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Role of radiotherapy in the management of breast cancer with skin involvement

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Purpose: This study aimed to evaluate the effect of radiotherapy (RT) on symptomatic relief and tumor control in patients with breast cancer with skin involvement.

Materials and Methods: This retrospective study included patients who received palliative RT of the breast or chest wall for breast cancer with skin involvement. Progression-free survival, freedom from local progression (FFLP), and symptomatic response were evaluated. The prescribed dose to tumor was calculated as the biologically effective dose (BED) using α/β of 4. Symptomatic responses were evaluated until 6 months after RT.

Results: Of the 43 patients included in this study, 48 Gy in 15 fractions was the most common regimen, and the median BED was 86.4 Gy (range, 24.0 to 120.0). With a median follow-up of 15.1 months (range, 1.6 to 63.5), the median FFLP and progression-free survival were 8.4 and 3.6 months, respectively. The 1-year FFLP rates in patients who received BED >75 Gy and BED ≤75 Gy were 78.3% and 49.7%, respectively ($p = 0.046$). Within 6 months after RT, 75% of patients showed relief of discharge, 67% showed relief of bleeding, and 37% showed relief of pain. There was no grade 3 or higher skin toxicity or other adverse events.

Conclusion: Palliative RT is a safe and effective treatment option for patients with breast cancer with skin involvement, providing symptomatic relief. The administration of BED ≥75 Gy can offer a benefit in achieving durable local control.

Keywords: Palliative radiotherapy, Breast neoplasms, Skin involvement

Introduction

Skin involvement frequently occurs, 5%, in breast cancer patients being the most common cancer with skin involvements. Skin involvement is associated with poor prognosis due to its advanced nature at diagnosis and the challenges in achieving local control of the disease [1,2]. Patients with advanced breast cancer with skin involvement often experience a wide range of distressing symptoms, such as pain, bleeding, mass effect, and malodorous discharge, that significantly impact their quality of life (QOL). In addition, such patients may suffer from psychologic distress, clinical depression, and anxiety [3,4]. While current guidelines focus on systemic therapy over primary tumor-directed therapies [5], palliative local management can be used to control symptoms and improve QOL in patients with a symptomatic breast tumor with skin involvement.

Radiotherapy (RT) is a widely used local treatment modality for palliative care in patients with cancer alleviating symptoms and improve QOL in patients with advanced cancer [6]. In a multi-institutional, prospective, observational study, palliative RT was shown to be an effective treatment for relief of symptoms [2]. Studies have shown that palliative RT can achieve symptom relief in 60%

of skin involvement cases, with notable improvements in pain management and reduction of malodor [7,8]. Nevertheless, there have been few studies specifically examining the use of RT in breast cancer with skin involvement. In this study, we aimed to evaluate the effect of RT on symptomatic relief and tumor control in patients with breast cancer with skin involvement.

Materials and Methods

From January 2016 to December 2020, data from 49 patients who received palliative RT of the breast or chest wall for breast cancer with skin involvement were retrospectively collected from a single institutional database. The skin involvement was determined by physical examination and imaging studies such as computed tomography (CT), positron emission tomography–computed tomography, and magnetic resonance imaging. In cases when imaging results varied, if any of the images indicated skin involvement, it was considered present. Five patients with a follow-up duration less than 4 weeks were excluded. Fifteen patients who had previously undergone partial mastectomy (PM) or total mastectomy (TM) were included; RT was administered as a salvage treatment following recurrence. One patient was excluded for pathology of phyllodes tumor. In total, 43 patients were included in the final analysis.

We evaluated tumor response, overall survival (OS), progression-free survival (PFS), freedom from local progression (FFLP), and symptomatic response. Tumor response was evaluated until 6 months after RT using the Response Evaluation Criteria in Solid Tumors. OS was defined as the time from the last day of RT to death from any cause. PFS was defined as the time from the last day of RT to any disease progression. FFLP was defined as the time from the last day of RT to disease progression at the irradiated field. Symptoms were defined based on the electronic medical record. Pain was considered present if the patient was already taking opioid analgesics, and improvement was assessed based on changes in the dosage and type of medication taken. For discharge and bleeding, we evaluated the patient's subjective perception as well as the physician's examination findings. Symptomatic response in pain, bleeding, and discharge was evaluated until 6 months after RT. For adverse effects after RT, Common Terminology Criteria for Adverse Events version 5.0.

