PART A

THE PROTOCOL

M.Med in Radiation Oncology

PROTOCOL

The role of adjuvant radiotherapy for breast cancer patients with axillary node negative or limited nodal disease after total mastectomy, axillary nodal clearance and systemic therapy.

By:

Dr Albert van Jaarsveld

Student No: vjradr002

Supervisor:

Dr Hannah M. Simonds

INTRODUCTION:

Worldwide controversy exists over the T1-2 (< 5cm breast lumps) breast cancer group with 1 – 3 axillary nodes that is positive for cancer spread, after a total mastectomy and axillary nodal clearance. The role of adjuvant chemo and/or hormonal treatment is well established but the question is whether post-mastectomy radiation is indicated.[1]

The Radiation Oncology Department at Groote Schuur Hospital does not routinely irradiate this specific group of patients, unless they meet the criteria set out in our protocol that puts them at high risk of relapse.

This study will show the outcome of a sample of our patients and when compared to international studies, whether there needs to be a change in our current protocol.

In addition I will compare two subgroups of patients; the node negative and node positive group.

LITERATURE REVIEW:

The landmark trial is the Danish 82b trial that showed that the addition of postoperative irradiation to mastectomy and adjuvant chemotherapy reduces locoregional recurrences and prolongs survival in high-risk premenopausal women with breast cancer.[2]They showed a 9% improvement in all subgroups of patients, but inadequate surgery was done in 15 – 18%

The controversy still remains; what to do with the 1-3 node positive group?

The Danish showed the patterns of failure as well. The majority failed locally in the chest wall (50%) & 39% failed in the axilla.

Why is this controversial?

There is conflicting evidence and not consensus if post mastectomy radiotherapy (PMRT) should be given in T1-2, N1 breast cancer patients

Overgaard et al revisited the controversial topic in 2007 and did a subgroup analysis of the original Danish trial of 1997 (DBCG 82 b&c) to evaluate the loco-regional recurrence rate and survival in relation to number of positive nodes.[3]

It was found that the benefit of PMRT is equally pronounced in patients with 1 – 3 positive nodes as in patients with 4 or more nodes. RT reduced the 15-year loco-regional failure rate from27% to 4% ($p < 0.001$) in patients with 1–3 positive nodes. Similarly, the 15-year survival benefit after RT was significantly improved in patients with 1–3 positive nodes (57% vs. 48%, $p = 0.03$)

Cosar et al also looked into the question whether there is a role for radiation therapy for post mastectomy patients with T1-2 and 1-3 nodes positive (i.e. N1).[4] It was a retrospective review of 66 patients who received Post mastectomy Radiotherapy (PMRT) and 24 patients who did not receive PMRT. They found that radiotherapy improved the loco-regional relapse rate (3% for RT vs. 17% for no-RT, $p = 0.038$), the distant metastasis rate (12% vs. 42%, $p = 0.004$) as well as the 5 year disease free survival rate (82.4% vs. 52.4%, $p = 0.034$), but the 5 year overall survival (OS) was statistically insignificant (90, 2% vs. 61, 9%, $p = 0.087$). In a multivariate analysis distant metastasis and lymphatic invasion were independent poor prognostic factors for OS.They concluded that PMRT for T1-2, N1-3 positive breast cancer patients has to be reconsidered according to the prognostic factors and the decision has to be made individually with the consideration of long-term morbidity and with the patient approval

Bucholz et al compared the outcome of 12,693 patients treated with breast-conservation therapy with radiation (BCT + RT) to 18,902 patients treated with mastectomy without radiation (MRM w/o RT).[1]

They found that radiation use was independently associated with improved survival for patients with Stage II breast cancer with one to three positive lymph nodes.

The 15-year breast cancer–specific survival rate was 72% for the MRM w/o RT group ($p < 0.001$). Cox regression analysis showed that MRM w/oRTwas associated with a hazard ratio for breast cancer death of 1.19 ($p < 0.001$) and for overall death of 1.25 ($p <0.001$).

Clarke et al did collaborative meta-analyses on 42 000 women in 78 randomised treatment comparisons with one of the comparisons being radiotherapy *vs.*no radiotherapy.[5]

They reviewed 8500 patients with mastectomy, axillary clearance, and node-positive disease in trials of radiotherapy(generally to the chest wall and regional lymph nodes), and found absolute gains from radiotherapy

(5-year local recurrence risks 6% versus 23%, and 15-year breast cancer mortality risks 54·7% versus 60·1%)

To help assess the life-threatening side-effects of radiotherapy, the trials of radiotherapy versus not were combined with those of radiotherapy versus more surgery. There was, at least with some of the older radiotherapy regimens, significant excess incidence of contralateral breast cancer and a significant excess of non-breast-cancer mortality in irradiated women. Both were minimal during the first 5years, but continued after year 15. The excess mortality was mainly from heart disease and lung cancer

Abi-Raad et al aimed to identify a subgroup of T1-T2 breast cancer patients with no positive lymphnodes who might benefit from PMRT.[6]They retrospectively reviewed 1,136 node-negative T1-T2 breast cancer cases treated with mastectomy without PMRT. This study suggests that selected patients with multiple risk factors including LVI, tumour size ≥2 cm, close or positive margin, age ≥50, and no systemic therapy are at higher risk of LRR and may benefit from PMRT.

AIMS OF THIS STUDY:

1) To assess the 5yr loco-regional relapse rate (LRR), distant metastasis rate (DM), disease free survival (DFS) and overall survival (OS) in my cohort of patients i.e. T1-2, N0-1 breast cancer patients diagnosed between 2004 & 2006 receiving a total mastectomy, axillary clearance and systemic therapy"

2) To compare findings with similar international studies of patients who did receive post operative radiotherapy.

PRIMARY ENDPOINTS:

- LRR
- DM
- DFS
- OS

RESEARCH QUESTION:

1. Null Hypothesis) There is no statistically significant difference in 5 year overall - and disease free survival between T1-2, N1 patients who received chest wall and supraclavicular radiotherapy after mastectomy and patients who did not receive radiotherapy.
2. Null Hypothesis) There is no statistically significant difference in 5 year overall - and disease free survival between the node positive (1-3 positive nodes) and node negative group.

METHODS & MATERIALS:

This will be a retrospective audit by means of folder review of patients diagnosed between years 2004& 2006.

A search will be made of the radiation department cancer registry and the NHLS database with permission from the pathology department.

Patients from this database that had bilateral breast cancer, secondary primary cancers, metastatic disease, neo adjuvant chemotherapy or radiotherapy, any T stage > 2 and any N stage > 1 will be excluded.

Data relating to patient demographics, dates, stage, pathology, systemic treatment and 5 yr prognosis will be captured and analysed. (See Appendix 1).

Data will be inputted into an Excel spreadsheet and kept on a password protected database by the principal investigator.

Patients no longer attending for follow up will be contacted per telephone. The patients will be informed that the telephone call is for study purposes but that arrangements will be made if they need to recommence their follow up at Groote Schuur hospital.

ANALYSIS:

1. Descriptive statistics for demographic characteristics

   Mean, Median and standard deviation for nominal data

2. Student's **t-test** to compare mean ages

3. **Sample size calculation**

   This is a survival study and it will be underpowered because of the small difference in survival seen in the literature between N0 & N1 disease and a small sample size.

   A power analysis will be performed and not a sample size analysis because of above limitations.

4. **Confidence Interval** chosen to be 95%

5. The **Chi-square test** to compare the numbers of the node positive and node negative groups and those who received radiotherapy or not.

   It will also be used to calculate the p-value

6. **2 x 2 tables** to measure odds ratios

7. **Kaplan Meier curves** for 5 year LRR, DM, DFS and OS to describe the fraction of patients at different times

8. **The log-rank test** to compare the survival curves between the Node + and node – group and to yield a p-value to assess if the survival curves are different. This will be expressed as hazard ratios.

9. **Multivariate analysis**: assume the response variable is influenced by multiple factors or a combination of factors and use the **Cox regression model** to quantify these relationships.

ETHICAL ASPECTS:

Strict patient confidentiality will be maintained and there will be no disclosure of patients' details. The patients will remain anonymous.

Ethics approval was obtained from the UCT Research Ethics Committee and the Groote Schuur Hospital Medical superintendent, Dr Patel.

The Ethics approval number is: HREC REF: 024/2012

RESOURCES:

No financial funding is needed

OUTPUTS:

M.Med Mini thesis

Presentation at SASCRO and AORTIC 2013

Publication in a peer-reviewed journal

REFERENCES:

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(3) Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. RadiotherOncol 2007 03;82(3):247-253.

(4) Cosar R, Uzal C, Tokatli F, Denizli B, Saynak M, Turan N, et al. Postmastectomy irradiation in breast in breast cancer patients with T1-2 and 1-3 positive axillary lymph nodes: Is there a role for radiation therapy? Radiation Oncology 2011;6(1):28.

(5) Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005 12/17;366(9503):2087-2106.

(6) Abi-Raad R, Boutrus R, Wang R, Niemierko A, Macdonald S, Smith B, et al. Patterns and risk factors of locoregional recurrence in T1-T2 node negative breast cancer patients treated with mastectomy: implications for postmastectomy radiotherapy. Int J RadiatOncolBiol Phys 2011 11/01;81(3):e151-e157.

APPENDIX 1: Data collection sheet

Patient demographics

- Initials
- Folder No.
- RT No.
- Age
- Date of initial diagnosis
- Date of total mastectomy and axillary nodal clearance

Post Operative Staging

- T-stage
- N-stage
- M (all should be 0)

Pathology

- Size
- Margins
- Grade
- Ductal/Lobular/Ca in situ
- Extra capsular spread
- Lymphovascular invasion
- Multifocality
- ER/PR/Her2neu Status

Treatment

- Chemo (CAF/CMF/AC)
- Endocrine (Tamoxifen/Arimidex)
- Radiotherapy

5 year PROGNOSIS

- Date of loco regional relapse
- Date of metastasis detected
- Date of death

PART B

THE LITERATURE REVIEW

LITERATURE REVIEW

SEARCH METHODS

Academic Search Premier, Medline and Pubmed were used as search engines. The following key words were used in the search: "*post mastectomy radiotherapy", "early breast cancer", "T1, N1 breast cancer" &"prognosis of early breast cancer".*

The inclusion criteria of chosen studies was non metastatic breast cancers with single tumours less or equal to 5cm diameter and zero to 3 nodes positive after a total mastectomy and axillary nodal clearance. Articles that incorporated multiple tumours, single tumours bigger than 5cm, more than 3 axillary nodes positive, secondary primaries, metastatic disease and patients who received neo-adjuvant chemo – or radiotherapy were largely excluded, unless a subset analysis was done applicable to the inclusion criteria.

The search was bias towards the most recent original randomised controlled trials, or systematic reviews published in reputable Oncology journals.

The articles were appraised with the following factors in mind:

- Sample size
- Inclusion – and exclusion criteria
- Type 1 - & 2 errors
- Power
- Clinical Significance

Summary & Interpretation of relevant articles

INDEX

The standard treatment for early breast cancer is controversial as there is still no definitive evidence in favour of post mastectomy radiotherapy (PMRT) in T1-2, N1 breast cancer patients.

T1-2, N0-1 breast cancer treatment (1-5)

The Danish trial of 1997 is seen as a landmark study.[1] 1708 premenopausal women, who had mastectomies for stage II or III breast cancers were randomised to receive eight cycles of CMF chemotherapy plus radiation of the chest wall and regional lymph nodes (n=852) or nine cycles of CMF alone (n=856).

Locoregional relapse (LRR) was 9% among the women who received radiotherapy (RT) plus CMF and 32% among those who received CMF alone. Disease free survival (DFS) after 10 years was 48% among the women assigned to radiotherapy plus CMF and 34% with CMF alone. The overall survival (OS) at 10 years was 54% among the patients who were given radiotherapy and CMF and 45% among those who received CMF alone. This showed that the addition of PMRT and adjuvant chemotherapy reduces LRR and prolongs survival in high-risk premenopausal women with breast cancer.

A multivariate analysis demonstrated that radiation after mastectomy significantly improved disease-free survival and

overall survival, irrespective of tumour size, the number of positive nodes, or the histopathological grade.

Overgaard et al revisited this topic in 2007 with a subgroup analysis of their original trial (DBCG 82 b&c), to evaluate the LRR and survival in relation to number of positive nodes.[2]

It was found that the benefit of PMRT is equally pronounced in patients with 1 – 3 positive nodes as in patients with 4 or more nodes. PMRT reduced the 15-year loco-regional failure rate from 27% to 4% ($p < 0.001$) in patients with 1–3 positive nodes. Similarly, the 15-year survival benefit after RT was significantly improved in patients with 1–3 positive nodes (57% vs. 48%, $p = 0.03$). It was found that the survival benefit after PMRT was substantial and similar in patients with 1–3 and 4+ positive lymph nodes.

