Efficacy and Toxicity of Hypofractionated Palliative Radiotherapy for Breast Cancer Patients with Skin Invasion

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ABSTRACT

Objectives: To determine the efficacy and toxicity of palliative radiotherapy for locally advanced breast cancer patients with skin invasion.

Study Design: Quasi-experimental study.

Place and Duration of Study: Radiotherapy Department Combined Military Hospital, Rawalpindi Pakistan, Jan 2019 to Jun 2020.

Methodology: Patients who received palliative radiotherapy for the breast cancer and received radiation of 24 Gray in 3 fractions to the breast/ chest wall were included. Radiation toxicity was assessed using RTOG criteria as the primary outcome of the study. Radiotherapy efficacy in controlling bleeding/discharge and improving pain and odour scores were the secondary outcomes.

Results: Twelve (80%) patients reported improvement in pain, 13/18 (72.2) patients reported improvement in bleeding and 24/25 (96%) patients a decrease in pain level (p-value < 0.001). 11/25 (44%) developed Grade-2 skin toxicity, and 8/25 (32%) developed Grade-3 skin toxicity. No patient experienced Grade-4 skin toxicity.

Conclusion: Our study has shown that hypofractionated radiotherapy is effective and safe for palliation of patients with locally advanced breast cancer and skin invasion.

Keywords: Breast cancer, Hypofractionated hypofractionated palliative radiotherapy, Palliative therapy.


INTRODUCTION

Breast cancer is the leading cancer in women worldwide, accounting for 24% of new cancer cases in 2018.1-2 Although there is a paucity of literature, limited literature has shown that Pakistani women have the highest incidence of breast cancer among all Asian women.3 Due to a lack of awareness and resources, patients in low and middle-income countries present very late to the hospital with advanced cancer.4 These patients with advanced tumours or chest wall recurrences develop symptoms like pain, odour and bleeding due to skin involvement. This lead to a lot of distress and depression.5 in the patient’s life leading to social isolation.6 Many radiotherapy regimens have been recommended for palliation of these symptoms, but they are of longer duration. It is inconvenient for patients coming from remote areas to have multiple visits to the hospital for radiotherapy.7 Shorter duration regimens are required as they are not only more convenient for the patient but they reduce the hospital burden as well. If proven to be efficacious and safe, the hypofractionated regimen of 24 Gy in 3 fractions will lead to a better quality of life for the patient and fewer hospital visits, especially in the current COVID-19 pandemic.

METHODOLOGY

The quasi-experimental study was conducted at Combined Military Hospital Rawalpindi from Jan 2019 to Jun 2020 after IERB approval. Sample size calculation was based on a 98% response rate using a Raosoft calculator.8

Inclusion Criteria: Female patients aged 18-70 years presenting in the OPD, diagnosed with invasive breast cancer with large fungating mass or surgically inoperable cases with East Cooperative Oncology Group (ECOG) Grades 1, 2 or 3 were included in the study.

Exclusion Criteria: The patient who had previously received radiotherapy to the chest wall were excluded from the study. Concurrent cytotoxic agents were not allowed during the study, and patients with skin disease of contraindication to radiation were also excluded.

Informed consent was obtained before patient enrolment. The patients were enrolled using consecutive sampling. We conducted a CT scan of the chest wall/ breast at the start of Radiotherapy. Clinical findings were recorded in the OPD the week before the radiotherapy was started. All patients were treated...
supine with parallel opposed tangential fields using a half-beam block. A dose of 24 Gray in 3 fractions was administered over three weeks. The biologically effective dose (BED), calculated using an alpha/beta of 3.5 for breast cancer, was 78.86 Gy. The patients were assessed weekly for the first month and then monthly for the next three months. The patients were assessed weekly to determine the acute skin toxicity during radiotherapy. This was followed by a monthly check-up for the following three months after the completion of radiotherapy according to our protocol. Radiation toxicity was measured using Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Bleeding, odour, and pain QOL scores were evaluated before the start and then at 1 and 3 months post radiotherapy. A five-point scale was used to measure odour (0: none, 1: subtle, 2: mild (local area only), 3: moderate (noticeable close to the patient), and 4: strong (noticeable in the same room) and bleeding (0: none, 1: on touching, 2: intermittent, 3: continuous (requiring permanent bandage), 4: requires surgical intervention). Patient pain was assessed using a 5-point scale of 0 (none) to 4 (severe).9,10

Statistical analysis was performed using a Statistical Package for the social sciences (SPSS) version 22.00. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. One-way analysis of variance (ANOVA) was applied to gauge the main differences. The p-value of ≤0.05 was considered significant.

