



UNIVERSITY OF CAPE TOWN
FACULTY OF HEALTH SCIENCES



MMed Part III (minor dissertation)

**ADVANCED BREAST CANCER: A RETROSPECTIVE REVIEW
COMPARING TWO PALLIATIVE RADIOTHERAPY PROTOCOLS
USED AT GROOTE SCHUUR HOSPITAL BETWEEN 2010 AND 2013**

by

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SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In partial fulfillment of the requirements for the degree

MMed Radiation Oncology

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DATE OF SUBMISSION: 31 January 2016

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DECLARATION

I, Dr Nazia Fokie, declare that the work on this study is originally my work except where acknowledgements are indicated. This is an unsponsored study and was carried out for educational purposes only as a MMED for a postgraduate degree. I therefore declare no conflict of interest whatsoever.

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PART A: ABSTRACT AND STUDY PROTOCOL

ABSTRACT

Purpose: To retrospectively evaluate and compare the loco-regional progression free survival (PFS), overall survival (OS) and acute effects of the two breast palliative regimes used in patients with locally advanced or metastatic breast cancer between 2010 and 2013 in a single institution.

Methods: Compliance to treatment, acute skin reactions, progression free and overall survival were retrospectively evaluated in patients who received palliative breast radiotherapy for locally advanced breast cancer between 2010 and 2013. The radiotherapy regimes were either 4Gy per fraction for 5 fractions treated 4 times a week (20Gy) or 6Gy per fraction for 6 fractions treated once a week (36Gy). They may have received previous chemotherapy with minimal or no clinical response, as well as hormonal treatment.

Results: Forty three patients were followed up over a median period of 24 months, 14 of which received 20Gy and 29 received 36Gy. The average age was 64 years old. Compliance was 88% in both groups. Both groups had either grade 1 (71% vs 62%), grade 2 (21% vs 24%) or grade 3 (8% vs 14%) acute skin reactions. No grade 4 skin reactions were documented. The PFS was shorter at 4.5 months in the 20Gy group compared to 7.7 months in the 36Gy group ($p=0.27$). The OS was also shorter at 25.8 months in the 20Gy group compared to 29.6 months in the 36Gy group ($p=0.51$)

Conclusion: This study did not show a statistically significant difference in terms of PFS and OS between the two radiotherapy regimes. They both remain reasonable options in local palliation in patients with locally advanced breast cancer.

Key Words: Locally advanced breast cancer, palliative radiotherapy, radiation regimes

MMED STUDY PROTOCOL

Background

Breast cancer is one of the leading types of cancer in women, in both the developing and developed countries. In countries with established screening programs, the majority of breast cancers are detected at an early stage. However, in countries, especially developing countries, where the screening programs are not as well established and access to medical care is not as efficient, many patients present with more advanced disease. Due to lack of adequate cancer registries in the developing countries, we are unable to accurately state what percentage of patients present with advanced disease.

The treatment of locally advanced breast cancer and metastatic breast cancer remain an oncologic challenge. Different institutions across the world have different protocols according to their resources.

According to the ESO-ESMO guidelines¹, the treatment of locally advanced disease involves multiple modalities. The aim is to downstage the tumour using neo-adjuvant chemotherapy or using hormonal treatment where appropriate, followed by surgery and adjuvant radiotherapy and biological agents. For metastatic disease, there is a lack of evidence on how to locally palliate the disease.

The issue that we face at our facility, and in many developing countries, is that we have limited access to modern chemotherapy regimes and no access to the required biological agents in the state sector. Therefore, if patients do not respond to the chemotherapy and/or the hormonal treatment, palliative radiotherapy remains the only option to treat complications of locally advanced disease (such as ulceration or bleeding). We also have a sub-set of patients with a good ECOG

performance status (see appendix c), but with metastatic disease. Due to the nature of their metastatic disease, they are expected to have a life expectancy of at least 6 months (for example those with bone metastases). There is no consensus as to how to treat these groups of patients.

The intent for patients with advanced disease is palliation, but, as the majority of patients have a significant lifespan of at least 6 months, we would aim to give them as good a quality of life as possible.

Previously the palliative radiotherapy regime of 20Gy in 5 fractions was used at Groote Schuur Hospital, as well as at the other facilities in South Africa.

Since 2012, Groote Schuur Hospital introduced the 36Gy regime, where the patient has one 6 Gy fraction per week for 6 weeks. The rationale behind using this regime is based on radiobiological studies, which have shown that the alpha/beta ratio of breast cancer is similar to those of late responding tissues. Fractionation sensitivity is quantified in terms of the linear quadratic equation. If cell survival is plotted on a graph, the point where the alpha component (non repairable damage) is equal to the beta component (repairable damage) is the alpha/beta ratio. Studies have shown that late responding tissues have lower alpha/beta ratios than early responding tissues. They are therefore more sensitive to dose per fraction.² Breast cancers respond to radiotherapy similarly to late responding tissues, therefore, they are more sensitive to dose per fraction. This is at the risk of more late effects, but as these patients are for palliative intent, they may not live long enough for those long terms effects to manifest.

Studies in elderly patients with breast cancer who could not cope with longer course of radiotherapy, have shown equivalent rates of loco-regional control using the hypo-fractionated regime compared to the normofractionated regime. The patients were given radiotherapy once a

week for 5 or 6 weeks at a dose of between 6Gy- 6.5 Gy.^{3,4,5} This regimen has been suggested for frail patients with fungating tumours.⁶

The clinical outcomes of these two palliative regimes have not been established nor compared. It is therefore the aim of this study to retrospectively review the outcomes of these two regimes.

Study aims and objectives:

Research question

WE propose to assess treatment outcomes of the breast radiotherapy regime used at Groote Schuur Hospital from 2010 to 2011 compared to the regime used from 2012 to 2013 for locally advanced or metastatic breast cancer.

Study Aim

To retrospectively compare the treatment outcomes of the 20Gy in 5 fractions (4 fractions per week) regime used from 2010 to 2011 to the 36Gy in 6 fractions (1 fraction per week) regime used from 2012 to 2013, in patients with locally advanced or metastatic breast cancer at Groote Schuur Hospital.

Study Objectives

Primary Objectives:

To compare the treatment outcomes of the two regimes, specifically looking at:

- Overall survival
- Acute effects of radiotherapy
- Loco regional progression free survival

Secondary Objectives:

- Determining percentage of patients presenting with advanced disease.
- Determining demographics of patients presenting with advanced disease.

Study population:

Inclusion criteria:

- Patients 18 years and older
- Registered with the Combined Breast Clinic at Groote Schuur Hospital between 2010 and 2013.
- They should have proven and documented evidence of locally advanced or metastatic breast cancer.
- Patients should have either been treated with the palliative regime of either 20.00Gy or 36.00Gy during the above time periods.
- They may have had previous chemotherapy with minimal or no clinical response.
- Patients who are oestrogen receptor and/or progesterone receptor positive on hormonal treatment may be included.

Exclusion criteria:

- Chest wall irradiation post mastectomy or breast irradiation post lumpectomy.