For equal comparisons of dose effects of various fractionations, the maximum prescribed dose to tumor was calculated as the biologically effective dose (BED) using a α/β of 4 in analyzing tumor control [9]. The BED was dichotomized into ≤75 Gy and >75 Gy. The cut-off value was determined by the receiver operating characteristic curve and the highest value of Youden Index. Survival outcomes were calculated using the Kaplan-Meier method and compared using the log-rank test. Survival outcomes were compared between patients who received BED of ≤75 Gy and >75 Gy. The Cox proportional hazards model was used for multivariable analyses. p-values of <0.05 were considered significant. Statistical analyses were performed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Among 43 patients, the median age was 56.8 years (range, 38.5 to 89.4). A total of 86.0% of patients had distant metastasis at the time that they received RT. Most patients were diagnosed with invasive ductal carcinoma (n = 37, 86.0%), the most common subtype of which was luminal type A/B (n = 21, 48.9%) with triple-negative breast cancer (n = 13, 30.2%) as the second most common subtype. All but one patient (n = 42, 97.7%) had systemic chemotherapy during RT and 15 patients (34.9%) had histories of PM or TM. Four patients (9.3%) had histories of RT of the same irradiated site. The median total radiation dose was 48 Gy (range, 8.0 to 66.0), and the median number of fractions was 15 (range, 1 to 33). The most common RT regimen was 48 Gy in 15 fractions used in 12 patients (28.0%). The median BED was 86.4 Gy (range, 24.0 to 120.0) (Table 1). An example of a CT scan and RT plan is shown in Fig. 1.

The median follow-up duration was 15.1 months (range, 1.6 to 63.5), and the median OS was 15.1 months (range, 1.6 to 63.5). The median FFLP was 8.4 months (range, 0.6 to 61.0), and the median PFS was 3.6 months (range, 0.5 to 52.7) (Fig. 2). Patients with BED >75 Gy had significantly better FFLP than patients with BED ≤75 Gy. The median FFLP was 11.8 months (range, 1.0 to 61.0) and the 1-year FFLP rate was 78.3% in patients with BED >75 Gy, while the median FFLP was 6.2 months and the 1-year FFLP rate was 49.7% in patients with BED ≤75 Gy (p = 0.046). There was no significant difference in PFS between patients with BED >75 Gy and those with BED ≤75 Gy (p = 0.594) (Fig. 3). BED >75 Gy, however, was not a significant prognostic factor for FFLP in multivariable analysis (hazard ratio, 0.37; 95% confidence interval, 0.11 to 1.26; p = 0.112) when adjusted for age, pathology, RT modality, molecular subtype, and type of surgery.

There was a negative correlation between BED and the probability of local progression. As the BED increases, the probability of local progression decreases, indicating that higher doses are associated with a lower likelihood of local progression (Fig. 4).

Forty-one patients were available for tumor response evaluation of all irradiated lesions after RT. The best tumor response within 6 months after RT was partial response in 32 patients (78%), stable disease in seven patients (17%), and progression of disease in two

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Table 1. Patients and treatment characteristics (n = 43)