There was, however, critique received from reputable names in the field of breast cancer. The surgery in the Danish trials was said to be inadequate because a maximum of only 8 axillary nodes were removed. The view is that the difference in survival will be less if a more radical axillary clearance is done.

The British Columbia trial [14, 15] was designed to determine the survival impact of locoregional radiation therapy in premenopausal patients with lymph node positive breast cancer treated by modified radical mastectomy and adjuvant chemotherapy. 318 patients were assigned to receive no further therapy or radiation therapy (37.5 Gy in 16 fractions). Compared to the Danish trial, the axillary lymph node dissections were adequate (median of 11 axillary lymph nodes removed from levels I and II)

The results at 15-year follow-up showed that radiation therapy was associated with a statistically significant improvement in breast cancer survival, but that improvement in overall survival was of only borderline statistical significance.

At the 20 year follow up, chemotherapy and radiation therapy compared with chemotherapy alone, were associated with a statistically significant improvement in all end points analysed including:

- Overall survival (47% versus 37%; 95% CI: 0.55 to 0.98; P-value: 0.03).
- Long-term toxicities, including cardiac deaths (1.8% versus 0.6%), were minimal for both arms.

In a subgroup analysis the authors found that the reduction in the relative risk of a recurrence that was obtained by adding radiation to chemotherapy was similar in the subgroup with one to three positive nodes and the subgroup with four or more positive nodes.

This finding suggests that the artificial - and outdated distinction between three versus four or more positive nodes is not an accurate indicator for risk of recurrence alone. The decision to give PMRT should therefore be based on each individual patient's specific risk factors.

Cosar et al did a retrospective review of 66 patients who received PMRT and 24 patients who did not.[3]Radiotherapy improved LRR (3% for RT vs. 17% for no-RT, p = 0.038), DM (12% vs. 42%, p = 0.004) as well as 5 year DFS (82.4% vs. 52.4%, p = 0.034), but the 5 year OS was statistically insignificant (90% vs. 62%, p = 0.087).

This study is in agreement with the Danish trials but it doesn't show a similar dramatic improvement in OS with adding PMRT.

Avril et al selected 1105 patients who were treated with total mastectomy and axillary nodal clearance, without adjuvant chemotherapy or hormonal treatment.[4]In this series at least 10 nodes were examined .The impact on overall survival was similar to the Danish trials. The OS for the N1 with RT-groups was 66% & 46% at 10 & 20years respectively compared to 56% & 40% in the N1 without RT-groups. The authors concluded that the similarity of results with those of the Danish trials strongly suggest that the effects of postoperative are independent from systemic therapies.

Fowble comments on a meta-analysis of the early randomised trials of postmastectomy radiation which showed a 66% reduction in locoregional recurrence with radiation compared to surgery alone.[5] This benefit, however, did not translate into a statistically significant improvement in overall survival. Radiation contributed to an increased incidence of non-breast cancer deaths resulting from cardiovascular disease.

The author identified a subgroup of patients who appeared to have a 25–30% risk of LRR:

- Patients < 50yrs old
- Close – or positive resection margin
- Inadequate axillary dissection

The role of Post Mastectomy Radiotherapy (6-7)

Clarke et al did a large metanalysis of 42 000 women in 78 randomised treatment comparisons.[6] Here the "4:1 rule" was first quoted. It states that, in the hypothetical absence of other causes of death, for every 4 local recurrences prevented in the long run, one life is saved with PMRT. In the trials of radiotherapy after mastectomy and axillary clearance, the 5-year risk of local recurrence among the controls depended strongly on the number of involved nodes. (6%, 16%, and 26% respectively for 0, 1–3, and ≥4 involved nodes). Among women with mastectomy, axillary clearance and node-negative disease, the absolute reduction in 5-year local recurrence risk after radiotherapy was only 4% (2% *vs.* 6%), so if one death from the original breast cancer is avoided for every four local recurrences avoided, then the expected reduction in 15-year breast cancer mortality after radiotherapy would be only 1%.

The authors combined node positive disease into one group and found that the absolute effects of radiotherapy in this group on 5-year LRR were substantial (6% *vs.* 23%)

There was, at least with some of the older radiotherapy regimens, a significant excess incidence of contralateral breast cancer and a significant excess of non-breast-cancer mortality in irradiated women. Both were minimal during the first 5years, but continued after year 15. The excess mortality was mainly from heart disease and lung cancer

Wang et al[25] did a prospective randomised controlled multi-centre trial which comprised 681 women with triple-negative stage I–II breast cancer who had mastectomies. 315 patients received systemic chemotherapy alone and 366 patients received radiation after the course of chemotherapy.

The authors found, after a median follow-up of 86.5 months, the 5-year Relapse Free Survival rates to be 88.3% and 74.6% for adjuvant chemotherapy plus radiation and adjuvant chemotherapy alone, respectively. (HR 0.77 [95% CI 0.72, 0.98]; P = 0.02).

The 5-year OS significantly improved in the adjuvant chemotherapy plus radiation group compared with chemotherapy alone (90.4% and 78.7%) (HR 0.79 [95% CI 0.74, 0.97]; P = 0.03). No severe toxicity was reported.

This trial created a lot of interest as it shows a significant benefit from PMRT in high risk node negative disease

Smith et al identified 18,038 women with T1-2 node-positive invasive breast cancer who were treated with mastectomy between 1988 and 1995.[7]The median follow-up was 8.1 years. A total of 11,051 patients (61%) had one to three positive nodes. Of those patients, only 8% received PMRT compared with 20% of patients with four to six involved nodes and 31% of patients with seven or more positive nodes. This study differs from the current practise, where PMRT is indicated in all patients with more than 3 positive nodes.

They found that the survival benefit from PMRT increased with the number of involved regional lymph nodes, reaching significance at a threshold of seven or more involved nodes. No OS benefit from PMRT was noted for patients with one to three involved nodes, and routine use of PMRT was not supported. They suggested that the decision to offer PMRT for such patients must be individualized based on clinicopathologic risk factors and patient preference.

Supra Clavicular Radiotherapy (8)

Yates et al commented that in many centres, supraclavicular fossa radiotherapy (SCFRT) is not routinely offered to breast cancer patients with one to three positive lymph nodes.[8] They aimed to identify a subgroup of these patients who are at high risk of supra- or infraclavicular fossa relapse and can benefit from SCFRT.

They performed a retrospective analysis of 1,065 cases. Patients underwent radical breast conserving surgery or mastectomy. A total of 45% of patients received adjuvant chest wall/breast RT. No patients received adjuvant SCFRT. The primary endpoint was supra clavicular failure rate. (SCFR)The SCFR rate was 9.2%. Median time from primary diagnosis to SCFR was 3.4 years (range, 0.7–14.4 years). A higher grade and number of positive lymph nodes were the most significant predictors of SCFR on multivariate analysis. 10 year SCFR rates were less than 1% in all patients with Grade 1 cancers compared with 30% in those having Grade 3 cancers.

The author concluded that patients with two to three positive axillary nodes and/or high-grade disease may warrant consideration of SCFRT.

RT related morbidity (9)

Hojris et al selected a subgroup of 84 patients from the Danish Trials (82b and c) and looked at the late treatment-related morbidity after mastectomy and adjuvant systemic treatment with and without postoperative irradiation.[9]

The median length of follow-up from mastectomy was 9 years (range 6–13 years). Lymphoedema was measured in 14% of the irradiated patients and 3% of the non-irradiated patients. Slightly decreased shoulder mobility was measured in 45% of the irradiated women and 15% of the non-irradiated patients, but moderate – to more severe impairment was seen in only 5% of the irradiated patients and in none of the non-irradiated patients (p=0.004). 17% of the irradiated patients and 2% of the non-irradiated patients found that impairment of shoulder movement caused symptoms (p=0.001)

Risk – & prognostic factors (10-11)

T1-2, N0 patients may warrant PMRT. In the past, PMRT was only considered for these patients if the surgical margins were involved and no further surgery was indicated. However, multiple studies have questioned whether early-stage disease with aggressive biological markers (such as LVI, ER0-2 and young age) should warrant PMRT.

Abi-Raad et al reviewed 1136 T1-T2, N0 cases treated with mastectomy without PMRT.[10] The 10-year LRR was 5.2% (95% CI: 3.9–6.7%). The chest wall was the most common site of LRR (73%).Tumour size, margin, patient age, systemic therapy, and lymphovascular invasion (LVI) were significantly associated with LRR on multivariate analysis. The 10-year LRR for patients with no risk factors was 2.0% (95% CI: 0.5–5.2%), whereas the LRR for patients with three or more risk factors was 19.7% (95% CI: 12.2–28.6%).

It was suggested that patients with T1-T2N0 breast cancer who undergo mastectomy represent a favourable group for which PMRT renders little benefit, but selected patients with multiple risk

factors including LVI, tumour size ≥2 cm, close or positive margin, age ≤ 50, and no systemic therapy are at higher risk of LRR and may benefit from PMRT.

Truong et al reviewed 821, T1–T2, N1 patients between 1989 and 1997 treated with mastectomy without adjuvant RT and aimed to define the individual - and combinations of factors associated with an increased risk of LRR that may justify PMRT. [11]

The median follow-up was 7.7 years. Systemic therapy was used in 94% of patients. The 10-year LRR was 12.7%. Without PMRT, a 10-year LRR risk of >20% was identified in women with one to three positive nodes plus at least one of the following factors: age <45 years, Stage T2, histological Grade 3, ER-negative disease, medial location, more than one positive node, or >25% of nodes positive (all $p < 0.05$ on univariate analysis).

On multivariate analysis, the following were statistically significant independent factors associated with greater LRR, which merited consideration for PMRT:

- Age <45 years,
- >25% of nodes positive (no. of positive nodes divided by number of nodes removed),
- a medial tumour location, and
- ER-negative status

This review showed that the number of lymphnodes is an important prognostic factor. The ratio of positive to total excised lymphnodes will be discussed in the following 4 articles.

Lymphnode ratios (12-19)

Truong et al noted discrepancies in reported baseline locoregional recurrence (LRR) risks in T1–T2, N1 patients. They postulated that it is attributed to variations in lymph node staging techniques, which have yielded different numbers of dissected lymph nodes. [12] They set out to evaluate the prognostic impact of the lymphnode ratio (LNR) on recurrence and survival in women with one to three positive lymph nodes.

542 women who received post mastectomy adjuvant systemic therapy without radiotherapy were reviewed. Ten-year LRR, distant recurrence (DR), and OS rates were stratified by the number of

positive lymph nodes, the number of dissected lymphnodes, and the percentage of positive lymph nodes.

The median follow-up was 7.5 years. LRR, DR, and OS rates correlated significantly with the number of positive lymph nodes and the percentage of positive lymph nodes, but not with the number of dissected lymph nodes. The cut-off level at which the most significant difference in LRR was observed was 25%positive lymph nodes (the 10-year LRR rates were 13.9% and 36.7% in women with≤ 25% and >25% positive lymph nodes, respectively; *P*=0.0001). Higher DR rates and lower OS rates were observed among patients who had > 25% positive lymphnodes compared with patients who had ≤ 25% positive lymph nodes (DR: 53% vs.30%, respectively; P =0.0001; OS: 43% vs. 63%, respectively; P =0.0001). On multivariate analysis, the percentage of positive lymph nodes and the histological grade were significant, independent factors associated with LRR, DR, and OS.

The authors concluded that the LNR may be used to identify patients at high risks of postmastectomy locoregional and distant recurrence. These patients may benefit from adjuvant radiotherapy and more aggressive systemic therapy regimens.

The extent of axillary dissection differs between centres and this makes the evaluation of results troublesome. Truong et al compared data between 2 centres to examine the power of the LNR. [13]

82 patients with N1 breast cancer treated without PMRT in the British Columbia (BC) randomized trial were compared with data from 462 patients treated without PMRT in prospective chemotherapy trials at the M. D. Anderson Cancer Centre (MDACC).[14, 15, 16, 17] The median number of excised nodes was 10 in BC and 16 in MDACC. The 10-year LRR rate for patients with 1–3 positive nodes was higher in BC compared with MDACC (21.5%vs. 12.6%; *p*= 0.02). However, when examining LRR using the LNR, no differences were found between institutions. Nodal ratio >20% was associated with LRR >20%, warranting PMRT consideration. In patients with 1–3 positive nodes, evaluating nodal positivity using LNR reduced inter-institutional differences in LRR estimates and the authors concluded that the LNR may be useful for extrapolating data from prospective trials to clinical practices in which axillary staging extent vary.

