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RESEARCH

Retrospective analysis of radiotherapy outcomes in breast cancer radiotherapy at a single institution

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Introduction: Breast cancer is the most commonly diagnosed cancer worldwide. With the challenges of cancer treatment in developing countries there is a need for a systematic and methodical approach to treatment in resource-limited settings.
Objective: To retrospectively evaluate the profile of breast cancer patients irradiated with curative intent and discuss the therapeutic outcomes, and to compare this cohort with the available developed-world data.
Methods: A retrospective cohort of 689 breast cancer patients from 2010–2014 at Tygerberg Hospital, Western Cape Province was analysed. The best-case disease-free survival was calculated at five years and compared with the SEER database. Various prognostic factors were calculated by univariate and multivariate analysis.
Results: The five-year best-case disease-free survival (DFS) for Stage I is 94.7% (95% CI 68–99) and for Stage IIIC, 71.3% (95% CI 39–88).
Conclusion: Outcomes of treatment at this institution are comparable to data reported in first-world countries. As two-dimensional radiotherapy compares with most Cobalt specifications, the majority of breast cancer patients in sub-Saharan Africa can be treated efficiently with Cobalt-type technology.

Keywords: Breast cancer, radiotherapy

Introduction
Breast cancer is the most commonly diagnosed cancer amongst women of all races in South Africa. According to information from the South African cancer registry 6 849 new breast cancer cases were reported in 2011. This constitutes 20% of total cancer cases.[1]

South Africa is a bridge model between developed and developing countries as it has the availability of better infrastructure, pathology services, staging and therapeutic modalities, yet still faces high patient to radiotherapy machine and medical personnel ratios. Another confounding factor that bridges the South African environment to the rest of sub-Saharan Africa is the presentation of patients with advanced disease, as well as socio-economic difficulties and poor health-seeking behaviour. Furthermore the National Institute of Health Public Access report reveals the increasing similarity of breast cancer regarding patient profile throughout Africa.[2]

Many studies over the last 20 years confirmed the advantage of adjuvant radiotherapy in the management of curable invasive breast cancer.[3–6] Infrastructure problems in Africa make it challenging to offer quality radiotherapy and gain its benefit.

Objectives
The primary objective of this study was to retrospectively evaluate the patient profile, at Tygerberg hospital and establish disease-free survival (DFS). Outcomes were then compared with those in the Surveillance, Epidemiology and End result Program (SEER) database (Figure 1).

Methods
This retrospective descriptive study investigated breast cancer patients at Tygerberg hospital (TBH) irradiated with curative intent over a five-year period (2010–2014). The local protocol is for chest wall or the intact breast to be treated with tangential fields. Where supraclavicular and axillary irradiation was indicated, field matches with half-beam block techniques were used. Energy preference was 6 MV and higher energies were used only for separations of 24 cm and higher.

Stage T1, T2 less than 3 cm and N0 disease were treated with tumour excision (TE), followed by irradiation. Factors influencing this decision were tumour site, size, histological type, grade, in situ disease, size of breast and patient preference. Post-mastectomy radiotherapy was recommended for T3, T4, patients with four or more axillary nodes and young patients with up to three nodes. Other poor prognostic indicators—grade 3, oestrogen receptor negative, lymphovascular invasion and lobular histology—were taken into account in radiotherapy decision-making.

Lymph nodes were irradiated to any sentinel-confirmed or FNA-positive node. Fields included supraclavicular, infraclavicular and intramammary nodes. Levels 1, 2 and 3 were added if not surgically addressed.

The population assessed were patients older than 18 years, presenting with Stage IB–IIIC breast cancer, post-mastectomy or breast-conserving therapy and indicated for radiotherapy. Patients were identified by searching the departmental electronic database and validated with the TBH breast cancer registry. Data were collected from files and the electronic hospital report system. Patients with incomplete medical records and second primary tumours were excluded. Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Health Sciences, Stellenbosch University.