Variable	Value
Age (year)	55 (39–89)
ECOG performance status	
0–1	36 (83.7)
2	4 (9.3)
3	3 (7.0)
N category	
N0–1	9 (20.9)
N2–3	34 (79.1)
M category	
M0	6 (14.0)
M1	37 (86.0)
Pathology	
Invasive ductal carcinoma	37 (86.0)
Other	6 (14.0)
Luminal type	
Luminal A/B	21 (48.9)
HER2+	9 (20.9)
TNBC	13 (30.2)
Concurrent systemic treatment	
Yes	42 (97.7)
No	1 (2.3)
Prior surgery	
Partial mastectomy	2 (4.7)
Modified radical mastectomy	13 (30.2)
No	28 (65.1)
RT modality	
3D CRT	7 (16.3)
IMRT	36 (83.7)
Re-irradiation	
Yes	4 (9.3)
No	39 (90.7)
Bolus	
Yes	11 (25.6)
No	32 (74.4)
Target volume	
Breast or chest wall	27 (62.8)
Including regional nodes	16 (37.2)
RT dose	
Total dose (Gy)	48 (8.0–66.0)
Biological effective dose (Gy, $\alpha/\beta = 4$)	86.4 (24.0–120.0)

Values are presented as median (range) or number (%). Data of patients and radiotherapy patients received.
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; RT, radiation therapy; 3D CRT, 3-dimensional conformal radiation therapy; IMRT, intensity modulated radiation therapy.

patients (5%).

All patients had at least one symptom that was caused by skin involvement of breast cancer. Before RT, 20 patients had discharge, 18 patients had tumor bleeding, and 38 patients had pain. Until 6 months after RT, 75.0% of patients showed relief of discharge, 66.7% of patients showed relief of bleeding, and 36.8% showed relief of pain (Table 2). Seventy-five percent of the patients showed relief of discharge in both BED ≤ 75 Gy group and BED > 75 Gy group. Patients reported relief from bleeding in 57.1% and 72.7% and from pain in 21.4% and 45.8% in the BED ≤ 75 Gy group and BED > 75 Gy group, respectively.

An acute skin reaction was reported in 10 patients (23.3%) after RT, with nine patients (20.9%) having grade 1 reaction and one patient (2.3%) having grade 2 reaction. A late skin reaction was reported in two patients (4.7%), with one patient (2.3%) having grade 1 reaction and one patient (2.3%) having grade 2 reaction. Acute grade 1 arm edema was reported in two patients (4.7%).

Discussion and Conclusion

Our study revealed that RT is a safe and effective treatment for patients with breast cancer with skin involvement, providing substantial symptomatic relief. The key finding of our research is the significant association between the BED and FFLP. Patients who received a BED > 75 Gy exhibited superior FFLP compared to those who received a BED ≤ 75 Gy. This emphasizes the importance of delivering an adequate radiation dose to achieve durable local control. While a BED > 75 Gy was not found to be a significant prognostic factor for FFLP in multivariable analyses, this lack of significance may be attributed to the limited number of patients in our study. The p-value being close to 0.05 indicates a trend that suggests further research with a larger cohort may be required to fully elucidate the relationship. Furthermore, our results demonstrated a high rate of symptomatic response, with many patients experiencing relief of discharge, bleeding, and pain within 6 months after RT. These findings underscore the beneficial impact of RT in alleviating distressing symptoms associated with breast cancer with skin involvement.

Psychological disorders, such as anxiety, distress, depression, and posttraumatic stress disorder, were readily seen in patients with breast cancer. With notable advancements in the diagnosis and treatment of breast cancer, QOL has been outcome measure [10,11]. Particularly in instances where the skin is affected, patients experience pain, bleeding, discharge, malodor, and a noticeable mass effect. These symptoms not only have cosmetic implications but also impact femininity, underscoring the importance of taking a proactive approach to palliative care.

FFLP improved significantly when treated with a BED of > 75 Gy compared with a BED ≤ 75 Gy. Similar results were found by Shel-