Voordeckers et al analysed 810 patients with invasive, node-positive breast cancer to evaluate if there was a correlation between the ratio of involved axillary lymph nodes and OS. All pT-stages were included.[18]

The ratio of nodal involvement (LNR) was categorized into three groups, pN ≤ 10% (n = 212); between 11% and 50% (n = 346) and between 51 and 100% (n =183). The OS at 5 and 10 years was 78% and 59% respectively. The cause specific survival rates were 84% and 69%. In univariate analyses, age; grade; pT-stage; chemotherapy, the number of involved nodes ≤ 3 versus >3 and the LNR were statistically significantly associated with overall survival. On multivariate analysis it was found that the LNR was the most significant prognostic factor.

Van der Wal et al noted that clarity regarding the axillary dissection and survival is essential, especially in a period of increasing popularity for the sentinel node biopsy. [19]

Data from 453 patients with stage I or II breast cancer were studied to investigate whether the total number of removed lymph nodes and the ratio of invaded/removed lymph nodes lymph node ratio (LNR) would prove to be independent prognostic factors for survival. The total number of removed lymph nodes and the LNR were analysed for their prognostic value in comparison with known prognostic factors.

Node-negative patients with <14 lymph nodes removed had a 10 year survival of 79% compared with 89% in patients with ≥14 lymph nodes removed (P = 0.005). The 10 year survival for patients with an LNR ≥ 0.2 was 52%, compared with 73% for patients with an LNR<0.2 (P=0.0001). For node-negative patients, only age and total number of removed lymph nodes were significant prognostic factors. For node-positive patients, age, total number of removed lymph nodes and the LNR were significant risk factors for survival outcome. The LNR was also significantly associated with the presence of distant metastases during follow-up(hazard ratio 3.56, range 1.63 - 7.77).

The authors concluded that for node-positive patients, the LNR proved to be an excellent predictor for survival outcome or development of metastatic disease and that the selection of lymph node-positive patients based on the LNR may guide specific adjuvant treatment choices.

Consensus statements and – guidelines (20-21)

Gnant et al summarized the 2011 St Gallen's consensus. Routine PMRT was clearly endorsed for patients with more than 3 involved nodes (88% yes, 5 % no). PMRT was declined for patients with 1-3 affected nodes (18% yes, 71% no) unless they were young (<45 yrs;

51% yes, 42% no) or presented with extensive vascular invasion (57% yes, 26% no). [20]

The NCCN guidelines (version1.2014) advises strong consideration of postmastectomy irradiation in women with 1 to 3 positive axillary lymphnodes based on data from the Danish- [1,2] and British Columbia trials [14,15]. It admits that it generated substantial controversy among their panel members because high level evidence exists but it is contradictory.

The ESMO guidelines of 2013 support the use of PMRT for patients with one to three positive axillary lymph nodes and call the evidence "as strong as for patients with more involved lymph nodes, however less accepted". ESMO recommends it should be considered, in the presence of additional risk factors such as young age, vascular invasion and a low number of examined axillary lymph nodes.

The latest version of Uptodate ® comments that decisions regarding the treatment of women with less than four pathologically involved nodes should be individualized based on the patient's specific risk profile and consideration of both the benefits and risks of RT. They recommend regional RT for women who wish to maximize the opportunity to reduce their risk of recurrence and potentially improve disease-specific survival. However, patients should be counselled about the higher risk of toxicities compared with breast RT only. For women at greater risk of toxicities for whatever reason and those not willing to be exposed to the increased risk of radiation-related toxicities (eg, lymphedema, radiation fibrosis), the authors would not proceed with regional RT, but offer local RT to the chest wall only.

Correspondence & Future Trials (22-24)

Marks et al entitled their article "One to Three Versus Four or More Positive Nodes and Postmastectomy Radiotherapy: Time to End the Debate".[22] This editorial was published in the JCO in 2008, but unfortunately, the debate has not yet ended.

The article mentions that the subsetting of patients into groups with one to three versus four or more positive nodes is an artificial distinction originating in the early days of adjuvant systemic therapy for breast cancer. The published data demonstrates that there is no magical change occurring at the 3 to 4 nodal boundary level. Locoregional relapse risk increases approximately linearly with the number of positive axillary nodes. The authors believed

that it is time to dispense with the artificial partitioning of patients into groups with one to three versus four or more positive nodes.

Regarding the toxicity of PMRT that is mentioned in earlier trials, the authors were not concerned. With modern treatment planning techniques, they feel that it is generally feasible to avoid the heart, and minimize lung exposure. With the RT fields designed to limit exposure to the dissected axillary tissues it is said that arm oedema should be a relatively uncommon event.

The author believes that comprehensive PMRT is appropriate for the great majority of node-positive patients undergoing mastectomy and some selection based on other clinical and biologic factors may be important and appropriate.

The JCO published a correspondence letter by Russel et al which referred to the editorial by Marks et al.[22] They did not agree that the PMRT debate is now closed.[23]

The first issue they addressed was the extent of the target volume for PMRT. The author mentions that it is unknown whether full locoregional radiation gives additional benefit beyond chest wall radiation alone, because there is an extremely low risk of axillary recurrence after adequate axillary dissection. The axillary fields are responsible for increasing the toxicity of PMRT (lung, brachial plexus, shoulder function, and arm oedema) as well. They feel that it is better attention to surgical technique in the axilla and widespread adoption of adjuvant anthracyclines, taxanes, trastuzumab, and hormonal therapy that are mainly responsible for substantial reductions in local recurrence rates.

They estimate the LRR of intermediate-risk patients is in the range of 5% to 15%,and that further reductions with PMRT may be too small to justify this treatment, especially if cardiac tissue is included in the treatment volume.

The authors agreed with Marks regarding the artificial cut-off at four or more positive nodes as an indication for PMRT. They suggested that the nodal ratios which have been shown to have prognostic value might be a more relevant parameter to determine local recurrence risk.

There is accumulating evidence that biologic factors, including genetic alterations and gene expression profiles will be able to predict the response to both adjuvant radiotherapy and chemotherapy. It is important to identify molecular markers which can guide treatment strategy for adjuvant radiotherapy.

The SUPREMO Trial (**S**elective **U**se of **P**ostoperative **R**adiotherapy Aft**E**r **M**astect**O**my) is currently recruiting patients and hopes to end the debate.

The role of postmastectomy chest wall irradiation without inclusion of the regional areas will be investigated in the intermediate-risk group (defined as T1N1, T2N1, or T2N0 with grade 3 or vascular invasion).[24]

Eligible patients will be randomised between no chest wall irradiation (standard) and chest wall irradiation (experimental arm). The primary end point is overall survival. Secondary end points are chest wall recurrence, disease-free survival, distant metastasis-free survival, acute and late morbidity, quality of life and cost effectiveness.

One of the most important aspects of the SUPREMO study is the TRANS-SUPREMO biological substudy. It provides an opportunity to prospectively study potential prognostic factors for local control as well as predictive factors of radiosensitivity. The latter may, in future, lead us to tailor-made medicine, predicting who will or will not benefit from postoperative radiotherapy.

In conclusion, The SUPREMO Trial will hopefully answer the question once and for all, and allow the radiation oncology community to move on from the 20th-century criteria of nodal status onto the 21st-century concepts of individual treatment tailoring, based on biology.

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PART C

THE PUBLICATION-READY MANUSCRIPT

THE ROLE OF ADJUVANT RADIOTHERAPY FOR BREAST CANCER PATIENTS WITH AXILLARY NODE NEGATIVE OR LIMITED NODALDISEASE AFTER TOTAL MASTECTOMY, AXILLARY NODAL CLEARANCE AND SYSTEMIC THERAPY.

AUTHOR: Dr Albert (A.Z.A) van Jaarsveld
Registrar: Clinical Oncology
Department of Radiation Oncology
Groote Schuur Hospital
Email: albert.vanjaarsveld@gmail.com
Contact no.0724909438

SUPERVISOR: Dr Hannah M. Simonds
Consultant: Clinical Oncology
Department of Radiation Oncology
Groote Schuur Hospital

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- Text: 3499

ABSTRACT

Background Breast cancer patients with tumours less than 5cm and zero to three positive axillary nodes(T1-2N0-1) are at intermediate risk for loco-regional relapse and distant relapse. Numerous consensus reports recommend that postmastectomy radiotherapy (PMRT) in addition to systemic therapy is indicated only in high-risk patients with four or more positive nodes. There is conflicting evidence and no consensus in favour of PMRT for T1-2, N0-1 breast cancer patients. This study aimsto evaluate the correlation of loco-regional relapse (LRR) rate, distant metastasis (DM) rate, disease free survival (DFS) and overall survival (OS) in this group of breast cancer patients treated with or without postmastectomy radiotherapy (PMRT) following modified radical mastectomy (MRM). In addition, this study compares outcomes between the node negative and node positive patients.

Patients & Methods Seventy two patients, with T1-T2 tumours, and 0-3 positive nodes who had undergone MRM between 2004 & 2006 at Groote Schuur hospital were analysed. Patient-related characteristics and treatment-related factors were evaluated in terms of LRR and OS through a Cox proportional hazard method. The 5-year Kaplan-Meier DFS and OS rates were analysed.

Results For the entire group, LRR and DM rates were 4% and 10%, respectively, and 5 years DFS and OS rates were 87% and 91%. In the T1-2, N1 group, the 5year LRR rate with PMRT was 0% vs. 5% without PMRT, DM rate 8% vs. 14%, 5 year DFS 92% % vs. 82%, 5 year OS 92% vs. 95%. None of these findings were statistically significant. There was no statistically significant difference in DFS & OS between the N0 & N1 groups. In multivariate analysis LVI, ER positivity and age > 50yrs showed a trend towards influencing OS, although not statistically significant.

Conclusions This study shows no convincing evidence in support of PMRT in early breast cancer. In a resource limited and patient loaded facility, the data do not support routine PMRT for T1-2, N1 patients. PMRT has to be reconsidered according to the prognostic factors and the decision has to be made individually with the consideration of long-term morbidity and with the patient approval. Key Words: *"post mastectomy radiotherapy", "T1, N1 breast cancer" & "prognosis of early breast cancer".*

INTRODUCTION

Breast carcinoma is the most common cancer in women worldwide. Treatment developments have aimed to reduce the recurrence of disease following primary surgery. Postmastectomy radiotherapy (PMRT) substantially decreases local recurrences and improves survival in patients with positive axillary lymph nodes.[1]It is also considered for patients with negative nodes if they have poor prognostic features such as unsatisfactory surgical margins and following neoadjuvant chemotherapy and surgery, amongst others.

Although potential benefits exist for delivery of radiation, treatment is not devoid of complications and therefore identifying the population with a favourable risk/benefit ratio for receiving radiotherapy is the goal of several studies. Breast cancer patients with small unilateral breast tumours (< 5cm) and no, or few, involved positive regional lymphnodes (1-3) have a good prognosis. There remains controversy whether all patients in this category needs adjuvant radiotherapy post mastectomy and systemic therapy.

The landmark trial that showed a benefit from PMRT is the Danish 82b trial.[2]It showed that the addition of postoperative irradiation to mastectomy and adjuvant chemotherapy reduces locoregional recurrences and prolongs survival in high-risk premenopausal women with breast cancer. High risk was defined as increased tumour size >5cm, positive axillary nodes, or skin or muscle infiltration. They showed a 9% OS improvement in all subgroups of patients. Overgaard et al revisited the controversial topic in 2007 and did a subgroup analysis of the original trials (DBCG 82 b&c) to evaluate the loco-regional recurrence rate and survival in relation to number of positive nodes. [3]It was found that the benefit of PMRT is equally pronounced in patients with 1 – 3 positive nodes as in patients with 4 or more nodes, both in terms of loco- regional recurrence and overall survival.

Contrary to this data there are trials suggesting that PMRT for early breast cancer may not be as beneficial. The negative result of the EBCTCG meta-analysis of clinical randomized trials [1] on adjuvant radiotherapy in breast cancer is in contrast with the Danish 82B, 82C - [2, 3] and British Columbia trials.[4, 5]

Clarke et al from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) did an extensive meta-analyses on 42 000 women in 78 randomised treatment comparisons with one of the comparisons being radiotherapy *vs.* no radiotherapy.[1] They reviewed 8500 patients with mastectomy, axillary clearance, and node-positive disease in trials of radiotherapy (generally to the chest wall and regional lymph nodes). PMRT produced similar *proportional* reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of radiotherapy versus not (recent or older; with or without systemic therapy), but large *absolute* reductions in local recurrence were seen only if the control risk was large. To help assess the life-threatening side-effects of radiotherapy, the trials of radiotherapy versus not were combined with those of radiotherapy versus more surgery. There was, at least with some of the older radiotherapy regimens, a significant excess incidence of contralateral breast cancer and a significant excess of non-breast-cancer mortality in irradiated women. Both were minimal during the first 5years, but continued after year 15. The excess mortality was mainly from heart disease and lung cancer. The conclusion of this article is the general assumption that only patients with very high risk of locoregional recurrence will benefit from postoperative radiotherapy in terms of survival.

