Editorials, Opinions, etc. should be about 1000 words and are welcome, but unless invited, will be subjected to the SAJS peer review process.

Review articles are rarely accepted unless invited.

Letters to the editor, for publication, should be about 400 words with only one illustration or table, and must include a correspondence address.

Obituaries should be about 400 words and may be accompanied by a photograph.

MANUSCRIPT PREPARATION
Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**.

Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and <) should be placed immediately preceding the relevant number, i.e. 'women >40 years of age'. The same applies to ± and º, i.e. '35±6' and '19ºC'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting
The manuscript must be in Microsoft Word or RTF document format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, with the exception of Tables).

ILLUSTRATIONS AND TABLES
If tables or illustrations submitted have been published elsewhere, the

a comparison of recipient groups

» A response to "Concepts in malignant transformation" - a pathologists perspective

KEYWORDS
Appendicitis
Burns Children
Endoscopic biliary drainage Hernia
Injury
Laparoscopic
Laparoscopy
Morbidity and mortality
Mortality
Obstructive jaundice
Outcome
Pancreatitis
Percutaneous transhepatic biliary drainage Pre-operative biliary drainage Time to treatment
Trauma
Tuberculosis
University of Cape Town
diagnosis
management

author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file or provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes or tabs), and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'. Figure legends: Fig. 1. 'Title...'

All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft Powerpoint or Excel must be accompanied by the original workbook.

REFERENCES
Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists must be generated manually and **not** with the use of reference manager software.

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All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.

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Journal references:
Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references:
Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.

Chapter/section in a book:
Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references:

World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

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