A cohort of 689 patients was evaluated for age, race, HIV status, stage, histology, pathological grading, molecular subtype, type of surgery, waiting time, and 2Dimensional (2D) vs. 3Dimensional (3D) radiotherapy planning. Indications for 2D planning are

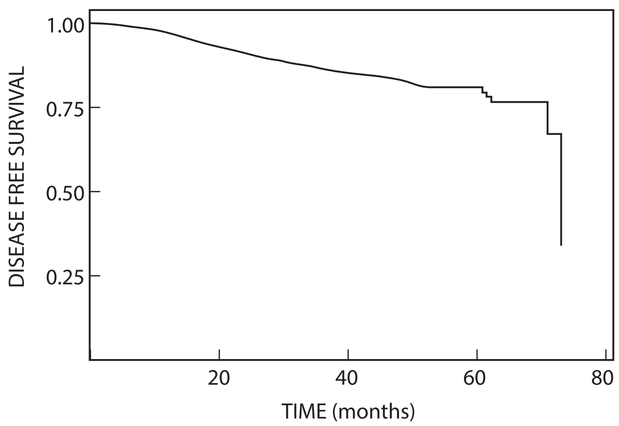

Figure 1: DFS over time up to 70 months.

patients who had undergone a mastectomy, and had no indication for supraclavicular nodal irradiation. Disease-free survival (DFS) by best- and worse-case scenario was statistically calculated.

Statistical considerations

The statistical consulting service at the Biostatistics Unit within the Centre for Evidence Based Health Care (CEHBC) assisted with the analysis of this study through support from university funding for local research. Data were analysed using STATA 14® (StataCorp, College Station, TX, USA). A sample-size calculation was not required, as all new patients diagnosed over the period 2010–2014 (2 223 patients) were included, and generalised to that cohort of 689 patients.

Simple descriptive statistics was used to describe the data. Data were reported as mean and standard deviation or median and interquartile range where appropriate. Normality of data was tested using both qualitative (graphs) and quantitative methods (test of normality). An appropriate parametric or non-parametric test was used with a significant *p*-value of 0.05. Survival analysis (Kaplan–Meier survival analysis) was performed for five-year recurrence-free survival and overall survival. Patients with censored data were assumed not to have recurrent disease (best-case scenario). A worst-case scenario was also used (loss to follow-up assumed to have the outcome of interest) in the analysis. Relevant outcomes and measures of effect are reported with 95% confidence intervals. No missing data were added.

Results

Table 1 details the study characteristics by different prognostic groups. Mixed-race women made up 63% of the total of this cohort, consistent with the demographics of the drainage area of the institution, and 4.9% were HIV-positive. The majority of the patients were stage IIB to IIIB (65.8%). The most common histology was with an infiltrating ductal carcinoma (84.6%), which was mostly grade 2 (43.9%). The patients who qualified for 2D radiotherapy comprised 59.3%. The remaining patients (40.3%) were planned using 3D conformal radiotherapy. Mastectomy was offered to 69.2% of the patients. The waiting time from surgery to radiotherapy was longer than 90 days, for 60.3% of patients.

Best- and worst-case analysis for five-year disease-free survival (DFS) is given in Table 2. Stage I best-case DFS was 94.7% (with 95% CI 68–99). Stage IIA best-case scenario was 92.1% (95% CI 85–95); 88.6% for Stage IIIA; 60% for IIIB and 71.3% for IIIC. There