In the Radiation Oncology Department of Groote Schuur hospital, the patients with tumours less than 50mm and 0-3 nodes involved previously did not *routinely* receive post mastectomy RT due to a lack of resources and treatment time. This study will assess a cohort of patients with N0-1 disease and will compare the node positive group to node negative patients in terms of relapse and survival, and the influence of radiotherapy, if any, on these outcomes.

PATIENTS AND METHODS

Patients

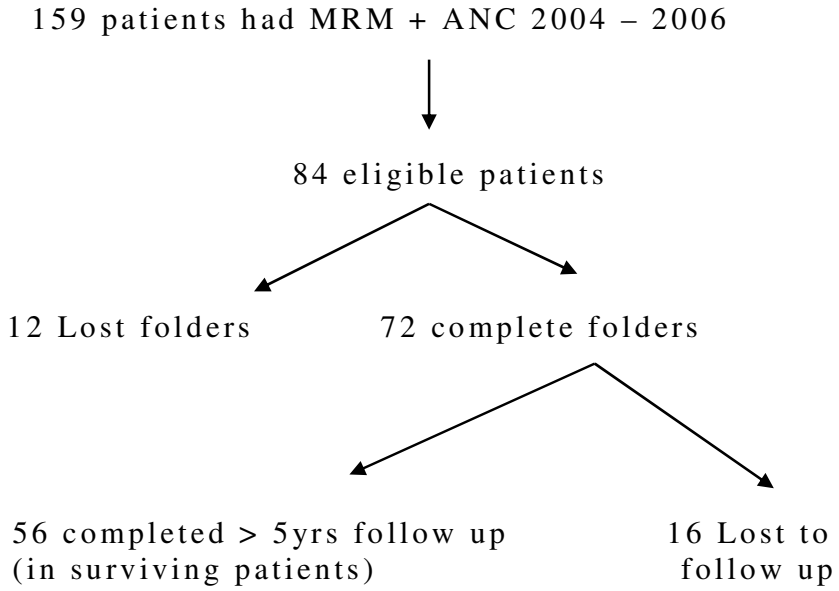
This is a single-institution retrospective study of all cases of invasive breast carcinoma treated by mastectomy with axillary dissection or sentinel node biopsy between 1 January 2004, and 31 December 2006. The cases were identified through the departmental cancer electronic patient registry (EPR) and the National Health Laboratory Service database. The author attempted to limit selection bias by using a pathology database to locate the patients who undergone mastectomies between 2004 and 2006. This eliminated bias towards patients who were followed up regularly in the department.

Patients were eligible if they had a modified radical mastectomy (MRM) + axillary nodal clearance (ANC) and the histology confirmed a T1-2, N0-1 breast cancer. The exclusion criteria were: Bilateral breast cancer; Secondary primary; Metastatic disease; Neo adjuvant chemotherapy or radiotherapy; Any T stage > 2; Any N stage > 1

A total number of 84 patients fit the inclusion criteria. Hospital records and pathology reports were reviewed. Ethics approval from the University of Cape Town was obtained prior to review of medical records. Complete anonymity of names and medical record numbers was maintained.

72 folders were found to be complete for data collection. 16 patients did not follow up for a full 5 years from date of mastectomy, because they were discharged to follow up at a secondary hospital. To eliminate possible bias these patients or their family were contacted telephonically in an attempt to complete a full 5 year follow up period.

The lost to follow up date, date of disease progression and death within 5 years post mastectomy for all patients were recorded as events. Locoregional recurrence was defined as tumour recurrence in the chest wall or regional lymph nodes. Local failure was defined as any recurrence of tumour in the ipsilateral chest wall. Regional failure was defined as any recurrence of tumour in the ipsilateral supraclavicular, infraclavicular, axillary, or internal mammary nodes. Any recurrence outside these areas was defined as distant mets. LRR occurring after DM is not included in the analysis of LRR.



Treatment

Surgery

The primary surgery performed was a modified radical mastectomy (MRM) and axillary node clearance (ANC). The pectoral fascia was stripped, but neither the major nor minor pectoral muscles were removed. Axillary clearance included removal of the central axillary lymphnodes involving level II. Pathological staging was reviewed based on AJCC 2002.

Chemotherapy

The most frequently used regimens were CMF (Cyclophosphamide, Methotrexate and 5-Fluorouracil at 28-day intervals for 6 cycles), CAF (Cyclophosphamide, Adriamycin and 5-Fluorouracil at 21-day intervals for 6 cycles) and AC (Adriamycin and Cyclophosphamide at 21-day intervals for 4 cycles)

Radiotherapy

All patients at this unit were simulated with a conventional simulator. The postmastectomy chest wall received a variety of doses i.e. 42 Gy (2.65Gy x 16), 45Gy (2.15Gy x 21) and 46Gy (2Gy x 23) through two tangential fields with 6 MV photons.

The technique used to irradiate the 18 patients was the opposing tangential field technique. This included 2cm of lung to compensate for breathing. An 18MV LINAC was used until late in 2005, when it was decommissioned - with half lead on a compensator plate, jig and full bolus of 1.5cm. Check films were done (for supraclav and med tan only) using the cassette holder made in the department's workshop.

Cobalt tangential fields were also done in between 2004 and 2006, using a jig and full bolus with check films as above.

A 6MV LINAC was used for some patients preferentially, as it had asymmetric jaws - a plan with no jig; 1.5cm bolus and a wedge were used.

No Portal imaging was available during the timeframe but the simulator was installed in 2005. This allowed for simulated images to be compared with the check films.

The axilla and supraclavicular fossa were included if there were extra capsular extension in any of the nodes (n=4).

The dose schedule varied:

- 2.15Gy x 21 fractions to 45.15Gy (ID2=46.5Gy3)were used in 9 patients,
- 2.65Gy x 16 to 42.4Gy (ID2= 48Gy3) were used in 4 patients,
- 2.35 Gy x 20 to 47Gy(ID2= 50Gy3) was used in 2 patients and the remaining 3 patients received
- 2Gy x 23, 2Gy x 25 and 2.65Gy x 15 each.

The BC trial[4] of 1997 used a Cobalt machine with 2.34Gy x 16 fractions to 37.5Gy to the chest wall (tangential fields).

The original Danish trial[2] of 1997 used a similar technique as above but patients received RT to the chest wall, including the surgical scar and regional lymph nodes (i.e., supraclavicular,

infraclavicular, and axillary nodes as well as internal mammary nodes in the four upper intercostal spaces). The prescribed dose was 2Gy x 25 to 50Gy. Most of the patients were treated with a LINAC, but 64 patients (7.5%) were treated at small departments that used 250-kV x-ray machines.

Radiotherapy quality assurance was achieved with immobilising the patients on a breastboard with the use of laser lights and tattoos on the patients' skin. A re-simulation was done before the patient started treatment and this was compared to the planning simulated x-ray image. Corrections were made if the difference in images were more than 5mm. In vivo dosimetry using a diode was carried out on day1 or 2 of treatment to ensure accurate delivery of the planned dose

Statistical Analysis

Age was calculated from date of birth to date of diagnosis. The primary end point was OS and it was calculated as the length of time in months from date of mastectomy until death, irrespective of cause. The secondary endpoints were LRR, DM & DFS. LRR and DM rates were calculated by first event analysis. When calculating DFS, any failure (local or distant) and/or death from any cause were considered as an event. The length of time until treatment failure was measured from the date of mastectomy.

OS - and DFS curves were estimated with the Kaplan-Meier method. The corresponding Hazard Ratio (HR) was calculated with their 95% CI. Statistical significance of outcome differences was determined using the log-rank test.

A univariate- and multivariate analyses using a Cox proportional hazard model to assess the association between the cause-specific hazards for DFS, OS and various prognostic variables were performed. All statistical tests were 2-tailed, with the level of significance established at $p \leq 0.05$.The Student's t-test was used to compare means, the Chi-square test & Fishers exact test of retrospective data was used to compare the numbers of the node positive and node negative groups and those who received radiotherapy or not.

We used IBM SPSS Statistics (version 21; SPSS Inc., Chicago, Il.) for survival analyses and GraphPad Prism (version 6; GraphPad Software Inc.; San Diego, California) for the remaining analyses.

RESULTS

Patient and disease characteristics (Table I)

The median age of this cohort is 54 (range 27-76). The main histological subtype was ductal carcinoma (81%).The node negative (N0) and node positive (N1) patients were equally distributed. Two patients did not undergo a nodal dissection.

33 patients had 1-3 positive nodes post mastectomy.11 patients had a LNR (ratio of positive lymphnodes to total number of lymphnodes removed) of less than 10%. 12 women had a ratio of between 10%& 20%, 6 between 21 & 30% and 4 between 31& 50%. The majority of patients had a nodal ratio of less than 20% and it demonstrates that in the majority of cases there was an adequate axillary dissection.
The surgical resection margins were documented as involved in 10% of patients. Nodal extracapsular extension (ECE) was reported in only 14% of the pathology reports. Four out of the 5 patients with reported extra capsular extension in the lymphnodes had PMRT.

One patient refused radiotherapy but she had 6 cycles of chemotherapy (CMF) and completed 5 years of endocrine treatment. She was disease free at 5 years.

The Her2/neu status was recorded in 43% of reports.

Adjuvant Treatment

All patients (n= 72) underwent a MRM + ANC. The median tumour size was 2cm (range, 0.2 – 5cm). Following MRM, 47 patients received chemotherapy and 26 patients received adjuvant endocrine therapy for 5 years after chemo. 24 patients received hormonal therapy only and no chemotherapy. 18 patients received PMRT and 54 patients did not.

When dividing the cohort into N0 and N1 patients it is noted that significantly less N0 patients received adjuvant chemotherapy (Table II). 64% of N0 and 68% of N1 patients were strongly ER positive. 73% of the N0, ER 6-8/8 group received 5 years of hormone treatment without chemotherapy, while 22% of the N1, ER 6-8/8 group received hormone treatment without chemotherapy.

Table II. COMPARING N0 TO N1 PATIENTS			
	Node - n=36 %	Node + n= 34 %	p-value
RT			
No RT	30 83%	22 65%	0.07
Chest wall RT	6 17%	12 35%	0.07
Chemo			
CAF X 6	6 17%	18 53%	0.01
CMF X 6	8 22%	4 12%	0.01
AC X 4	1 3%	1 3%	0.01
Incomplete	4 11%	5 15%	0.01
No Chemo	17 47%	6 17%	0.01
Endocrine Treatment for ER positive	N = 24	N = 25	
Received 5 yrs Tamoxifen	21 88%	24 96%	0.30
Received 5 yrs AI	2 9%	1 4%	0.50
Did not receive	1 4%	0 -	-

Post Mastectomy Radiation Therapy (Table III)

In the N0 cohort, 83% of patients did not receive PMRT, consistent with departmental guidelines. Of the six patients (17%) who did receive PMRT all had a close or involved surgical margin. This appeared to be the only statistically significant factor in the decision making progress to deliver PMRT. However in the group that did *not* receive PMRT 25% had a close margin. Although the percentage of patients who received PMRT had a higher incidence of other poor prognostic indicators such as high grade tumours or LVI, this was not statistically significant.

On examination of the N1 patients, twelve patients (35%) received PMRT. There was a statistically significant difference between the 2 groups with regards to positive margins. However, once again it is noted that 32% of the patients who did not receive PMRT had close margins (≥ 0 but < 5mm)

Looking at N1 patients who received PMRT, 83% of the patients had close- or involved margins (<5mm). The patients with clear margins (≥5mm) had both LVI and high grade ductal carcinoma. All the patients received adjuvant chemotherapy.