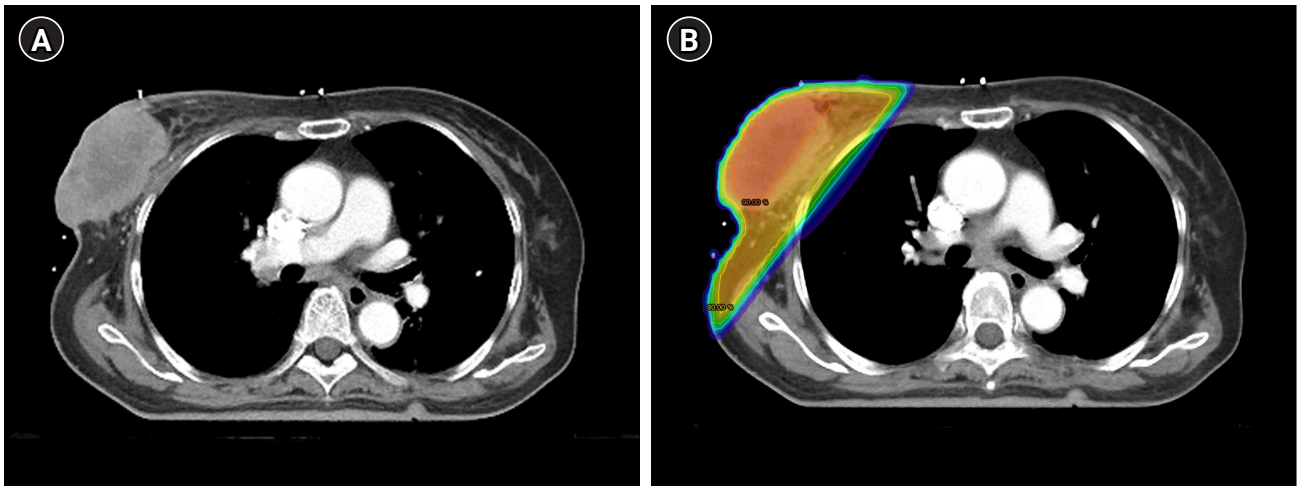

Fig. 1. Computed tomograhly (CT) scan and radiotherapy plan for a breast cancer patient with skin involvement. (A) Axial CT image showing extensive tumor involvement in the right breast, including skin invasion. (B) Radiotherapy plan demonstrating the treatment field for the same patient. The radiation dose distribution is depicted with color wash. The patient received 45 Gy in 15 fractions in total.

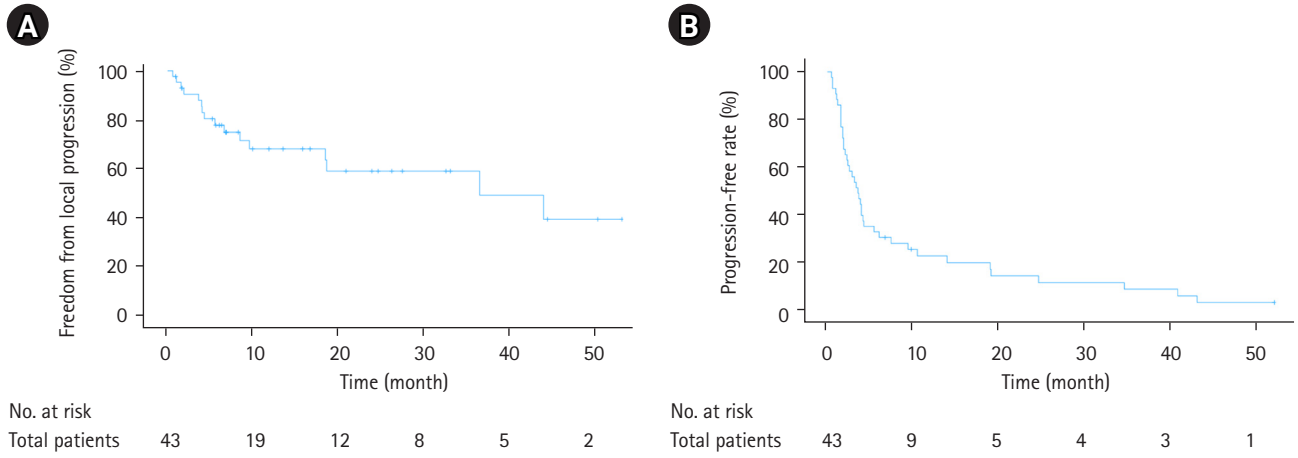

Fig. 2. Freedom from local progression (A) and progression-free survival (B) in all patients.

