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.3–5 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. Indications for 2D planning.
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

| 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 (2.5)             | 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-

(Continued)
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 1: (Continued)

| Characteristics                        | n (%) | Mortality n (%) | Local recurrence n (%) | Metastasis n (%) |
|----------------------------------------|-------|-----------------|------------------------|-----------------|
| Tumour excision (TE) only              | 3 (0.4)| 1 (33.3)        | –                      | 1 (33.3)        |
| TE and sentinel node                   | 125 (18.3)| –              | 2 (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 (3.2)                | 7 (8.6)         |
| 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)       |

### 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)                              |
| >84               |                                          | 44% (9–76%)                              |
| Stage:            |                                          |                                          |
| I                 | 94.7% (68–99) [at 56 months]             | 90.7% (67–97)                            |
| II                | 92.1% (85–95)                            | 74.4% (60–84)                            |
| IIB               | 84.2% (74–90)                            | 71.3% (61–79)                            |
| III               | 88.6% (74–95)                            | 75.1% (61–84)                            |
| IIIB              | 60% (46–71)                              | 44.6% (32–56)                            |
| IIC               | 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% (73–86)                            | 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)                            |
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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### 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. 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.