Table III. COMPARING HISTOLOGICAL FEATURES AND SURVIVAL IN N0 & N1 GROUPS BETWEEN NO PMRT AND PMRT

N0 Group (n = 36)	No PMRT n =30 83%	PMRT N=6 17%	p-value
LVI	5 17%	3 50%	0.07
GRADE 3	7 23%	1 17%	0.72
MARGINS +	2 7%	1 17%	0.42
CLOSE MARGINS	**6 20%**	**5 83%**	**0.002**
MULTIFOCAL	10 33%	1 17%	0.42
5 yr LRR	1 0.3%	0 -	0.45
5yr DM	2 7%	1 3%	0.42
5yr PFS	27 90%	5 83%	0.72
5yr OS	27 90%	5 83%	0.72

N1 Group (n = 34)	NO PMRT n = 22	65%	PMRT n = 12	35%	p-value
LVI	7	32%	8	67%	0.08
GRADE 3	6	27%	3	25%	0.89
MARGINS +	**0**	**-**	**4**	**33%**	**0.01**
MARGINS CLOSE	7	32%	6	50%	0.40
MULTIFOCAL	7	32%	5	42%	0.44
5 yr LRR	1	5%	0	-	0.45
5yr DM	3	14%	1	8%	0.65
5yr DFS	18	82%	11	92%	0.18
5yr OS	21	95%	11	92%	0.80

Survival (Table III)

For the entire group, LRR and DM rates were 4% and 10%, respectively, and 5 years DFS and OS rates were 87% and 91%.

In dividing the N1 group into patients who received PMRT and who did not, there was one death in each arm. There was a trend for an improved DFS in the irradiated patients. (Figure 1 and Figure 2)

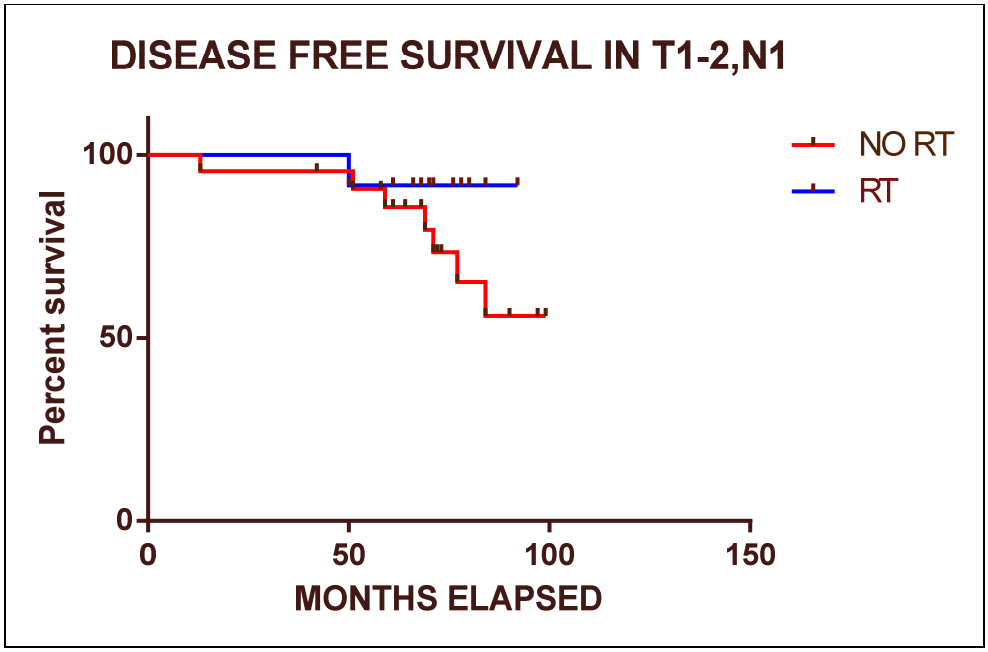


FIG.1 (p-value: 0.18; Test: Log-rank; HR: 3.84 (95% CI 0.64 – 11.62)

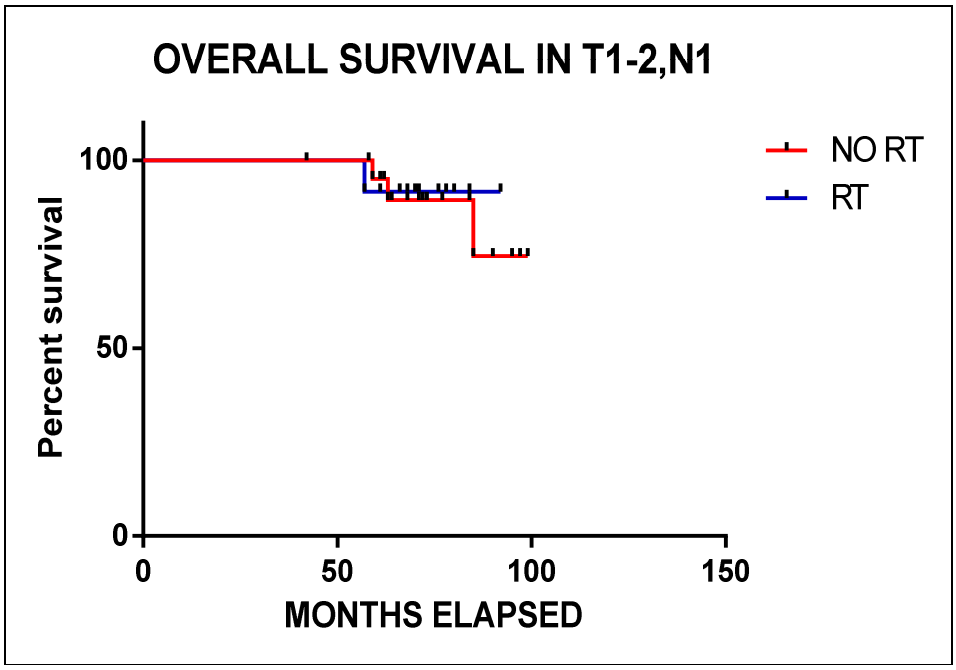


FIG.2 (p-value: 0.80; Test: Log-rank; HR: 1.33 (95% CI 0.15 – 11.63)

A subset analysis was done on 62 patients (Table IV) comparing the 5year survival- and progression rates between the node positive and node negative patients irrespective of PMRT or not. The patients who were discharged from Groote Schuur before 5 years of follow up were excluded from the analysis as they were interviewed telephonically and not in the clinic.

The groups were evenly distributed in numbers and the survival statistics were very similar with non-significant p-values. The Kaplan-Meyer survival curves demonstrate similar findings. (Figures 3 and 4)

TABLE IV. COMPARING SURVIVAL BETWEEN N0 & N1 GROUPS

N = 62

	Node +		Node –		p-value
	N = 32	%	N = 30	%	
5 yr LRR	2	6%	1	3%	0.59
5yr DM	7	22%	4	13%	0.38
5yr DFS	26	81%	25	83 %	0.32
5yr OS	28	88%	26	87%	0.87

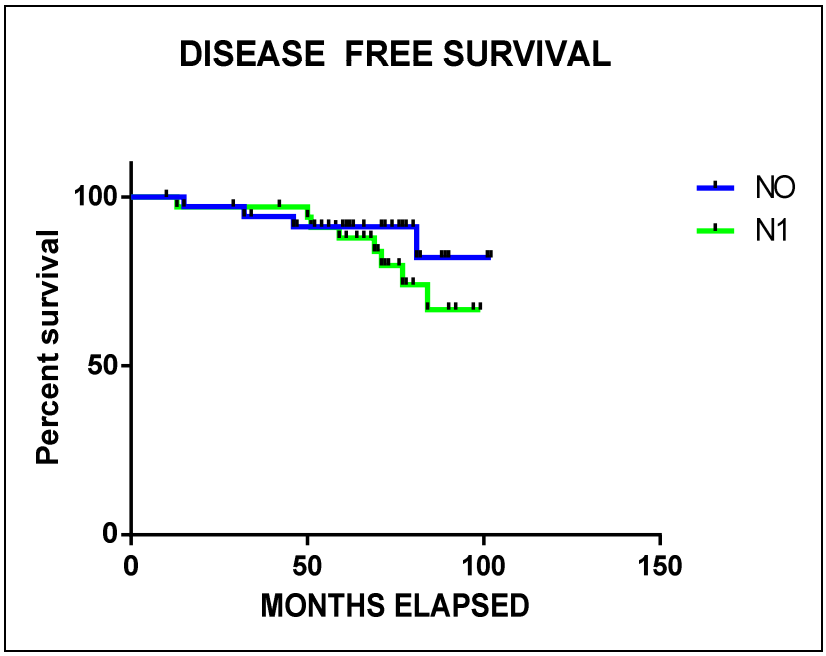


Fig.3 (p-value: 0.318; Test: Log-rank; HR: 0.55 (95% CI 0.18 – 1.74)

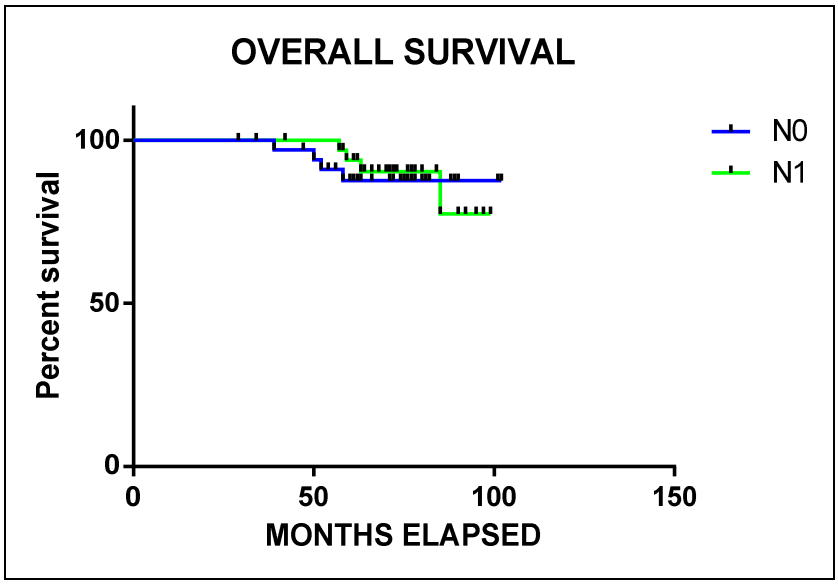


Fig.4 (p-value: 0.87; Test: Log-rank; HR: 1.13 (95% CI 0.28 – 4.52)

Uni- & Multivariate analysis (Table V)

On univariate analysis the T-stage (p = 0.07), N-stage (p= 0.11), grade (p = 0.24) and multifocality (p = 0.15) showed a trend towards influencing DFS but none were statistically significant. Positive margins (p = 0.19), high grade (p = 0.13) and negative ER status (p= 0.23) showed a trend towards influencing OS, but none of these factors were statistically significant. The T-stage was the only factor to (p = 0.02) show statistically significance for OS.

In the multivariate analysis for DFS, using the Cox proportional hazards model, N1 disease (p = 0.13; HR = 4.7, 95% CI 0.65 – 34),a high grade (p = 0.20; HR = 4.5, 95% CI 0.43 – 48), lobular ca (p = 0.15; HR = 4.6, 95% CI 0.57 – 38), multifocality (p = 0.27; HR = 2.8, 95% CI 0.44 – 19) and positive margins (p = 0.41; HR = 2.8, 95% CI 0.24 – 33) showed a trend towards influencing DFS.

In multivariate analysis, LVI (p = 0.25; HR = 0.20, 95% CI 0.12 – 3.19), ER Positivity [6-8] (p = 0.33; HR = 0.33, 95% CI 0.037 – 2.89) and age > 50yrs (p = 0.25; HR = 3.58, 95% CI 0.41 – 31) showed a trend towards influencing OS.

Table V. UNIVARIATE & MULTIVARIATE ANALYSES

UNIVARIATE	DFS (p-value)	OS (p-value)	
T-Stage	0.07	0.02	
N-Stage	0.11	0.38	
Grade	0.24	0.13	
Multifocality	0.15	0.44	
Positive margins	0.70	0.19	
ER Status	0.56	0.23	
MULTIVARIATE FOR DFS	HR	95% CI	p-value
N1 disease	4.7	0.65 – 34	0.13
High grade	4.5	0.43 – 48	0.20
Lobular Ca	4.6	0.57 – 38	0.15
Multifocality	2.8	0.44 – 19	0.27
Positive margins	2.8	0.24 – 33	0.41
MULTIVARIATE FOR OS	HR	CI	p-value
LVI	0.20	0.12 – 3.19	0.25
ER positive	0.33	0.037 – 2.89	0.33
Age > 50yrs	3.58	0.41 – 31	0.25

DISCUSSION

This small cohort study shows that PMRT did not influence LRR rate, DM rate, DFS and OSin the T1-2, N1 group of patients and that there was no difference in LRR, DM, DFS and OS between N0 and N1 patients.

The demographics of the patients in this study are similar to numerous international studies. The mean age and range is surprisingly similar to international data as we expected a younger mean in our cohort.[4,6,8,10,11,12,13,14,15,16]There were inconsistencies found in the pathology reports. In 2004 – 2006, ECE and her2/neu status were not frequently included. Since the dawn of the Herceptin era, the her2 status is now essential to all pathology reports. Two inconsistencies were found in the type of surgery. In these, an axillary nodal clearance (ANC) was not performed. It was the surgeon's decision and based on clinical findings.