Scientific Design:**Methods and Materials:**

The patients diagnosed with locally advanced or metastatic breast cancer between 2010 and 2013, were identified using the Groote Schuur Hospital Department of Radiation Oncology Electronic Patient Registry. The Electronic Patient Registry is registered with the Human Research Ethics Committee (approval number R016/2013). Their hospital and Radiotherapy folders will be retrospectively reviewed and the relevant data extracted.

The relevant data required, is the age of the patient, stage of disease (see appendix 1), HIV status, previous chemotherapy, ER or PR positivity, grading of skin reactions while on radiotherapy (see appendix 2) and time interval to local progression and death. There would be approximately 50 patients in total in the study group.

A univariate analysis will be done to assess the influence these factors have on the overall response and loco regional recurrence free survival.

The information will be obtained by noting the patients' disease status at each follow up visit to the Breast Clinic at Groote Schuur Hospital.

As these are palliative patients with disseminated disease, it will be noted in patients who have demised, whether the cause was due to distant disease or lack of local response to radiotherapy.

Date of Audit:

The folders to be reviewed will be those who presented with locally advanced or metastatic breast cancer and received either 20.00Gy or 36.00Gy radiotherapy to the breast, from 2010 to 2013 at Groote Schuur Hospital.

Data Collection:

The data will be collected from the GSH radiotherapy and hospital folders. It will then be recorded into customized data sheets and then transferred onto an Excel spreadsheet.

Statistical analysis:

Statistical analysis of the data will be performed, using GraphPad prism version 6 for Windows. Survival curves will be generated using the Kaplan-Meier method and compared using the log rank test. A p-value of <0.05 will be considered as statistically significant. Categorical variables will be calculated using the Fisher test or the Chi-Square test.

Access to records

The routine clinical records will be assessed using the electronic patient registry of the Radiation Oncology Department at Groote Schuur Hospital.

As this is a retrospective audit, only the patient folders will be used for data collection. There will be no patient contact.

Ethical considerations:**Risk and Benefits**

This is a retrospective audit; therefore there is minimal risk to the patients. All patients will be de-identified.

The benefit of this audit, is that we will be able to compare two breast radiotherapy regimes and assess clinical outcomes of the two palliative regimes.

Informed consent

This is a retrospective study using the patients' folders only. As there is no patient contact, we would request a waiver of informed consent. All patients will be de-identified during data collection and analysis.

Privacy and confidentiality

Confidentiality and privacy will be maintained by de-identifying patient data, using passwords on electronic documents, etc.

Resources

For the literature review, Pubmed, Google and available journal articles will be used.

No other resources will be used, besides the patient data available on the Groote Schuur Hospital Department of Radiation Oncology patient registry and in patient folders.

What happens at the end of the study?

The data results will be documented in a publication style format and will be submitted to the University of Cape Town as part of the MMed in Radiation Oncology degree requirements.

Glossary

Treatment regime 1: Total dose:20.00Gy @ 4.00Gy per fraction in 5 fractions. Four fractions per week. (2010-2011)

Treatment regime 2: Total dose 36.00Gy @ 6.00Gy per fraction in 6 fractions. One fraction per week. (2012-2013)

Overall survival: the time from diagnosis to last follow-up or demise due to any cause. *Time to*

Loco regional recurrence: time from start of treatment to first documented local progression of disease or death.

Locally advanced breast cancer:

- Tumours which involve the skin of the breast or underlying muscles of the chest
- Involve multiple local lymph nodes (axillary, supraclavicular, infraclavicular)
- Inflammatory breast cancer

Metastatic breast cancer

- Distant metastasis e.g. bone, lung, liver

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PART B: STRUCTURED LITERATURE REVIEW

LITERATURE REVIEW

Objectives of literature review

The objectives of this literature review are to provide the reader with a background of the management of locally advanced and metastatic breast cancer and the current, international treatment guidelines recommended in developed countries. It also provides the reader with insight into the history of hypofractionation in breast cancer.

Literature Search strategy

For this study, articles relating to locally advanced and metastatic breast cancer were searched using the following search engines: Google Scholar, Google, Pubmed, Text books and journal articles. The main search terms were: locally advanced breast cancer, metastatic breast cancer, once weekly hypo-fractionated radiotherapy in breast cancer and palliative radiotherapy in breast cancer. Only publications in English were considered.

The majority of the data published on metastatic and locally advanced breast cancer are from developed countries, where there has been a shift towards treating patients with improved chemotherapy regimes and targeted agents. There were a few studies using the hypo-fractionated once weekly regime in the elderly population, but these were patients with radical treatment intent. These are retrospective studies and no meta-analyses or Phase III trials were found in the databases. There are currently no studies using the hypo-fractionated once weekly regime in the palliative setting.

Interpretation of literature

In order to understand and discuss the results of the current study, a detailed review of the available literature was performed and discussed.

The review summarized the available literature as follows:

- Background and Epidemiology
- Definition of Locally Advanced Breast Cancer (LABC) and Metastatic Breast Cancer (MBC)
- Treatment
- Radiobiology
- Radiotherapy
- Conclusion

Background and epidemiology

Breast cancer is the most frequently diagnosed cancer (23% of total cancer cases) and the leading cause of death (14% of deaths), in females, worldwide.¹ According to the Globocan 2008 estimates, approximately 1.37 million women are diagnosed with breast cancer per year. In economically developing countries, it's the leading cause of cancer related deaths amongst women. According to Vorobiof et al, the incidence of breast cancer in South Africa was approximately 16.6% in 2001.² At that time, 70% of the patients presenting with breast cancer were white, Asian or mixed race and 30% were black. But, majority of the black patients presented with stage 3 and 4 disease. In higher income countries, such as the USA, the breast cancer mortality incidence has been decreasing by approximately 2% per year since 1990 with only about 15% of patients presenting with advanced stage disease.³ This may be attributed to the earlier detection of breast cancer by the implementation of awareness and screening programs, easier access to diagnostic testing and timeous implementation of effective treatment. In contrast, in low to middle income countries, approximately 60-80% of the patients present at more advanced stages.⁴ Due to lack of adequate cancer registries in the developing countries, we are unable to accurately state what percentage of patients present with more advanced disease. The advanced presentation, as well as poorer access to care and limited treatment options, results in higher breast cancer mortality

incidences. However, research at Groote Schuur Hospital, revealed that there may be other factors at play in developing countries, which may affect cancer survival.³ Factors such as patients' distrust of "western medicine" and the use of traditional medicine first, lack of understanding of the disease and allowing older, often conservative, family members to make treatment decisions are commonplace. There are also the financial implications, as patients cannot afford to lose working hours to come for investigations, chemotherapy and daily for radiotherapy.