Table 1: Proportions within different prognostic groups

Characteristics	*n* (%)	Mortality *n* (%)	Local recurrence *n* (%)	Metastasis *n* (%)
Age (years):				
20–34	26 (3.8)	2 (7.6)	1 (3.8)	5 (19.2)
35–44	112 (16.3)	3 (2.6)	6 (5.3)	15 (12.3)
45–54	198 (28.9)	5 (2.53)	7 (3.5)	22 (11.1)
55–64	208 (30.3)	4 (1.9)	7 (3.3)	19 (9.1)
65–74	114 (16.6)	2 (1.7)	3 (2.6)	5 (4.3)
> 75	27 (3.9)	–	–	–
Race:				
European	168 (26.9)	2 (1.1)	4 (2.3)	16 (9.5)
Mixed	393 (63)	12 (3.3)	15 (3.8)	40 (10.1)
Black	54 (8.6)	1 (1.8)	4 (7.4)	5 (9.2)
Indian	5 (0.8)	–	–	–
Unknown	3 (0.4)	–	–	–
HIV status:				
Positive	25 (4.9)	–	1 (4)	5 (20)
Negative	483 (95.1)	12 (2.4)	18 (3.7)	53 (10.7)
Stage:				
I	33 (5)	–	–	1 (3)
IIA	168 (25.5)	1 (0.6)	4 (2.3)	8 (4.7)
IIB	169 (25.7)	2 (1.1)	3 (1.7)	15 (8.8)
IIIA	95 (14.4)	3 (3.1)	2 (2.1)	4 (4.2)
IIIB	169 (25.7)	9 (5.3)	12 (7.1)	33 (19.5)
IIIC	23 (3.5)	1 (4.3)	2 (8.7)	3 (13)
Histology:				
Infiltrating ductal	569 (84.6)	14 (2.4)	23 (4)	61 (10.7)
Lobular	34 (5)	1(2.9)	–	2 (5.8)
Medullary	7(1)	1 (14.2)	–	–
Mucinous	22 (3.2)	–	–	–
Poorly differen-tiated	5 (0.7)	–	–	–
Non-specific type	14 (2)	–	1 (7.1)	2 (14.2)
Other	21 (3.1)	–	–	–
Pathological grading:				
I	121 (21.9)	1 (0.8)	3 (2.4)	7 (5.7)
II	242 (43.9)	5 (2)	8 (3.3)	26 (10.7)
III	188 (34.1)	7 (2.3)	13 (6.9)	27 (14.3)
Molecular subtype:				
Luminal A	291 (43.8)	3 (1)	8 (2.7)	27 (9.2)
Luminal B (Her neg.)	92 (13.8)	1 (1)	3 (3.2)	11 (11.9)
Luminal B (Her pos.)	169 (25.4)	7 (4.1)	5 (2.9)	15 (8.8)
Basal like	107 (16.1)	5 (4.6)	7 (6.5)	11 (10.2)
Unclassified	5 (0.75)	–	–	–
Waiting time				
<= 90 days	252 (39.2)	4 (1.5)	8 (3.1)	24 (9.5)
> 90 days	384 (60.3)	12 (3.1)	15 (3.9)	37 (9.6)
Planning:				
Sim mark up (2D)	399 (59.3)	11 (2.7)	14 (3.5)	40 (10)
CT Plan (3D)	272 (40.6)	4 (1.4)	9 (3.3)	23 (8.4)

(Continued)

Table 1: (*Continued*)

Characteristics	*n* (%)	Mortality *n* (%)	Local recurrence *n* (%)	Metastasis *n* (%)
Type of surgery:				
Tumour excision (TE) only	3 (0.4)	1 (33.3)	–	1 (33.3)
TE and sentinel node	125 (18.3)	–	4 (3.2)	6 (4.8)
TE and axillary dissection	81 (11.8)	2 (2.4)	1 (1.2)	7 (8.6)
Simple mastectomy (SM)	11 (1.6)	–	–	–
SM and sentinel node	81 (11.8)	–	–	2 (2.4)
SM and axillary dissection	13 (1.9)	–	1 (7.6)	1 (7.6)
Modified radical mastectomy	368 (53.9)	13 (3.5)	18 (4.8)	49 (13.3)

were no differences in outcome for waiting times more vs. less than 90 days. Outcomes for 2D vs. 3D planning are comparable, 82.8 vs. 77.9%.

When looking at the multivariate analysis we found age, Stage IIIB, and tumour excision (TE) with sentinel node significantly impacted outcome (Table 3).

The arbitrary cut-off for waiting times from surgery to adjuvant radiotherapy of 90 days revealed no differences in outcome.

Discussion

The Breast Health Global initiative (BHGI) derived guidelines for the implementation of breast cancer healthcare in low- and middle-income countries, where they classified the level of resources from these countries into basic, limited, enhanced and maximal. Therefore clinical practice will be dependent on which category an institution falls into. It is expected that better outcomes in practice would be associated with better resources.[7,8] In our institution outcomes for breast cancer treated with curative intent are very similar to outcomes in the first-world scenario.

We found stage at presentation in our cohort to be similar to the SEER data.[2]

Ideally all patients should be planned on a three-dimensional (3D) planning system.[9] Two-dimensional (2D) planning is used in most of the low-income countries where radiotherapy is available. At our institution only 40.5% of breast patients underwent 3D planning and the remainder were treated using 2D techniques. The 2D plans are adequate for small patients who have had a mastectomy and require chest wall radiotherapy only, as the dose distribution and normal tissue dose volume histograms (DVH) compare well with those of a 3D plan.[10] It was notable that there is a lower incidence of breast-conserving surgery, due to many patients presenting with more advanced disease—but outcomes were still comparable by stage.[2]

The use of linear accelerators (LINACS) with 3D conformal capability is the gold standard, but the availability and stability of electricity supply, quality assurance, maintenance and human resources remain a challenge. Munshi *et al.*, based in Mumbai, compared the quality of life of patients treated on Cobalt-60 machines versus those treated on linear accelerators and found no difference in outcome.[11] Development of Cobalt-60 technology in modern radiation therapy is slowly making space for more conformal treatment.[12] Despite the growing pressures to abandon use of Cobalt-60 radiotherapy machines, their reliability and relatively easier maintenance remain an attractive option for developing countries in sub-Saharan Africa.[13,14]

Our study indicates comparable survival and DFS when compared with international outcomes by stage, despite the more advanced presentation of the disease and higher use of 2D planning.