A significant larger percentage of N1 patients received PMRT than N0 patients, and this is consistent with international data. [(9)]. There is consensus that T1-2, N0 patients do not warrant routine PMRT. There are well known indications for PMRT and our study indicated that close margins and LVI were the most predominant indications. Abi-raad et al identified patients with LVI, tumour size ≥2 cm, close or positive margin, age ≤50, and no systemic therapy that are at higher risk of LRR and may benefit from PMRT.[8]The chest wall was the most common site of LRR in their study. Two thirds of the patients in our study with node negative, involved margins who did not receive PMRT developed distant mets within 5 years of mastectomy. 1 patient died within 5 years. This shows the importance of PMRT when indicated.

The average 5year OS of the N0-group in 4 prominent international studies was 69% with PMRT and 62.5% without PMRT.[3,2,1,8] The OS in our study was significantly higher with PMRT (83%) and without PMRT (90%). We expected PMRT to increase OS in this study, but there were only 6 patients in the N0 with PMRT group and the cancer specific cause of death was not clear from the records. The good OS rate is encouraging. A possible explanation for these figures could be the low percentage of poor prognostic factors, and the fact that the majority of the patients received adjuvant chemo- and/or hormonal treatment.

In the comparison between the T1-2, N1 patients with – or without PMRT, this study found the 5year OS to be less in the PMRT group. This was an unexpected finding, although not statistically significant. The findings were compared to 10 international studies where the average 5year OS for the N1-group was 66% with RT and 60% without RT. [3,2,6,7,1,14]. The possible reason why our study failed to show a survival benefit from PMRT in the N1-group is the fact that there was only one death in each of N1 with PMRT and N1 without PMRT groups. The DFS, in contrast, shows a benefit from PMRT and this finding is consistent with above studies. LVI and positive margins were the predominant prognostic factors present in the N1 with PMRT group. These are important indications for PMRT and supported by the literature.

This study can be closely compared in numbers and demographics to the Turkish study of Cosar et al.[6] They showed that PMRT in T1-2, N1 patients caused a statistically significant improvement in the DFS. They identified the tumour size, involved lymph node ratio ≥ 25%, high grade, LVI and PNI as prognostic factors that warrants PMRT. This study is in agreement with the Danish trials but it doesn't show a similar dramatic improvement in OS with PMRT. In contrast, Smith showed no OS benefit from PMRT for patients with one to three involved nodes. They didn't support the routine use of PMRT.[16]This was in keeping with our findings.

The 5yr LRR of this study was 5% without RT and 0% with RT in the node positive group. This in encouraging when compared to Overgaard et al (PMRT reduced the 15-year LRR from 27% to 4% in patients with 1–3 positive nodes) [3]and Cosar et al (3% with RT vs. 17% with no-RT). Ragaz et al. reported a 5- year LRR rate of 21% with PMRT and 10% without PMRT. [5]

From the data comparing node positive to node negative patients (irrespective of PMRT), this study cannot confirm that N1 disease is a poor prognostic factor. The node positive group had a better OS than the node negative group, but this finding was non-significant. The DM - and LR rates, on the other hand, show that nodal positivity may contribute towards disease progression.

The interesting finding from the univariate analysis is that the size of the tumour (T1 vs. T2) seemed to influence the DFS and OS more than the expected prognostic factors like the LVI, grade, MF and nodal status. One expects positive margins to influence

survival, but due to the small numbers, it didn't reach significance. Truong et al saw the following factors on univariate analysis that influenced survival in T1-2,N1 patients: age<45 years, Stage T2, Grade 3, ER-negative disease, medial location, more than one positive node, or >25% of nodes positive (all $p < 0.05$). [12]

On multivariate analysis, several prognostic factors showed a tendency in our study to influence DFS & OS but none were statistically significant. The subtype of histology is seen to influence both DFS and OS and the less common invasive lobular-, mixed- and squamous carcinoma subtypes seem to have a poorer prognosis than ductal ca. In comparison to the studies from Truong et al, the age <45 years, >25% of nodes positive, a medial tumour location, and ER-negative status were statistically significant independent factors on multivariate analysis associated with greater LRR, which merited consideration for PMRT.[17,19]

A surprising finding is the HR of 0.20 associated with positive LVI. One would expect LVI to have a HR of > 1. The CI in this instance is quite wide and this is interpreted as a statistical error.

The predominant indication for PMRT in our study was close or positive margins, followed by LVI and high grade tumours. The one patient who died within five years post mastectomy + PMRT was at high risk of relapse due to N1 disease, Her2 positivity and the fact that most of the poor prognostic factors were positive (Grade 2, MF, margins ≤ 5mm, ECE). In addition, the chemo regime had to be changed from FAC to CMF after 3 cycles due to a decrease in left ventricular ejection fraction. (Appendix A.5)

The strength of the study is its high DFS and OS and lower LRR for both the N0 and N1 groups compared to international research. (Table VI) The limitation was the small number of patients, which resulted in an underpowered study. Only the patients who were alive and seen on follow up in the last 1 – 2 years were captured on the radiation oncology department's electronic patient registry. This necessitated extra data collection avenues to be explored to avoid a forced bias.
The follow up protocol was not standardised, and early breast cancer patients were frequently discharged before a follow up period of 5 years post mastectomy.

Table VI (N0& N1)

Series/ Author	n	Follow up (in months)	N-Stage	LRR w/o RT(%)	LRR With RT(%)	DFS w/o RT(%)	DFS With RT(%)	OS w/o RT (%)	OS with RT (%)
DBCG 82c	132	123	N0	23	6	40	43	55	56
DBCG (82b)	135	114	N0	17	3	62	74	70	82
Clarke	1428	60	N0	6	2	-	-	-	-
Abi-Raad	1136	120	N0	-	5	-	-	-	-
Van Jaarsveld	36	60	N0	0.3%	0 %	90%	83%	90	80

Series/ Author	n	Follow up (in months)	N-Stage	LRR w/o RT	LRR with RT(%)	DFS w/o RT(%)	DFS with RT(%)	OS w/o RT	OS with RT
DFCI	83	53	N1	5	2	75	79	85	77
Glasgow	141	63	N1	-	-	54	63	68	76
British Columbia	183	150	N1	33	33	49	63	-	-
DBCG 82c	794	123	N1	31	31	31	44	44	55
DBCG (82b)	1061	114	N1	30	30	39	54	54	62
Cosar	90	60	N1	17	3	52	82	62	90
Buchholz	18902	120	N1	-	-	-	-	63	-
Clarke	8505	60	N1	23	6	-	-	40	46

Voordeckers	419	60	N1	-	-	-	-	86	-
Arriagata	1105	120	N1	-	-	-	-	56	66
Arriagata	1105	240	N1	-	-	-	-	40	46
Van Jaarsveld	34	60	N1	5%	0%	82%	92%	95 %	92 %

The author recommends a strict follow up protocol that limits the discharge of patients within 5 years from diagnosis. There is a need to expand this study, by increasing the sample size of T1-2, N0-1 patients and evaluating the 10year survival rates.

So far no trial dedicated to solve this issue has been conducted. The National Cancer Institute of Canada Clinical Trials GroupMA25 study was designed to randomly assign patients with 1–3 positive nodes to receive either loco-regional radiotherapy or no radiotherapy after mastectomy, but the study was closed because of lack of accrual.

The SUPREMO trial (**S**elective **U**se of **P**ostoperative **R**adiotherapy Aft**E**r**M**astect**O**my) is currently ongoing andwas designed to evaluate the results ofchest wall irradiation in management of the patientswho underwent MRM with and without nodal disease, with only 1-3 nodes being included in the study. The results of this trial are eagerly awaited.

CONCLUSION

The results of this study are consistent with recent literature where the role for PMRT in early breast cancer is not clearly indicated. PMRT did not influence OS in the T1-2, N1 group of patients although a trend in improved DFS from PMRT was seen. This finding could be related to the small sample size and the short follow-up time of 5 years.

There was no difference found in OS and DFS between N0 and N1 patients, but the high survival rate is noted which is an indication of success in treating oncology patients in a resource limited country.

The much awaited results of the SUPREMO Trial will hopefully put an end to the controversy. The author recommends that the current indications for PMRT should remain based on poor prognostic factors of the patient and the discretion of the radiation oncologist.

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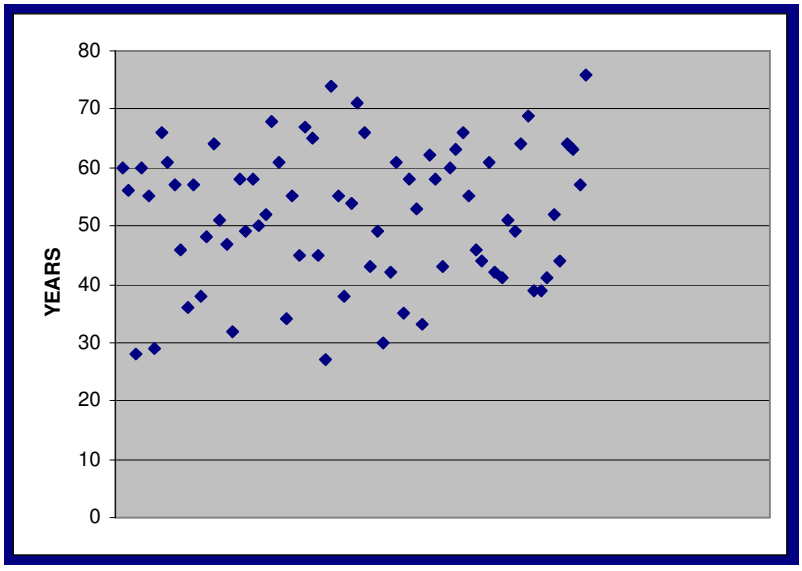
PART D

APPENDIX

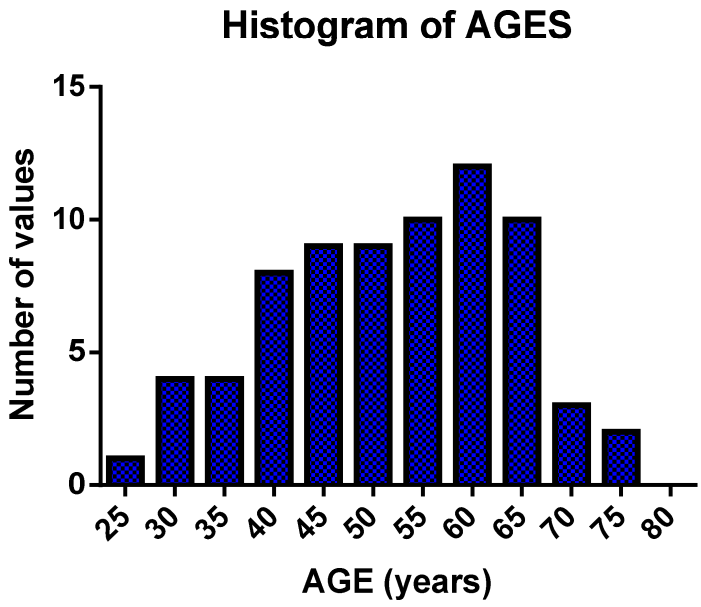
INDEX

A) ADDITIONAL RESULTS

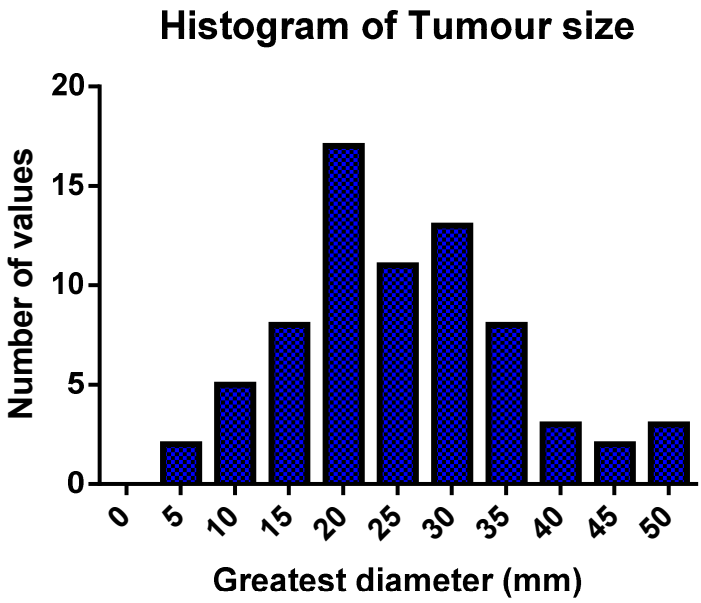
1) DESCRIPTIVE DATA



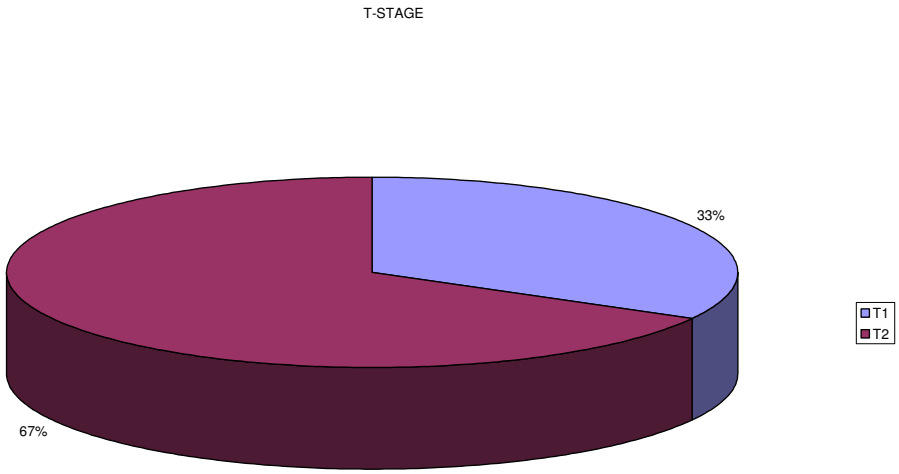
a) The scatter plot demonstrates a wide distribution of ages in the cohort