Worldwide, the treatment of locally advanced breast cancer and metastatic breast cancer is an oncologic challenge. In developing countries, this is confounded by the situations mentioned previously. Protocols for the treatment of advanced breast cancer differ amongst institutions, based on the resources available to that country. In the Western Cape, despite the fact that we have the advantage of expert multidisciplinary teams, there is limited access to many of the chemotherapy agents and no access to the targeted agents used in advanced breast cancer. The rest of the South African state sector as well as other developing countries mirror this.^{3,4} In fact, other developing countries especially in Africa, are significantly limited with regard to oncology care and resources.⁵⁻⁷

Definition of Locally Advanced Breast Cancer (LABC) and Metastatic Breast Cancer (MBC)

Advanced breast cancer comprises of locally advanced breast cancer (LABC) and metastatic breast cancer (MBC).⁸ The definition of locally advanced breast cancer is non metastatic disease, with any tumour more than 5cm in diameter or that involves the skin or chest, as well as the presence of fixed axillary lymph nodes or ipsilateral supraclavicular, infraclavicular and internal mammary nodes. It also includes a more homogenous form of LABC called inflammatory breast cancer (IBC).^{8,9} According to the American Joint Committee on Cancer (AJCC) staging system, it includes

all Stage 3 disease and well as Stage 2b disease.¹⁰ Metastatic breast disease (AJCC Stage 4) is the presence of distant metastasis, with or without locally advanced disease.

Treatment Guidelines: Overview

According to the European Society of Medical Oncology (ESMO) guidelines, the treatment of locally advanced disease involves multiple modalities, ideally, under the guidance of a multi disciplinary team.⁸ The aim is to downstage the tumour using neo-adjuvant chemotherapy and hormonal treatment (if the patient is oestrogen receptor (ER)/ progesterone receptor (PR) positive), followed by surgery, adjuvant radiotherapy and biological agents. The choice of first line treatment for LABC depends on disease related and patient related factors.

In patients who are Triple Negative (HER-2-Neu, ER and PR negative), Anthracycline and Taxane-based chemotherapy is recommended.

In approximately 33% of locally advanced and metastatic breast cancers and 40% of inflammatory breast cancers, there is amplification or overexpression of the human epidermal growth factor receptor-2 (HER-2). It's a trans membrane receptor tyrosine kinase, which is associated with more aggressive disease and poorer outcomes. If the patient is HER-2-Neu positive, anti-HER-2 therapy is recommended since it increases the rate of pathological complete response.^{3,11} The addition of Trastuzumab (anti-HER-2 monoclonal antibody) neo-adjuvantly and adjuvantly significantly improves 3 year event-free survival (71% vs 56% without Trastuzumab).¹² Patients with ER or PR positive LABC, may also benefit from Anthracycline and Taxane based treatment, as well as from endocrine therapy. The decision whether to use endocrine therapy or chemotherapy as initial treatment, depends on the tumour grade and biomarker expression, as well as the patients' menopausal status, comorbidities, performance status and personal preferences.

For patients who responded adequately to neo-adjuvant chemotherapy, local therapy is followed by surgery. This entails a radical mastectomy and axillary node clearance in majority of cases. If there has been a significant response to chemotherapy, breast conservation surgery may be considered. Subsequently, all patients will have loco-regional postoperative radiotherapy to the chest wall and loco-regional nodes.

Treatment Guidelines MBC: Overview

Metastatic breast cancer (MBC) is incurable, but still treatable, especially if there are limited metastases. The intent of treatment is palliative, providing symptomatic relief and optimization of the length and quality of life. Median survival is approximately 18 to 24 months in these patients, though in some circumstances, for example with bone metastasis, the life expectancy may be longer. If the patient has a good performance status and has locally advanced disease as well, local palliation could optimize their quality and length of life.¹³ There are, however, limited randomized studies in these groups of patients.

Treatment Guidelines MBC: Systemic treatment

The systemic treatment of MBC includes endocrine therapy, chemotherapy and targeted biological agents. The choice of treatment depends on disease related factors such as hormone status, HER2 status, tumour burden and need for rapid disease control; as well as patient related factors such as biological age, menopausal status, co-morbidities, performance status, socio-economic and psychological factors, patient preference and therapies available.^{3,13}

If patients are ER/PR positive, without extensive or symptomatic visceral involvement, endocrine therapy is the first choice of treatment. Types of endocrine therapies available are: selective oestrogen receptor modulators (Tamoxifen), oestrogen receptor down regulators (Fulvestrant),

luteinising hormone-releasing hormone analogues (Goserelin), third generation aromatase inhibitors (Anastrozole, Letrozole, Exemestane), Progestins and anabolic steroids. Patients on long-term endocrine therapy may develop resistance^{14,15} Clinical studies have shown that mammalian target of rapamycin (mTOR) inhibitors enhances the efficacy of endocrine therapy.^{16,17} If patients are HER2 positive, the addition of Trastuzumab to endocrine treatment has shown to improve progression free survival.¹⁸ Lapatinib is a second anti Her2 agent. Trials have looked at using Lapatinib in combination with Capecitabine in patients who progressed on Herceptin, Anthracyclines and Taxanes. It showed a progression free survival of 8.4 months versus 4.4 months in the placebo arm.¹⁹ Studies have also considered combining Lapatinib with Trastuzumab, if the patient progresses on Trastuzumab alone.²⁰

If patients are ER positive with symptomatic or extensive visceral metastasis, ER negative or have progressed on hormonal treatment, chemotherapy is the treatment of choice.¹³ Chemotherapy agents that may be used include Anthracyclines, Taxanes, Vinca Alkaloids, Capecitabine, 5-Fluorouracil, Methotrexate, Platinum agents, Mitomycin C and Gemcitabine. If the patient is HER2 positive, the chemotherapy may be used with the targeted agents as mentioned previously. Other targeted agents available are Pertuzumab, Palbociclib and Ado- Trastuzumab Emantasine (T-DM1).

Radiotherapy: Overview

The challenge that we face at our facility, and in many developing countries, is the limited access to modern chemotherapy regimes and almost no access to the required biological agents in the state sector. Therefore, patients who do not respond to the chemotherapy and/or the hormonal treatment, palliative radiotherapy is the only option to treat complications of locally advanced disease (such as ulceration of breast and bleeding). There are a group of patients, often triple negative or hormone receptor negative patients, with a relatively good ECOG performance status,

but with limited metastatic disease. Those who are hormone receptor negative, are treated with systemic therapy. In the public sector the options include Anthracycline based chemotherapy, Taxane based chemotherapy (on a named patient basis), Navelbine and Capecitabine. Those who are hormone receptor positive are treated initially with hormonal treatment. There is no access to targeted biological agents in the state sector due to cost restrictions. If a patient's disease progresses on the hormonal treatment, as well as on chemotherapy or are unfit for chemotherapy, palliative local radiotherapy is the remaining option available for local control. As mentioned previously, if they have limited metastatic disease, they are expected to have a life expectancy of at least 6 months. Radiotherapy plays an important role in local palliation by reducing risk of further haemorrhage, ulceration and malignant brachial plexopathy, thereby improving their quality of life, as well as potentially increasing their life span.^{3,21}

Current radiotherapy regimes

There are various palliative breast radiotherapy regimes prescribed for local control of disease. Institutions in South Africa use a variety of regimes: a single fraction of 8Gray (Gy), fractioned treatment of 20Gy at 4Gy per fraction for 5 fractions or 30Gy at 3Gy per fraction for 10 fractions.²² The treatment plan depends on the resources available at the facility, patient ECOG performance status and disease factors. Since 2012, Groote Schuur Hospital has been prescribing a hypo-fractionated 36Gy regime, where the patient has one 6Gy fraction per week for 6 weeks to a total of 36Gy.