Table 2: Disease-free survival (DFS) by best- and worse-case scenarios

Prognostic factor	Five-year best-case analysisDFS (95% CI)	Five-year worse-case analysisDFS (95% CI)
Age at diagnosis:		
20–34	76% (46–90) [at 56 months]	53% (29–72) [at 56 months]
34–44	76.4% (63–85)	64.4% (51–74)
45–54	78.1% (66–86)	67.7% (54–77)
55–64	82.8% (74–88)	68% (59–76)
65–74	85.1% (70–92)	72% (58–82)
75–84	–	44% (9–76%)
> 84	–	–
Stage:		
I	94.7% (68–99)	90.7% (67–97)
IIA	92.1% (85–95)	74.4% (60–84)
IIB	84.2% (74–90)	71.3% (61–79)
IIIA	88.6% (74–95)	75.1% (61–84)
IIIB	60% (46–71)	44.6% (32–56)
IIIC	71.3% (39–88)	58.9% (29–79)
HIV status:		
Positive	74.3% (48–88) [at 58 months]	51.5% (28–70) [at 58 months]
Negative	79.4% (73–84)	67.1% (60–72)
Waiting time:		
<= 90 days	82.8% (75–88)	69.1% (61–75)
> 90 days	81.4% (75–86)	68.2% (61–74)
Planning:		
Sim mark up (2D)	82.8% (77–87)	66.6% (59–72)
CT Plan (3D)	77.9% (67–85)	67.3% (56–76)
Type of surgery:		
Tumour excision (TE) only	–	–
TE and sentinel node	89.9% (79–95)	82.7% (70–90)
TE and axillary dissection	82.5% (63–92)	65.9% (45–80)
Simple mastectomy (SM)	–	88.8% (43–98) [at 54 months]
SM and sentinel node	96.2% (85–99)	86% (73–92)
SM and axillary dissection	90% (47–98)	81.8% (44–95)
Modified radical mastectomy	74.7% (67–80)	58.4% (51–65)

Table 3: Measure of effect hazard ratio (HR) for disease-free survival (DFS)

Prognostic factor	Univariate HR for DFS (95% CI)	Multivariate* HR for DFS (95% CI)
Age	0.97 (0.95–0.99)**	0.97 (0.95–0.99)**
Stage:		
I	1	1
IIA	1.93 (0.24–15.15)	2.03 (0.25–15.92)
IIB	3.39 (0.44–25.64)	2.36 (0.44–25.41)
IIIA	2.24 (0.25–18.86)	2.12 (0.25–17.83)
IIIB	10.63 (1.45–77.48)**	10.45 (1.43–76.16)**
IIIC	6.61 (0.73–59.40)	6.14 (0.68–55.15)
HIV status:		
Negative	1	–
Positive	2.49 (0.99–6.22)	–
Waiting Time		
<= 90 days	1	–
> 90 days	0.73 (0.46–1.18)	–
Planning:		
Sim mark up (2D)	1	–
CT Plan (3D)	0.88 (0.55–1.41)	–
Type of surgery:		
Tumour excision (TE) only	1	–
TE and sentinel node	0.09 (0.01–0.74)**	–
TE and axillary dissection	0.1 (0.01–0.9)**	–
Simple mastectomy (SM)	–	–
SM and sentinel node	0.04 (0.003–0.44)**	–
SM and axillary dissection	0.09 (0.005–1.47)	–
Modified radical mastectomy	0.23 (0.03–1.72)	–

*Forwards stepwise modelling included only age and stage. Collinearity was found between HIV status and age.
**Indicates significant results at $p < 0.05$.

The strengths of this study include a large patient cohort, where treatment was consistent.

The study weakness is a single-institution, retrospective study.

Conclusion

Patient profiles in Western Cape can be expected to be similar to those described elsewhere in Africa. If the best-case scenario is accepted in this study, our institutional outcomes compare well with first-world results, as seen in the SEER report.[2] A large number of patients present with locally advanced cancer, and are therefore less likely to undergo breast-conserving surgery. Many of these patients were treated successfully with 2D techniques alone, similar to many centres in sub-Saharan Africa. Basic Cobalt machines will thus be able to successfully treat the majority of breast cancer patients in need of radiotherapy.

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