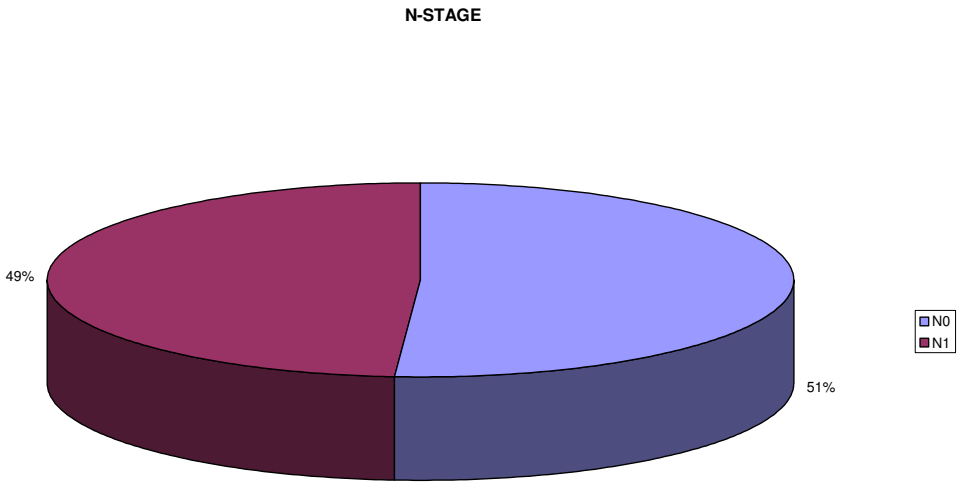
b) The histogram shows that breast cancer is predominantly a disease of the middle-aged and elderly population.



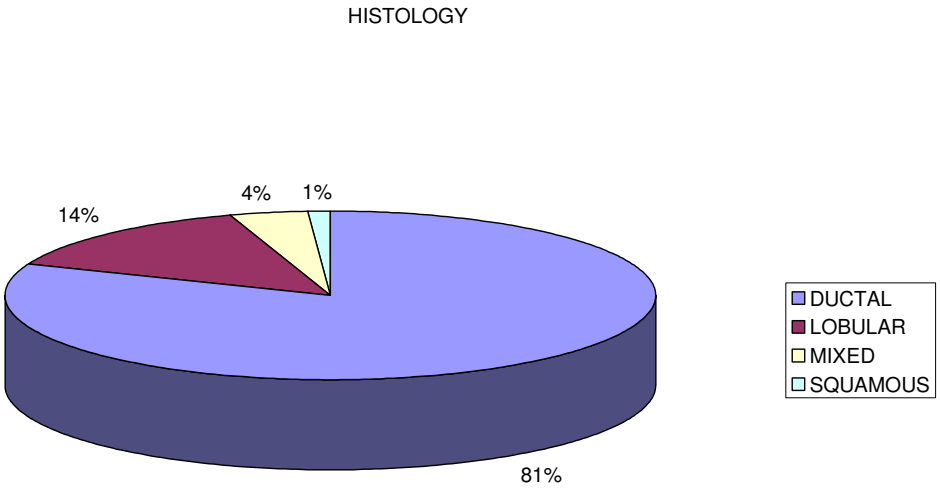
c) The histogram of tumour sizes shows a bell-shaped curve for T1 – T2 size breast cancers in this cohort.



d) The pie chart of T-stages shows a predominance of T2 breast cancers in the cohort. This correlates with most international studies.



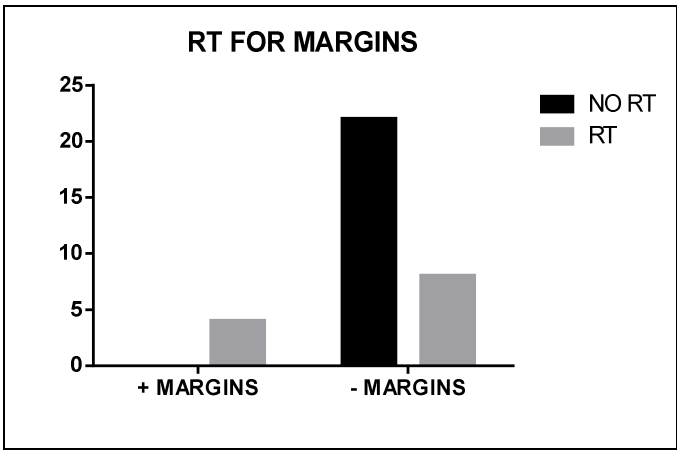
e) The pie chart of N-stages shows a well balanced distribution



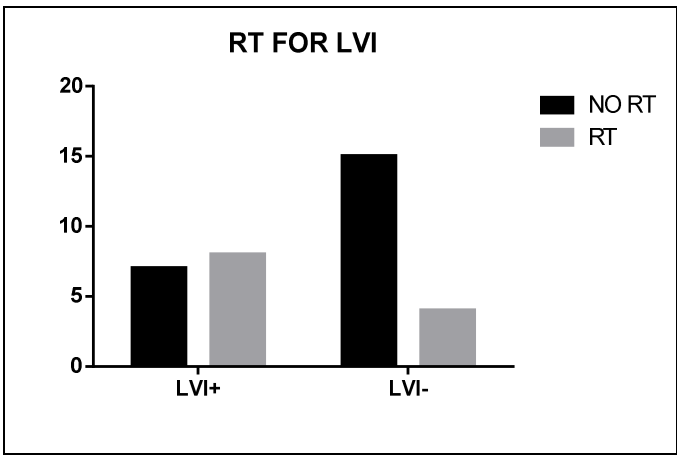
f) The pie chart of histology subtypes correlates with the well known fact that ductal carcinoma is the most commonly found histology in breast cancer.

2) COMPARATIVE DATA

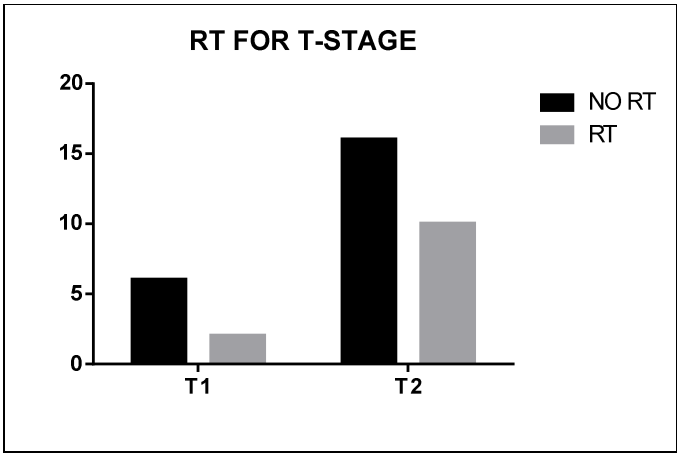
a. RT vs. No RT in N1-Disease Histograms



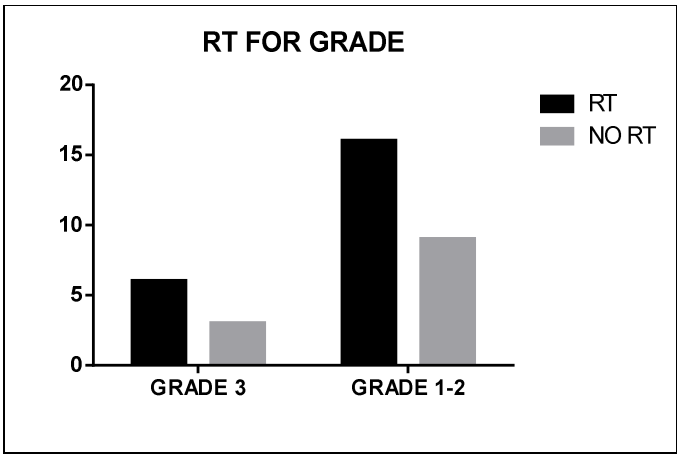
All patients with positive margins, received PMRT and most patients with negative margins did not, although there were factors present in this group that warranted PMRT.

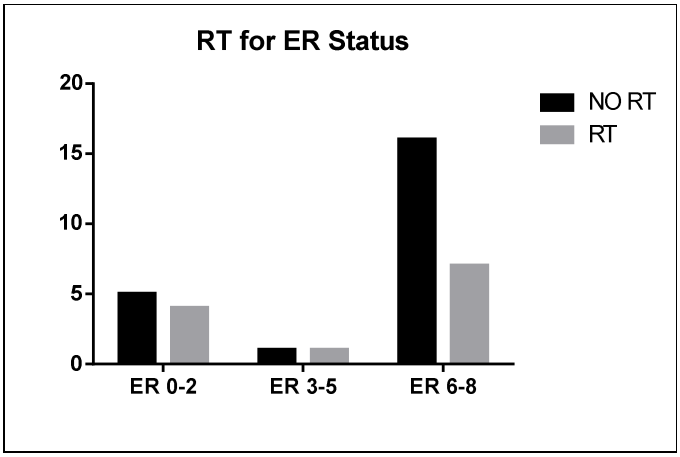


LVI played a role in deciding on PMRT. LVI is a known poor prognostic factor.

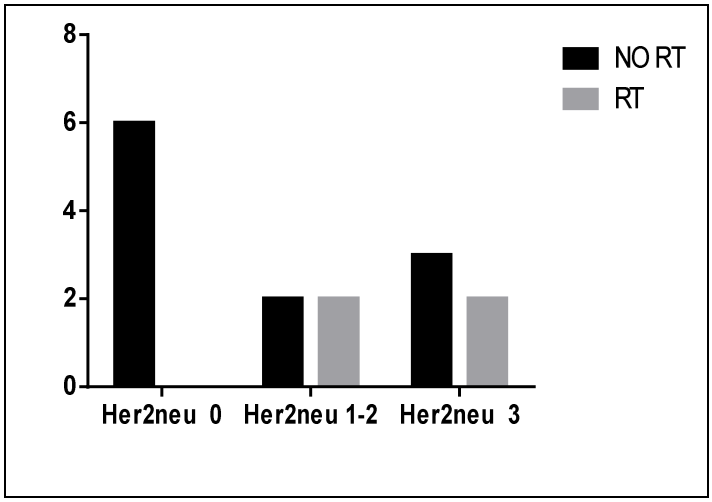


There were more T2N1 patients than T1N1 patients but the T-stage didn't seem to have an impact on the PMRT decision



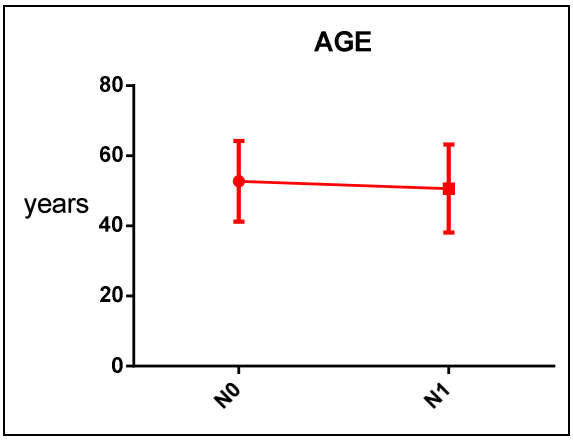


One cannot draw significant conclusions from above 2 histograms except the finding that strongly ER positive patients did not routinely receive PMRT.