In the 1960's a limited number of studies were performed examining hypofractionation in the palliative setting. These trials were, however, abandoned due to poor technique, poor radiation

quality and subsequent severe late effects.^{23,24} A review of literature failed to find any recent studies investigating the optimal radiotherapy dose and fractionation for local breast palliation.

There are studies and retrospective reviews that have been published using the once weekly hypofractionated radiotherapy regime. It was, however, investigated in the elderly population as definitive radiotherapy^{25,26} or as adjuvant treatment post mastectomy.^{27,28} Breast cancer is known to increase in incidence as women age.²⁷ With increasing age, other factors such as medical factors (stage of disease, performance status, co-morbidities) as well as socio-economic factors need to be taken into consideration when deciding on the appropriate treatment approach. The elderly, often, cannot attend multiple sessions of radiotherapy per week for a few weeks and may present with more advanced disease. For these reasons, elderly patients are, sometimes, unable to receive adequate multimodality treatment. This was the rationale behind the studies done using a hypofractionated radiotherapy regime in the elderly as it afforded the patients therapeutic advantages without being too cumbersome on the patient physically, socially and financially.²⁷ These trials looked at the incidence of acute and late side effects of hypofractionated radiotherapy, tolerance and compliance to radiotherapy, the local control rate, disease free survival, cause specific survival and overall survival.

Radiobiology

The rationale behind using this specific radiotherapy regime is based on radiobiological studies, which have shown that the alpha/beta ratio of breast tissue is similar to those of late responding tissues. Fractionation sensitivity is quantified in terms of the linear quadratic equation, which describes the relationship between fractionation size and tissue response.²⁹ If cell survival is plotted on a graph, the point where the alpha component (non-repairable damage) is equal to the

beta component (repairable damage) is the alpha/beta ratio. Studies have shown that late responding tissues have lower alpha/beta ratios than early responding tissues. They are therefore more sensitive to dose per fraction. Numerous studies have proven that squamous carcinomas of the head and neck region, cervix and bronchus are less sensitive to the size of the fraction compared to the late-responding tissue. Therefore, if they are hypo-fractionated (i.e. >2Gy per fraction), the probability of tumour cure is less and with more normal tissue complications than if they were given 2Gy per fraction in the same overall treatment time.³⁰ Data has suggested that primary breast adenocarcinomas are more sensitive to fraction size compared to the squamous carcinomas and therefore respond to radiotherapy similarly to dose limiting normal tissues such as skin, subcutaneous tissues, muscle and ribs.³⁰

Evidence for Hypofraction in Breast Cancer

A randomized clinical trial was undertaken in 1986, with the aim to test the hypothesis that hypofractionation is as effective as the standard 2Gy per fraction and offered reduced cost to patients and the health facilities.³¹ The primary endpoint was the late effect of healthy tissue and secondary endpoints were tumour recurrence and palpable fibrosis. This trial generated reliable estimates for α/β for late change in breast (3.6Gy) and late change in breast appearance (3.1Gy). It did not generate reliable estimates for α/β for tumour control. This trial was used as a basis for the UK Standardisation of Radiotherapy Trial (START trial).³² These α/β ratios were confirmed by a similar randomized phase three trial in 2005³¹. The START A Trial studied women with early breast cancer who received adjuvant radiotherapy post breast conserving surgery or mastectomy.³² The patients were either randomized to 50Gy in 25 fractions or 41.6Gy in 13 fractions or 39Gy in 13 fractions. Treatment duration in all three arms was 5 weeks. The data was consistent with the hypothesis that breast cancer and dose limiting normal tissue respond similarly to change in

radiotherapy fraction size. The adjusted estimates of the α/β ratio for tumour control was 4.6Gy and for late change in breast appearance was 3.4Gy.³² The START B trial ran concurrently with the START A trial. It compared 40Gy in 15 fractions of 2.67Gy per fraction in 3 weeks to the control group of 50Gy in 25 fractions 2Gy in 5 weeks. The results were consistent with the START A trial that hypo-fractionation, over a reduced treatment time (accelerated therapy), produced the same rate of loco-regional relapse and late adverse effects as the standard 50Gy treatment. The hypofractionated regimes tested in the START trials are now standard practice in most institutions. The risk of hypofractionation is the effects on the late responding tissue. The larger the fraction, the greater the expected late effect will be. Results of studies on the long-term side effects of hypofractionated radiotherapy for breast cancer show comparable results for the risk of local recurrence and cosmetic outcome.^{33,34}

Evidence for once weekly radiotherapy

In 1987, Rostom *et al*, investigated using once weekly hypofractionated radiotherapy (6.5Gy weekly for 6 fractions) as definitive or adjuvant treatment in elderly patients. Of the 84 participants, 18 had undergone a mastectomy. This study demonstrated that the hypofractionated regime was well tolerated. There were less acute side effects than conventional radiotherapy (50Gy) and only 1 of the 66 patients who had an intact breast developed late fibrosis of the breast.³⁵

Maher *et al* published a retrospective review, evaluating ER positive elderly women who were unfit for surgery or normofractionated radiotherapy, in 1995.²⁵ The patients had received Tamoxifen 20mg daily, as well as once weekly radiotherapy of 6.5Gy for 5 fractions to the involved breast and 2 fractions to the tumour bed. The majority of the patients were stage 1 and 2. This study showed that at 36 months, the overall survival was 87%, the disease specific survival

was 88% and the local control rate was 86%. Ten percent of the patients had WHO grade 2 skin reactions and 3% had WHO grade 3 skin reactions. There was late fibrosis of the breast in 39% of the patients, but late tissue damage was accepted as adverse sequelae in the patients. No pneumonitis or rib fractures were reported. These patients were however treated in the lateral decubitus position, which would reduce dose to lung and ribs.

Courdi *et al* performed a similar study in 2006 with the same dose fractionation.²⁶ A third of these patients had T3 and T4 tumours. Their local control rate was similar at 85%. They had grade 1 and grade 2 skin reactions in 20% and 9% of the patients respectively. No grade 3 skin reactions were reported. There was late fibrosis in the breast of 49% of the patients, majority being grade 1 and grade 2. The progression free survival at 5 years was 78%.