RESULTS
A total of 25 patients with breast cancer with skin involvement were included in the study. The mean age at the time of RT was 60.1±2.4 years (Range 45-71 years). Most of the patients in our study had an ECOG score of 0-1. All patients had received some form of chemotherapy or hormone therapy before RT, but symptoms were progressive on treatment.

Out of 25 patients, five patients had previously undergone surgery; 18(72%) cases had metastatic disease, while 2(8%) patients had inoperable disease. 11(44%) of these patients had right-sided breast cancer, while 14(56%) had left-sided disease. The mean tumour size at the start of treatment was 8.58±3.0cm (Range 4.5-18cm). Seven patients (28%) had a tumour size of more than 10cm. The indication of Radiotherapy included Bleeding(84%), Pain (76%), Odour (84%) or a combination. 12/15(80%) patients reported improvement in pain, 13/18(72.2%) patients reported improvement in bleeding and 24/25(96%) patients a decrease in pain level. Six patients (24%) developed Grade-1 skin toxicity, while 11 patients (44%) developed Grade-2, and 8 patients (32%) developed Grade-3 skin toxicity significantly improved with radiotherapy (Table).

| Table: Clinical Characteristics of the Patients (n=25) |
|--------------|--------------|--------------|--------------|--------------|--------------|
|              | Day-1        | Day-30       | Day-90       | p-value      |
|              | (Mean±Score) | (Mean±Score) | (Mean±Score) |              |
| Pain score   | 2.81±0.21    | 1.81±0.23    | 1.28±0.15    | <0.001       |
| Bleeding score| 2.63±0.89    | 1.89±0.36    | 1.61±0.08    | <0.001       |
| Odour score  | 2.48±0.54    | 1.88±0.47    | 1.64±0.99    | <0.001       |

DISCUSSION
Breast cancer is the most commonly diagnosed cancer among women in Pakistan. Most patients are diagnosed at a locally advanced stage due to a lack of access to the health care system.9 These patients are treated with palliative intent, as a cure is not possible considering the advanced nature of the disease.10 The role of palliative radiotherapy has been established in the symptomatic treatment of advanced and metastatic breast cancer. Different radiation fractionation protocols have been used in this respect depending upon the patient’s performance status and extent of disease. Different radiation protocols have been used worldwide,11 but the most commonly used fractionation protocols include 30 Gy in 10 and 20 Gy in 5 fractions over 1-2 weeks. Shorter fractionation protocols are being evaluated to improve the quality of life of patients with advanced disease and decrease hospital visits, leading to less burden on resources.12 Although such protocols have been used extensively in other malignancies,13 there is a paucity of literature regarding the use of hypofractionated protocols in breast cancer. Hypofractionation is already being done in a curative setting after breast cancer resection.14 In this study, we share our experience of hypofractionated palliative radiotherapy for treating breast cancer using 24 Gy in 3 fractions.

In our series, we studied the effect of radiation on 25 breast cancer patients to manage pain, odour and bleeding. Different studies have reported the effect of RT in palliation for advanced breast cancer with varied responses. A previous study have reported improvement in bleeding and odour but no improvement in pain.15 One study reported a 46.2% response rate of palliative RT with a median dose of 27.5 Gy in 11
fractions in patients with skin ulceration over the breast. In another study only patients who received a dose of 30 Gy in 10 fractions (with an EQD2 34.5 Gy) or more showed a significant clinical benefit in contrast to those patients receiving a lower dose. Our fractionation protocol of 24 Gy in 3 fractions has an EQD2 of 36GHy for the early effects.

Jacobson et al. have reported that a single fraction dose has an inferior response compared to fractionated radiation, and such patients required re-irradiation more frequently. However, patients selected for single fractionation had a lower ECOG performance status and relatively poor prognosis. This lower and less durable response rate can also be attributed to lower EQD2 of 12 Gy, but more studies are required to evaluate this protocol. The significant advantage of our fractionation protocol is delivering a higher dose quickly with good palliation, resulting in fewer hospital visits, less cost and an earlier start of systemic therapy.

CONCLUSION

In conclusion, our fractionation protocol of 24 Gy in 3 fractions effectively palliates symptoms of patients with locally advanced breast cancer. At this time of the COVID-19 pandemic, it is beneficial as fewer hospital visits are required, which are convenient for the patient and the health care professionals.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

TM: & AZ: Data analysis, drafting the manuscript, critical review, approval of the final version to be published.
ZAA: & SH: Data acquisition, conception, study design, approval of the final version to be published.
MIW: & OR: Data acquisition, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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