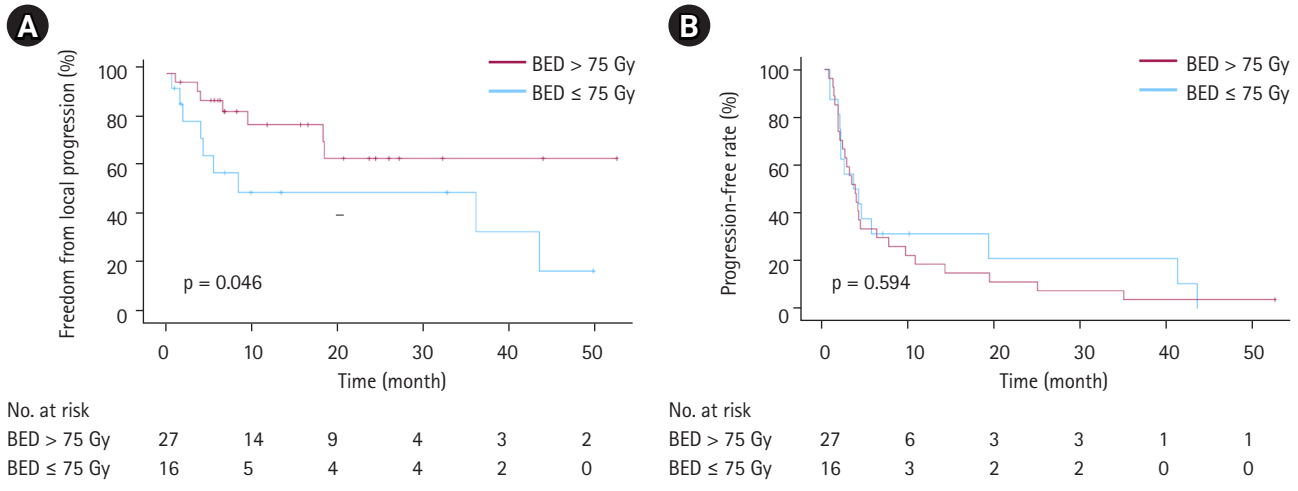

Fig. 3. Freedom from local progression (A) and progression-free survival (B) according to the radiation dose. BED, biologically effective dose.

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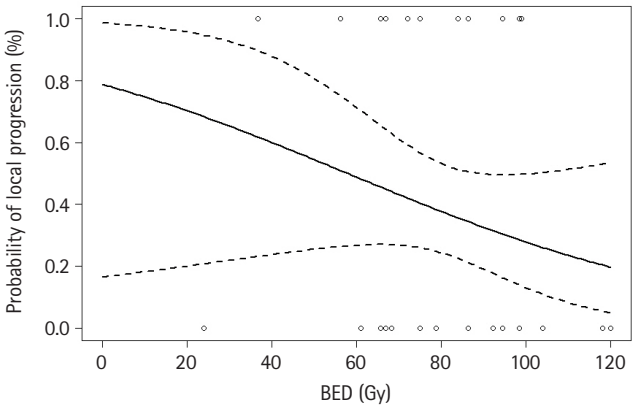

Fig. 4. The probability of local progression as a function of biologically effective dose (BED). The 95% confidence intervals are plotted around the hazard ratios. Data points, plotted as individual dots, indicate the observed outcomes of local progression (1) or no progression (0).

Table 2. Symptomatic response

	BED ≤ 75 Gy (α/β = 4)	BED > 75 Gy (α/β = 4)	Total
Discharge			
Relief	6/8 (75.0)	9/12 (75.0)	15/20 (75.0)
No change	2/8 (25.0)	2/12 (16.7)	4/20 (20.0)
Aggravate	0/8 (0.0)	1/12 (8.3)	1/20 (5.0)
Bleeding			
Relief	4/7 (57.1)	8/11 (72.7)	12/18 (66.7)
No change	3/7 (42.9)	2/11 (18.2)	5/18 (27.8)
Aggravate	0/7 (0.0)	1/11 (9.1)	1/18 (5.5)
Pain			
Relief	3/14 (21.4)	11/24 (45.8)	14/38 (36.8)
No change	10/14 (71.4)	12/24 (50.0)	22/38 (57.9)
Aggravate	1/14 (7.1)	1/24 (4.2)	2/38 (5.3)