In 2005, Orthalan *et al* studied the same hypofractionated regime at the same institution as Courdi.²⁷ They, however, reviewed those patients who received the radiotherapy in the post-operative setting. Seventy six percent of the patients received adjuvant hormones as well. More than 85% of the patients tolerated the treatment. The outcomes showed a 5- and 10- year disease free survival of 80% and 71.5% respectively and an overall survival of 71.6% and 46.5%. The local relapse rate was 2.3%. WHO grade 1 and 2 skin effects were seen in 26% of patients, with no grade 3 effects. Late effects was comparable to those seen in patients receiving 42.5Gy in 16 fractions.³³

Kirova *et al* compared adjuvant hypo-fractionated radiotherapy to normofractionated radiotherapy in the post-operative setting.²⁸ Patients either received 50Gy in 25 fractions or 6.5Gy once weekly for five fractions. The outcomes were very similar to the above trial, except that there was a higher rate of late effects (33%) in the hypofractionated regimen. Thus also affirming that once-weekly ultra hypofractionated radiotherapy is an acceptable alternative to normofractionated radiotherapy.

Conclusion

Patients with advanced disease, particularly in developing countries, may display a similar combination of disease and social characteristics. Control of local disease could improve quality and length of life, especially if no distant metastasis or limited metastasis is present. Based on the studies in the elderly population, using the once weekly regimen is an acceptable regimen to use in palliative patients.

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PART C: PUBLICATION-READY MANUSCRIPT

ADVANCED BREAST CANCER: A RETROSPECTIVE REVIEW COMPARING TWO PALLIATIVE RADIOTHERAPY PROTOCOLS

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ABSTRACT

Purpose: To retrospectively evaluate and compare the loco-regional progression free survival (PFS), overall survival (OS) and acute effects of the two breast palliative regimes used in patients with locally advanced or metastatic breast cancer between 2010 and 2013 in a single institution.

Methods: Compliance to treatment, acute skin reactions, progression free and overall survival were retrospectively evaluated in patients who received palliative breast radiotherapy for locally advanced breast cancer between 2010 and 2013. The radiotherapy regimes were either 4Gy per fraction for 5 fractions treated 4 times a week (20Gy) or 6Gy per fraction for 6 fractions treated once a week (36Gy). They may have received previous chemotherapy with minimal or no clinical response, as well as hormonal treatment.

Results: Forty three patients were followed up over a median period of 24 months, 14 of which received 20Gy and 29 received 36Gy. The average age was 64 years old. Compliance was 88% in both groups. Both groups had either grade 1 (71% vs 62%), grade 2 (21% vs 24%) or grade 3 (8% vs 14%) acute skin reactions. No grade 4 skin reactions were documented. The PFS was shorter at 4.5 months in the 20Gy group compared to 7.7 months in the 36Gy group ($p=0.27$). The OS was also shorter at 25.8 months in the 20Gy group compared to 29.6 months in the 36Gy group ($p=0.51$)

Conclusion: This study did not show a statistically significant difference in terms of PFS and OS between the two radiotherapy regimes. They both remain reasonable options in local palliation in patients with locally advanced breast cancer.

Key Words: Locally advanced breast cancer, palliative radiotherapy, radiation regimes

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Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of death in women worldwide.¹ According to Vorobiof et al, in 2001, the incidence of breast cancer in South Africa was approximately 16.6% with a fair percentage of the patients presenting with advanced disease². Despite great strides in the treatment of breast cancer, the management of locally advanced breast cancer remains an oncologic challenge. This is especially true in developing countries where health resources and access to care are not readily available to the general population.^{4,7}

According to the European Society of Medical Oncology guidelines, the treatment of locally advanced breast cancer involves multiple modalities.⁸ The aim of treatment is to downstage the tumour utilising neo-adjuvant chemotherapy or hormonal treatment where appropriate followed by surgery, adjuvant radiotherapy and biological agents. If patients present with distant metastases, the aim of multimodality treatment is local control, as well as improvement in quality and length of life without the treatment being too taxing on the patient physically, socially and financially.

Our institution boasts an expert, multidisciplinary team, but we have limited access to certain chemotherapy agents and no access to the biological targeted agents used in advanced breast cancer treatment. This lack of treatment agents is mirrored in other South African state hospitals and in developing countries as well.^{3,7} In fact, in many of the developing countries especially in Africa, the institutions are significantly limited with regard to oncology care and resources.⁵

In patients who do not respond to chemotherapy and/or hormonal treatment, palliative radiotherapy is the remaining option in the treatment of complications of locally advanced disease such as ulceration bleeding of the breast primary. There are various palliative breast radiotherapy regimes prescribed for local control of disease.²²

Institutions in South Africa use a variety of regimens: a single fraction of 8 Gray (Gy), fractionated treatment of 20Gy at 4Gy per fraction for five fractions or 30Gy at 3Gy per fraction for 10 fractions.²²

The treatment plan depends on the resources available at the facility, patient Eastern Collaborative Oncology Group (ECOG) performance status and disease factors.

Since 2012, our institution adopted a hypofractionated 36Gy regime, where the patient has a single 6Gy fraction per week for six weeks to a total of 36Gy. This regime has been studied in the elderly population who required adjuvant radiotherapy after breast conserving surgery for early breast cancer^{27,28} and elderly patients who were unfit for surgery but eligible for hormonal treatment.^{25,26}

Studies indicate that elderly patients tended to present with more advanced disease, have multiple comorbidities and poorer performance status, rely more on social support, have poor access to transportation to hospital and have more financial constraints.^{27,36} This was the rationale behind the studies done using a hypofractionated radiotherapy regime in the elderly as it afforded the patients therapeutic advantages without it being too cumbersome on the patient physically, socially and financially.²⁷

Patients with advanced disease, particularly in developing countries, may display a similar combination of disease and social characteristics.³ This is the rationale behind investigating this regime for locally advanced breast cancer in our institution. The aim of this study is to retrospectively evaluate the outcomes of the 20Gy and 36Gy fractionation regimes, Specific primary objectives were overall survival, acute effects of radiotherapy and loco regional progression free survival. The secondary objective was to determine the demographics of patients presenting with advanced disease.

METHODS AND MATERIALS

Patients

This is a retrospective cohort analysis. Patients, treated between 2010 and 2013, with palliative radiotherapy to whole breast for locally advanced breast cancer (with or without distant metastasis), were identified using the Groote Schuur Hospital Department of Radiation Oncology Electronic Patient Registry.

The inclusion criteria were patients 18 years and older, registered with the Combined Breast Clinic at Groote Schuur Hospital, with proven and documented evidence of inoperable locally advanced breast cancer. Patients were treated with either a total dose of 20Gy or 36Gy to the involved whole breast. Patients on hormonal treatment, if they were oestrogen or progesterone receptor (ER/PR) positive, were also included as well as those who received prior chemotherapy. Patients were excluded if they received chest wall irradiation post mastectomy or breast irradiation post lumpectomy. Department clinical notes were used to obtain the relevant data.

Variables included age, stage at presentation, ER/PR status, hormonal and chemotherapy received, radiotherapy (RT) regimen received, compliance to RT, time of local progression and time and cause of death.

Treatment

Between 2010 and 2011, the standard palliative regimen used for patients with relatively good performance status, was a total of 20Gy to whole breast (4Gy weekly for five fractions). The equivalent dose in 2Gy per fraction (EQD2) was 26.67Gy, using an α/β of four for late effects.^{30,31} Since 2012, an alternative palliative regimen was introduced. Patients received a total of 36Gy to the whole breast (one fraction weekly for six weeks). The EQD2 was 60Gy, once again using an α/β of four for late effects. The time factor was not taken into account.