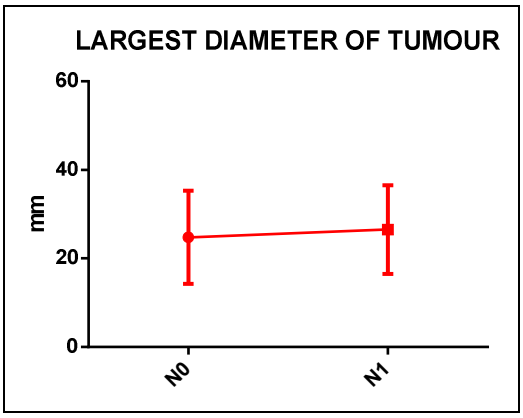


The Her2neu status was poorly reported but a negative status was seen as a positive prognostic factor and no Her2 negative patients received PMRT

b) N0 vs N1



A Box plot of age distributions in the N0 and N1 group, calculated by the two tailed unpaired t test, shows no statistically significant difference between the groups (p-value:0.48)



A Box plot of tumour size in the N0 and N1 group, calculated by the two tailed unpaired t test, shows no statistically significant difference between the groups (p-value:0.48)

SECTION 3 – UNIVARIATE ANALYSIS

a) Disease Free Survival

FACTORS	P-VALUE
Age	.825
Size	.799
T	.077
N	.110
Margins	.704
Histology	.086
LVI	.567
Grade	.243
MF	.155
ER	.562
RT	.636
Chemo	.507
Endocrine Rx	.895

b) Overall Survival

FACTORS	P-VALUE
Age	.567
Size	.993
T	.018
N	.379
Margins	.191
Histology	.192
LVI	.561
Grade	.126
MF	.441
ER	.237
RT	.433
Chemo	.830
Endocrine Rx	.948

SECTION 5 - MULTIVARIATE ANALYSIS

a) Disease Free Survival

FACTORS	HR	LOWER 95% CI LIMIT	UPPER 95% CI LIMIT	P-VALUE
N	4.707	.652	33.990	.125
Sizes	2.162	.324	14.440	.426
LVI	.930	.102	8.480	.949
ERSTATUS	.799	.138	4.635	.802
GRADES	4.543	.430	47.956	.208
HISTO	4.659	.565	38.394	.153
MARGIN	2.805	.236	33.359	.414
AGES	.738	.107	5.063	.757
MF	2.877	.439	18.869	.271
RT	.359	.039	3.334	.368
CHEMOT	.520	.054	5.009	.571

b) Overall Survival

FACTORS	HR	LOWER 95% CI LIMIT	UPPER 95% CI LIMIT	P-VALUE
N	1.269	.176	9.152	.813
LVI	.195	.012	3.194	.252
MF	1.750	.187	16.375	.624
RT	1.219	.175	8.506	.841
Sizes	1.774	.266	11.852	.554
ERSTATUS	.330	.037	2.989	.324
GRADES	.481	.040	5.800	.564
HISTO	1.025	.102	10.314	.983
MARGIN	.000	.000	.	.989

AGES	3.582	.414	31.013	.247
CHEMOT	2.047	.138	30.466	.603

SECTION 5 - SUMMARY OF T1-2,N1 PATIENTS WITH PMRT

	Patient1	Patient2	Patient3	Patient4	Patient5	Patient6	
SIZE(mm)	25	18	35	17	45	15	
MARGINS	2	2	1	0	0	1	
HISTO	2	1	1	1	1	3	
ECS	n/r	1	n/r	n/r	0	0	
LVI	0	0	0	1	1	1	
GRADE	1	1	2	2	3	2	
MF	0	0	0	0	1	1	
ER	2	2	2	0	0	2	
HER2	n/r	n/r	n/r	0	0	3	
FRACTIONS	23	21	21	16	20	16	
DOSE/#	2Gy	2.15	2.15	2.65	2	2.65	
CHEMO	FAC x6	FAC x6	FAC x6	FAC x6	FAC x6	FAC x6	
OVERALL SURVIVAL	> 5yrs	> 5yrs	> 5yrs	> 5yrs	> 5yrs	> 5yrs	

	Patient7	Patient8	Patient9	Patient10	Patient11	Patient12
SIZE(mm)	22	16	30	36	35	43
MARGINS	2	2	1	1	1	1
HISTO	1	1	1	1	1	1
ECE	n/r	1	0	n/r	1	1
LVI	1	1	0	1	1	1
GRADE	3	3	1	2	2	2
MF	0	1	1	0	1	0
ER	0	2	2	2	2	0
HER2	2	3	n/r	n/r	2	0
FRACTIONS	21	21	16	25	20	16
DOSE/#	2.15Gy	2.15Gy	2.65Gy	2	2.35Gy	2.65Gy
CHEMO	CMF x6	AC x 4	0	CMF x6	FACx3 + CMF x3	FAC x 6
OVERALL SURVIVAL	> 5yrs	> 5yrs	> 5yrs	> 5yrs	57months	> 5yrs

GENERAL GUIDE

Negative/NO = 0

Positive/YES = 1

ER:

Negative (0 – 2/8) = 0

Intermediate (3 – 5/8) = 1

Positive (6-8/8) = 2

MARGINS:

5mm = 0

0 ≤ 5mm = 1

0mm/involved = 2

HISTO:

Ductal = 1

Lobular = 2

Mixed = 3

Squamous = 4

CHEMO:

None = 0

CAF = 1

CMF = 2

AC = 3

(Ex. 1.6 = CAF X 6 cycles)

n/r = not reported

SECTION 6 - SAMPLE SIZE CALCULATION

This is a survival study which is expected to be underpowered because of the small difference in survival seen in the literature between N0 & N1 disease and it has a small sample size.

A power analysis was performed for a two-sample comparison of proportions for:

a) N0 without RT vs. N1 without RT

b) N0 with RT vs. N1 with RT

From extensive Literature review it was seen that:

1. The N0 without RT group has a mean 5year survival of 62.5%
2. The N1 without RT group has a mean 5year survival of 60%
3. N0 with RT group has a mean 5year survival of 69%
4. N1 with RT group has a mean 5year survival of 66.7%

The calculation

a) Test Ho: p1 = p2, where p1 is the proportion of survivors after 5 years in N0 disease without RT (n1 = 30) and p2 is the proportion of survivors after 5 years in N1 disease without RT (n2 = 22)

Assumptions:

alpha = 0.0500 (two-sided)
p1 = 0.6250
p2 = 0.6000
n1 = 30
n2 = 22
n2/n1 = 0.73

Result: Power = 0.02

b) Test Ho: p1 = p2, where p1 is the proportion of survivors after 5 years in N0 disease with RT (n=6) and p2 is the proportion of survivors after 5 years in N1 disease with RT (n=12)

Assumptions:

alpha = 0.0500 (two-sided)
p1 = 0.6900
p2 = 0.6670
n1 = 6
n2 = 12
n2/n1 = 2.00

b) Result: Power = 0.01

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room [illegible] Falmouth Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

23 January 2012

HREC REF: 024/2012

Dr A Van Jaarsveld
Radiation Oncology
L -Block

Dear Dr Van Jaarsveld

PROJECT TITLE: THE PROGNOSIS IN A GROUP OF BREAST CANCER PATIENTS WITH T1-2, 1-3 POSITIVE AXILLARY NODES AFTER TOTAL MASTECTOMY, AXILLARY NODAL CLEARANCE AND SYSTEMATIC THERAPY.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

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

Approval is granted for one year till the 30th January 2013.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

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

Please quote the HREC. REF in all your correspondence.

Yours sincerely

Signed by candidate

pp PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF 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 Policies

Dear Dr Van Jaarsveld

Candidature Approval (VJRADR002)

Degree
MMed in Radiation Oncology

Title
The prognosis in a group of breast cancer patients with T1-2, 0-3 positive axillary nodes after total mastectomy, axillary nodal clearance and systemic therapy

Department
Radiation Medicine

Supervisor
Dr H Simonds

Ethics Approval
024/2012

I am pleased to advise that the Chair of the Dissertations/Doctoral & Masters Committee has approved your candidature for the above degree on behalf of the Committee. Formal approval was obtained by publication in the Dean's Circular, PG-Med Sept 2012.

Yours sincerely

Jackie Cogill

Jackie Cogill | Senior Secretary: Postgrad Academic Administration |Faculty of Health Sciences | University of Cape Town * Room N2.19, Wernher & Beit North, Health Sciences Campus, Anzio Rd, Observatory, 7925 (+ 27 21 406 6750 6 + 27 86 5565 5778 Office Hours: 08h00-16h00 Unavailable Hours: 10h00-11h00 & 13h00-13h30

D) INSTRUCTIONS TO AUTHORS

FROM: THE SOUTHERN AFRICAN JOURNAL OF GYNAECOLOGICAL ONCOLOGY (SAJGO)

Introduction:

The SAJGO aims to be the prime journal on women' s cancer for local health care workers and gynaecologists, focusing on all aspects of cancer prevention, detection, diagnosis and treatment. The SAJGO is also a specialist journal catering for sub-specialist gynaecologic oncologists, for other specialists with a specific interest in breast and gynaecologic cancer, including medical oncologists, radiation oncologists, surgeons, radiologists, pathologists, geneticists, specialised nurses and research scientists.

Document requirements:

Please include the following documents with your submission:

- A cover letter as a supplementary file with the following:
    1. Surnames, initials and qualifications of all authors in the correct sequence
    2. Full contact details of corresponding author: Title, first name, surname, e-mail address, mobile, office and fax number and postal address.
    3. Declaration on copyright and originality of paper and acknowledgement of any third party sources (references and images) exempting the author(s), journal and publisher of plagiarism.
    4. Declaration regarding authorship
    5. Ethics committee approval
    6. Conflicts of interest
- Conflict of interest and funding statements.
- Manuscript which should contain a title page, abstract, text and references. It may also contain tables and figures, acknowledgements and a foot note page.

Abstract

The abstract may be structured with the headings Background, Methods, Results, and Conclusions (250-word limit) or unstructured (200-word limit). Include up to 10 key words, separate from the abstract

Text

The body of the article must not exceed 3500 words. The Editor reserves the right to shorten and stylise any material accepted for publication. Authors are solely responsible for the factual accuracy of their work.

The manuscript must be in English, should be in MS Word and follow the Vancouver style. Abbreviations and acronyms should be defined on first use. Pages should be numbered consecutively preferably with sections for introduction, materials and methods, results, discussion, acknowledgements followed by references.

Tables and Figures

Articles are limited to a maximum of 7 insets (tables and figures combined) and 50 references.

Written permission from the author or copyright holder must be submitted for reprint of previously published figures or tables. Don't publish other articles. Figures should be saved as high resolution (300 dpi) jpeg files.Tables should be constructed in MS Word.Graphs can be copied from MS Excel and pasted in the document.

For large, intricate graphs, the coordinates and graphs must be provided as separate MS Excel files and uploaded as supplementary files.Tables and figures can be in the text at the relevant place.

Large tables (landscape A4) and photographic images are best saved as separate supplementary files. Please number them appropriately.

Figures and photographs should be of high quality with symbols, letters or numbers clear enough and large enough to remain legible after reduction. Each figure must have a separate self-explanatory legend.

Tips on how to prepare your manuscript

1. The submission must be in UK English, typed in Microsoft Word with: no double spaces after the full stops, double paragraph spacing, font size 12 and font type Times New Roman.
2. All author details (Full names, qualifications and affiliation) must be provided.
3. The full contact details of corresponding author (tel, fax, e-mail, postal address) must be on the manuscript.
4. There must be an abstract and keywords.
5. References must be strictly in Vancouver format. (Reference numbers in the text must be strictly numerical and be typed in superscript, not in brackets and must be placed AFTER the full stop or comma.)
6. All numbers below ten, without percentages or units, must be written in words.
7. Figure numbers: Arabic numbering
8. Table numbers: Roman numbering
9. Abbreviations: These should be spelt out when first used in the text and thereafter used consistently.

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. This work is original and all third party contributions (images, ideas and results) have been duly attributed to the originator(s).
2. Permission to publish licensed material (tables, figures, graphs) has been obtained and the letter of approval and proof of payment for royalties have been submitted as supplementary files.
3. The submitting/corresponding author is duly authorised to herewith assign copyright to the SAJGO.
4. All co-authors have made significant contributions to the manuscript to qualify as co-authors.
5. Ethics committee approval has been obtained for original studies and is clearly stated in the methodology.

E) ACKNOWLEDGEMENTS

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- Mr Charles Wessels, administrative clerk, for locating folders.