Values are presented as number (%).
Symptomatic response outcome in patients with biologically effective dose (BED) 75 Gy or less, BED more than 75 Gy, and total patients based on electronic medical records and pain killer use. The symptomatic response described above is the best symptomatic response during the 6-month follow-up duration after palliative radiotherapy.
Percentage values may not add up to 100 because of rounding.

don et al. [12]. Locally advanced breast cancers with T3–4 or N2–3 stage in 192 patients who received primary RT without mastectomy were retrospectively studied. The results showed that more than 60 Gy to the primary site resulted in better local control (83% vs. 70%, p = 0.06), with more than 75 Gy being preferable for patients with large tumors not suitable for resection [12,13]. Consequently, delivering an adequate radiation dose is crucial for achieving durable local control, especially in patients with good performance status and a long life expectancy.

Seventy-five and fifty-seven percent of patients in the group with a BED ≤75 Gy showed reduced discharge and bleeding, respectively, suggesting that considerable symptomatic relief can be expected even with the application of low-dose radiation. However, in terms of pain relief, the response was less favorable in the BED ≤75 Gy group compared with that in the BED >75 Gy group (21.4% vs. 45.8%). Jacobson et al. [14], previously conducted a retrospective study on patients with breast cancer with skin involvement or ulcerative/mass-forming lesions who were treated with RT. In their study, 77% of patients receiving a single 8 Gy fraction and 100% of those receiving multifractionated RT (45 Gy/15 fractions, 39 Gy/13 fractions, 50 Gy/25 fractions) experienced symptomatic relief, including reduced pain, discomfort, ulceration, bleeding, and malodor. The authors assert that RT can palliate symptoms, even with a single fraction of RT with low BED [14]. In contrast, Nakamura et al. [2] conducted a prospective study with 21 patients across three institutions to evaluate bleeding/discharge, odor, pain, and QOL before and after RT. The most commonly used radiation dose regimen was 36 Gy in 12 fractions. Their findings indicated significant relief in bleeding/discharge and odor post-RT, while no significant improvements in pain or QOL were observed [2]. Considering our results and those from previous studies, it appears that palliative RT for symptoms, such as bleeding and discharge, may be effective with a BED of 75 Gy. However, for pain palliation, a dose that is higher than BED of 75 Gy may be necessary.

As this study was a retrospective study, there was a limitation in gaining symptomatic responses from patients. As pain evaluation was also based on opioid usage, for patients receiving medication from other hospitals were not included in the study. The extent of skin involvement could influence clinical outcomes. However, there are no established criteria for grading the severity of skin involvement. Therefore, this study did not categorize the severity of skin involvement, which is a limitation that should be considered when interpreting the results.

In conclusion, our study demonstrates that RT is a safe and effective treatment for patients with breast cancer with skin involvement. It provides significant symptomatic relief, including relief of discharge, bleeding, and pain. Additionally, our findings highlight the importance of delivering an adequate BED to achieve durable local control and improve long-term outcomes. Overall, RT plays a crucial role in the palliative management of patients with breast cancer with skin involvement, enhancing their QOL and providing effective symptom control.

Statement of Ethics

The study protocol was reviewed and approved by the Yonsei University College of Medicine, Yongin Severance Hospital, Institutional Review Board (9-2023-0235). Written informed consent was not required decided by the Yonsei University College of Medicine, Yongin Severance Hospital, Institutional Review Board committee.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contributions

Conceptualization, SHM, HKB; Data collection and anonymization, SHM, JSC, YBK, SHC, IJL, JL, HC, YHJ; Statistical analysis, SHM; Supervision, HKB; Writing–original draft, SHM, HKB; Writing–review & editing, HKB; Approval of final manuscript: all authors.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the information could compromise the privacy of research participants but are available from the corresponding author upon reasonable request.

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