In both regimens, the patients were marked up on the simulator. They were positioned supine on a breast board, angled at 7.5 degrees. The patients were treated with Cobalt⁶⁰ γ -rays and no bolus was used on the skin.

The local skin effects were documented according to the Radiation Therapy Oncology Group (RTOG) Skin Toxicity Guidelines. Overall survival was defined as the time from registration at the Combined Breast Clinic at GSH to death or end of follow-up period. The progression free survival was defined as the time from the start of radiotherapy to the first sign of loco-regional progression or death.

Statistical Analysis

Statistical analysis of data was performed using Stata (version 13). The differences between the two treatment groups were analysed using *t*-tests for continuous variables and chi-square analysis for categorical variables. Survival curves for overall survival (OS) and progression free survival (PFS) were generated using Kaplan Meier method. The statistical significance of differences in survival between the two regimes was determined by the log-rank test. A *p*-value of <0.05 was considered statistically significant for all variables.

Results

The median follow up was 25 months (range 3.1 to 83.2 months). Overall, there were 43 patients who received radiotherapy, with palliative intent, to their whole breast. Fourteen patients received a total dose of 20Gy (regimen 1) and 29 patients received a total dose of 36Gy (regimen 2).

Demographics

Patient demographic information is presented in table 1. The median age was 66 years (range, 36-78 years) in the 20Gy group versus 63 years (range 36-86 years) in the 36Gy group (*p*=0.28). The disease

stage at presentation was not statistically significant between the two groups. In the 20Gy group, 64% (vs 66% in regimen 2) of the patients presented with inoperable, locally advanced disease (Stage 3) and 36% (vs 34% in 36Gy group) presented with locally advanced disease, as well as distant metastasis (Stage 4).

Table 1: Patient Demographics: age, clinical stage and hormone receptor status

Characteristics	20Gy	36Gy	Total	<i>p-value</i>
	n = 14	n = 29	n = 43	
Age (years) Median Range	66 36- 78	63 36 - 86	68 36 - 86	0.28
Stage 3 4	64% 36%	66% 34%	65% 35%	0.93
ER status Positive Negative	57% 43%	62% 38%	60% 40%	0.76

Additional treatment (concurrent, adjuvant or neoadjuvant)

Table 2 represents additional treatment received by patients. In terms of hormonal treatment, 13% of the 20Gy group was treated with Tamoxifen alone and 87% received Tamoxifen and an aromatase inhibitor during the course of their disease. In the 36Gy group 22% were treated with Tamoxifen alone, 17% were treated with an aromatase inhibitor and 61% received both Tamoxifen and aromatase inhibitor. There was no significant difference in hormonal therapy received between the two study groups. However, the data indicates a trend towards a significant difference between the two groups with regards to a trial of chemotherapy before radiotherapy. In the 20Gy group 71% received chemotherapy compared to 41% in the 36Gy group (p=0.065).

Table 2: Additional treatment received

Treatment	20Gy	36Gy	Total	p-value
	n = 14	n = 29	n = 43	
Hormonal therapy	57%	62%	60%	0.53
Tamoxifen (1)	13%	22%	12%	
Aromatase Inhibitor (2)	0%	17%	7%	
Both (3)	87%	61%	42%	
Chemotherapy	71%	41%	51%	0.06

Radiotherapy

Results of radiotherapy received are presented in Table 3. The radiotherapy was well tolerated in both groups, with 88% of patients completing their course of radiotherapy. Of the patients who received 20Gy, 93% completed the course versus 86% who received 36Gy. Of the five patients who did not complete radiotherapy, one (in 36Gy group) died before completion of treatment. The other four patients defaulted treatment for unknown reasons. The median equivalent dose received was 26.40Gy and 59.20Gy by the 20Gy and 36Gy regimes respectively.

Table3: Radiotherapy received

Radiotherapy	Regimen 1 (20Gy in 5 fractions)	Regimen 2 (36Gy in 6 fractions)
EQD2*	26.67Gy	60.0Gy
EQD2 mean dose (range)	26.4Gy (5.33 Gy- 26.67Gy)	59.2Gy (10.0Gy- 60.0Gy)
Completion of RT n (%)	13 (93)	25 (86)

*EQD2: equivalent dose in 2Gy per fraction

Skin Toxicity

In the 20Gy group, 71% had RTOG Grade 1 acute skin effects, 21% had Grade 2 effects, and 8% had Grade 3 effects (Table 4). Similarly, in the 36Gy group, 62% had grade 1 effects, 24% had Grade 2 effects and 14% had grade 3 effects. In both groups, grade 4 effects were not evident.

Table 4: Skin Toxicity Grading according to the Radiotherapy Oncology Group (RTOG)

Treatment	20Gy	36Gy	Total
	n = 14	n = 29	n = 43
Grade 1	71%	62%	65%
2	21%	24%	23%
3	8%	14%	12%
4	0%	0%	0%

Survival

There was a statistically significant difference in survival between the two groups. In the 20Gy group 92% of the patients had died at the end of the follow up period compared to 58% in the 36Gy group (p=0.045; CI 0.12-0.94). The cohort follow up period was 25 months (range 3.1 to 83.2 months).

The median overall survival (OS) was 29.1 months (range 19.35 to 44.81 months) for the cohort. The median OS in the 20Gy group was 25.8 months (range 11.56 - 43.03 months) and 29.6 months (range 25.62 - 44.81 months) in the 36Gy group (p=0.27).

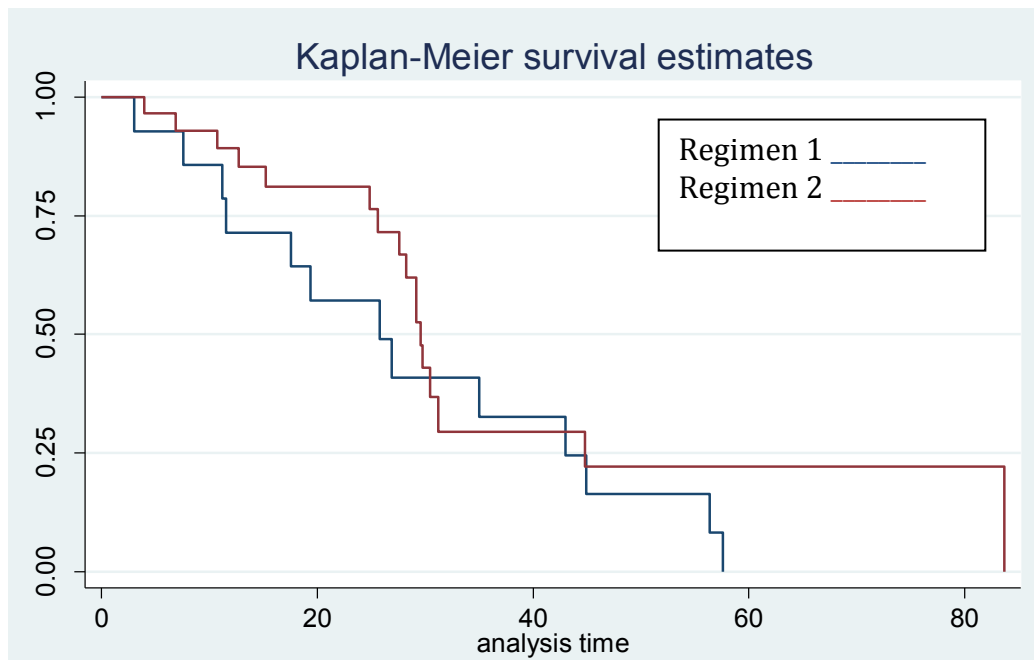


Figure 1: Overall survival (months) by treatment regimen

The overall median progression free survival (PFS) was 5.1 months (range 3.44 -10.61). In the 20Gy group PFS was 4.5 months (range 3.61-5.81) and 7.7 months (range 3.44-19.81) in the 36Gy group (p=0.51).

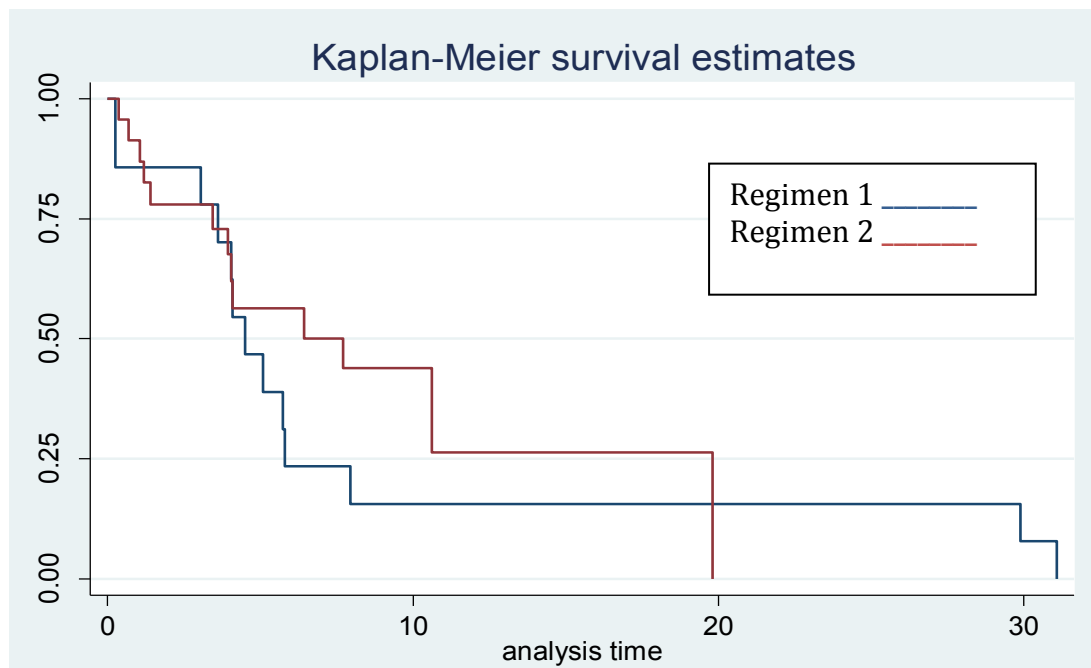


Figure 2: Progression free survival (months) by treatment regimen

A univariate analysis of the patient demographics, with regard to its influence on survival, showed that ER status was a statistically significant prognostic factor ($p=0.01$). In the 20Gy group, 71% ($n=10$) of the patients died due to progression of local disease, two patients due to visceral metastasis and one patient died secondary to brain metastasis. Conversely, in the 36Gy group, only 14% ($n=4$) died due to local progression, nine patients due to distant metastasis, and four patients due to medical co-morbidities.

Of the 14 patients that progressed locally, 80% was Stage 3 in the 20Gy group (compared to 75% in the 36Gy group) and 20% Stage 4 (compared to 25% in the 36Gy group) ($p=0.837$). The median age in the 20Gy group was 60 years and in the 36Gy group was 73 years ($p=0.08$; CI 56.28-71.5). In the 20Gy group 60% were ER negative compared to 50% in the 36Gy group ($p=0.733$). The differences between the two groups were not statistically significant, the exception being with regards to chemotherapy treatment. In the 20Gy group, 80% received chemotherapy, compared to 0% in the 36Gy group ($p=0.006$). A multivariate analysis could not be performed, as the sample size was too small.

Discussion

This was a small, single institution, retrospective study of two palliative breast hypofractionation radiotherapy regimens, used for locally advanced breast cancer between 2010 and 2013.

In the 1960's a limited number of studies were performed examining hypo-fractionation in the palliative setting. These trials were, however, abandoned due to poor technique, radiation quality and subsequent severe late effects.^{23,24} A review of the literature failed to find any recent studies investigating the optimal radiotherapy dose and fractionation for local breast palliation.

There are studies and retrospective reviews that have been published using the once weekly hypofractionated radiotherapy regime. It was, however, investigated in the elderly population as

definitive radiotherapy or as adjuvant treatment post mastectomy. These trials looked at the incidence of acute and late side effects of hypofractionated radiotherapy, tolerance and compliance to radiotherapy, the local control rate, disease free survival, cause specific survival and overall survival.

In 1987, Rostom *et al*, investigated once weekly hypofractionated radiotherapy (6.5Gy weekly for 6 fractions) as definitive or adjuvant treatment in elderly patients.³⁷ Of the 84 participants, 18 had undergone a mastectomy. This study showed that the hypofractionated regime was well tolerated. Maher *et al*, published a retrospective review of elderly patients who received once weekly adjuvant radiotherapy (6.5Gy weekly for 6 to seven fractions) and Tamoxifen in 1994.²⁵ The majority of the patients were stage 1 and 2. This study also showed that the regime was well tolerated by 87% of the patients. In our study the weekly hypofractionated regime was also well tolerated with 88% of patients completing treatment.

In the study by Rostom *et al*, there were less acute side effects than conventional radiotherapy (50Gy) and only 1 of the 66 who had an intact breast had late fibrosis of the breast.³⁷

Ten percent of the patients in the study by Maher *et al*, had grade 2 skin reactions and 3% grade 3 reactions.²⁵ There was late fibrosis of the breast in 39% of the patients. No pneumonitis or rib fractures were reported. These patients were, however, treated in the lateral decubitus positions, which would reduce dose to lung and ribs. In our study, the acute skin reactions in the 36Gy group were higher, with 62%, 24% and 14% having Grade 1, grade 2 and grade 3 skin reactions, respectively. However, the previous study groups were majority T1 and T2 breast tumours, whereas our study group was only T3 and T4 tumours.

In 2006, Courdi *et al* performed a study with definitive RT at the same dose fractionation as the Maher trial.²⁶ This study is comparable to our cohort as a third of these patients had T3 and T4 tumours. However, they had grade 1 and grade 2 skin reactions in 20% and 9% of the patients respectively. No

grade 3 skin reactions were reported. There was late fibrosis in the breast of 49% of the patients, majority being grade 1 and grade 2. As it is difficult to assess skin reaction when the skin is red, ulcerated and inflamed, the presence of T3 and T4 tumours in the our study may have resulted in over-reporting of skin toxicity

The main concern with hypofractionation is the increased incidence of late effects, with fibrosis occurring in 39% of patients according to the studies done in elderly.^{27,28} Of note, Kirova *et al* compared normofractionated radiotherapy to hypo-fractionated radiotherapy in the postoperative setting. Results were similar between the two groups, except that there was a higher rate of late effects (33%) in the hypofractionated regimen.²⁸ However, due to the palliative intent of our treatment, the late complication risk was accepted. Skin necrosis and rib fractures were not reported in patient folders but this non-reporting may be due to patients not surviving a long period of time in which to experience late effects. This is in keeping with previously reported trials.^{25,26}

The local progression free survival (PFS) was not statistically significant between the two groups. This may be due to the study being underpowered. The 36Gy group received a higher equivalent dose compared to the 20Gy group. Therefore it was hypothesised that they would have a better PFS. The results found that ER status was a significant prognostic factor. This could be due to the added benefit of hormonal treatment in local control. Previous studies have also found that ER status; nodal status and tumour size were independent prognostic factors.^{25,27} This PFS cannot be compared to the previous studies, as most of the patients in the previous trials were either early stage cancers or treated adjuvantly with radiotherapy.^{25,37}

Similarly, the overall survival was also not statistically significant between the two groups. It cannot be compared to other studies as these patients are being treated with palliative intent.

There were a number of limitations in this study. Firstly, the cohort reported on was small. Secondly, since the study was retrospective, patient records were heavily relied upon. However, these records did not adequately document patient and treatment characteristics such as performance status, quality of life, early and late effects of radiotherapy and cosmesis. In addition, skin reactions were not graded according to the RTOG skin toxicity guidelines, making grading susceptible to observer bias. It should be noted that T3 and T4 patients are difficult to grade due to the presence of ulceration and bleeding, secondary to disease. As mentioned previously, late effects were not well recorded, but it was not of great concern as these were palliative patients with limited life span and the benefit of local control outweighed the risk of late effects due to higher overall dose.

In conclusion, the 36Gy regime may be a reasonable alternative for local control to the 20Gy regime in patients with locally advanced breast cancer. There is no statistically significant difference between the two regimens in term of overall survival, progression free survival and acute skin effects. Previous trials have shown promising results using a once weekly hypo-fractionated regime in the curative setting. Trials however need to be performed in the palliative setting to assess its clinical effectiveness in terms of local control and to assess its impact on the quality of life of the patients compared to daily doses.

Competing interests

Dr Nazia Fakie declares no competing interests. No funding or fees were received in any form in the preparation of this manuscript.

Prof Hannah M Simonds and Dr Thurandarie Naiker declares no competing interests. No funding or fees were received in any form in the preparation of this manuscript

Authors Contribution

Dr Nazia Fakie was responsible for the literature research, data analysis and write up of the manuscript.

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APPENDICES

A: TNM CLINICAL CLASSIFICATION (AJCC 7th edition, 2010)

Primary tumour (T):

TX: Primary tumour cannot be assessed

T0: No evidence of primary tumour

Tis: Carcinoma in situ; intraductal carcinoma, lobular carcinoma in situ, or Paget's disease of the nipple with no associated tumour. Note: Paget's disease associated with a tumour is classified according to the size of the tumour.

T1: Tumour 2.0 cm or less in greatest dimension T1mic: Micro invasion 0.1 cm or less in greatest dimension T1a: Tumour more than 0.1 but not more than 0.5 cm in greatest dimension T1b: Tumour more than 0.5 cm but not more than 1.0 cm in greatest dimension T1c: Tumour more than 1.0 cm but not more than 2.0 cm in greatest dimension

T2: Tumour more than 2.0 cm but not more than 5.0 cm in greatest dimension T3: Tumour more than 5.0 cm in greatest dimension

T4: Tumour of any size with direct extension to (a) chest wall or (b) skin, only as described below. Note: Chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle.

T4a: Extension to chest wall T4b: Oedema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast T4c: Both of the above (T4a and T4b) T4d: Inflammatory carcinoma*

Regional lymph nodes (N):

NX: Regional lymph nodes cannot be assessed (e.g., previously removed)

N0: No regional lymph node metastasis

N1: Metastasis to movable ipsilateral axillary lymph node(s)

N2: Metastasis to ipsilateral axillary lymph node(s) fixed to each other or to other structures

N3: Metastasis to ipsilateral internal mammary lymph node(s)

Distant metastasis (M):

MX: Presence of distant metastasis cannot be assessed

M0: No distant metastasis

M1: Distant metastasis present (includes metastasis to contralateral supraclavicular lymph nodes)

AJCC Staging

Stage 0 Tis, N0, M0

Stage I T1, N0, M0 (T1 includes T1mic)

Stage IIA T0, N1, M0/ T1, N1, M0 /T2, N0, M0

Stage IIB T2, N1, M0/ T3, N0, M0

Stage IIIA T0, N2, M0 /T1, N2, M0 /T2, N2, M0 /T3, N1, M0

Stage IIIB T4, Any N, M0

Stage IIIC Any T, N3, M0

Stage IV Any T, Any N, M1

B: RTOG guidelines: ACUTE RADIATION DERMATITIS

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
ACUTE EFFECTS	<ul style="list-style-type: none"> • Follicular, faint or dull erythema, • Epilation, • Dry desquamation • Decreased sweating 	<ul style="list-style-type: none"> • Tender/bright erythema • Patchy moist desquamation • Moderate oedema 	<ul style="list-style-type: none"> • Confluent/moist desquamation other than skin folds • Pitting oedema 	<ul style="list-style-type: none"> • Ulceration • Haemorrhage • Necrosis

C: ECOG performance status

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on self-care. Totally confined to bed or chair.

PART D: APPENDICES

I. Data Capture Instrument

II. Official Ethics Approval Letters

I. Data Capture Instrument

1. DATA SHEET

1. Folder number
2. Age: 1)<35 2)35-55 3)56-69 4)>69
3. Stage: 1) iii 2)iv
4. Date of diagnosis
5. ECOG Performance status at diagnosis: 1 2 3 4
6. Palliative Regime: 1)1 2)2
7. Date of start of treatment
8. Date of progression
9. Date of death
10. Cause of death: 1) local 2)distant metastasis 3) other
11. Date last seen:
12. ECOG performance status at last visit: 1 2 3 4
13. Estrogen receptor/progesterone receptor: 1) positive 2)negative
14. Hormonal treatment: 1)Tamoxifen 2)Aromatase Inhibitor 3)Both
15. Chemotherapy: 1)yes 2)no
16. Skin reaction during RT: 1)Grade 1 2)Grade 2 3)Grade 3 4)Grade 4
17. Completion of radiotherapy: 1) yes 2)no

II: OFFICIAL ETHICS APPROVAL LETTERS:

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