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Review Article

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Palliative Radiotherapy for Symptomatic Primary Tumors in Patients With Locally Advanced Breast Cancer

Jae Sik Kim [1], **Jee Suk Chang** [2], **Kyubo Kim** [3,4]

[1]Department of Radiation Oncology, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Korea
[2]Department of Radiation Oncology, Yonsei University College of Medicine, Seoul, Korea
[3]Department of Radiation Oncology, Seoul National University Bundang Hospital, Seongnam, Korea
[4]Department of Radiation Oncology, Seoul National University College of Medicine, Seoul, Korea

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Correspondence to
Kyubo Kim
Department of Radiation Oncology, Seoul National University Bundang Hospital, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea.
Email: kyubokim.ro@gmail.com

ORCID iDs
Jae Sik Kim
https://orcid.org/0000-0002-0039-8667
Jee Suk Chang
https://orcid.org/0000-0001-7685-3382
Kyubo Kim
https://orcid.org/0000-0001-6093-1294

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ABSTRACT

Breast cancer remains a significant health concern for women, with a significant number of women facing unresectable, symptomatic, and advanced disease that severely affects their quality of life. Palliative radiotherapy (RT) is a well-established modality for managing such cases and alleviating symptoms. Recent advancements in systemic therapies and the resulting increase in long-term survival rates have not only heightened the need for retreatment in certain patients, but have also emphasized the importance of achieving durable local control. Additionally, inconsistencies in RT referral timing and variations in disease severity and extent contribute to diverse RT objectives and expected outcomes. The optimal dose fractionation for RT remains underexplored. Furthermore, a deeper understanding of breast radiobiology, along with the introduction of ultra- and moderately hypofractionated regimens and the widespread adoption of conformal techniques such as intensity-modulated RT, has diversified the approaches in RT dose and target volume. This review aimed to provides a comprehensive summary of the current evidence on the efficacy, outcomes, and toxicity profiles of palliative RT for symptomatic breast cancer. It highlights the need for more optimized regimens and further research to address the evolving treatment landscape and differing expectations of patients and physicians regarding RT.

Keywords: Breast Neoplasms; Palliative Care; Radiotherapy; Toxicity; Treatment Outcome

INTRODUCTION

Breast cancer is the predominant malignancy affecting women in 2023, showing a persistent increase in incidence, and is the second leading cause of cancer-related mortality [1]. In developed countries, national screening programs have reduced the incidence of locally advanced breast cancer (LABC) [2]. However, cases of neglected LABC persist, including patients who either did not receive standard care treatment or experienced significant treatment delays (up to 30%). Additionally, patients with persistent/recurrent disease despite current standard treatments (5%–15%) and those with *de novo* metastatic breast cancer (3%–6%) have been reported [1,3-7]. In developing nations, 40%–90% of women present with stage III–IV disease owing to the absence of a comprehensive healthcare system [8].

Data Availability

In accordance with the ICMJE data sharing policy, the authors have agreed to make the data available upon request.

Author Contributions

Conceptualization: Kim K; Data curation: Kim JS, Chang JS, Kim K; Formal analysis: Kim JS, Kim K; Investigation: Kim JS, Chang JS, Kim K; Supervision: Kim K; Writing - original draft: Kim JS; Writing - review & editing: Kim JS, Chang JS, Kim K.

Systemic cancer treatment remains the primary line of care for these patients [9,10]. However, the absence of surgery increases the likelihood of progression of unresected primary breast cancer [11]. In patients with metastatic breast cancer receiving only systemic treatment, locoregional progression was observed in 16%–43% of patients [12,13]. These breast lesions progress into ulcerofungating masses, causing symptoms such as pain, bleeding, discharge, and malodor, significantly affecting the patients' quality of life (QOL) [14-19]. Furthermore, these factors could lead to a vicious cycle of disease progression by causing delays in cancer treatment or presenting challenges to treatment adherence [20]. When primary breast tumors develop resistance to systemic treatment, the efficacy of subsequent therapies often diminishes, indicating that systemic treatment alone may not always effectively alleviate symptoms [21,22]. As advancements in systemic agents have increased the overall survival (OS) of these patients, a growing interest in considering locoregional treatments, such as radiotherapy (RT), has emerged [23]. RT is a nonsurgical locoregional approach that minimizes interruptions to systemic therapy, increases convenience, and decreases morbidity. Therefore, palliative RT is suitable for such patients and holds high priority among the breast-directed treatments for local symptom relief.

Historically, both surgery and RT have been used to palliate the symptoms. However, surgery has several drawbacks. In cases of tumor infiltration into adjacent structures, such as T4a, performing surgery may pose technical difficulties [24]. After surgery, a certain interval is required before initiating systemic treatment [23]. If complications arise due to wound healing, an additional delay in systemic treatment may be unavoidable [23]. Several studies have suggested that surgical procedures might increase tumor cell dissemination and that postoperative physiological alterations could contribute to the survival of these cells [25]. Furthermore, recent findings from the randomized E2108 trial examining patients with *de novo* metastatic breast cancer showed that early locoregional therapy, surgery, and RT according to the standards for managing non-metastatic disease improved locoregional control but did not affect the OS or QOL [13]. Consequently, unless in special circumstances, primary surgery is not performed to increase the OS of patients with stage IV.

This review article aimed to provide a comprehensive summary of the recent landscape of palliative RT as a significant modality for managing unresected symptomatic breast cancer, focusing on the efficacy, outcomes, and toxicity profiles of various RT regimens. Given the evolving treatment landscape and the diversity in patient needs and disease presentations, we highlight the necessity for optimized RT protocols and encourage a consensus on optimal dose fractionation to maximize benefits and minimize toxicities.

SYMPTOMS RELATED TO LOCALLY ADVANCED DISEASE

The progression of primary breast lesions can manifest in various ways, including ulceration/large open wounds, chronic breast pain, local bleeding/discharge, and frequent infection. Regional disease progression can lead to ipsilateral arm edema, brachial plexopathy, and pain [14-19].

The median or mean size of the primary tumor was approximately 6 cm [16,18]. Chia et al. [24] reported that 91.4% of patients had tumors of > 5 cm in size, while another study [16] reported that 16.9% of patients had tumors of > 9 cm in size. Jacobson et al. [16] reported that all patients (n = 53, 100.0%) experienced discomfort. Excluding this report,

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the distribution of symptoms has generally shown consistent patterns across studies: pain (35%–84%), ulceration (49%–62%), discharge (43%–59%), bleeding (15%–30%), malodor (22%–23%), and arm edema (9%–13%) [16-19]. Compression of the vessels or brachial plexus (8%) is less frequently reported [17]. In addition to other symptoms, fever was observed in some patients [15]. Most patients present with two or more symptoms [16,19].

In most studies, patients' performance was relatively good, suggesting that the symptoms are the most crucial factors that determine the need to refer for palliative RT [15,17,19,24,26]. However, clear indications for initiating palliative RT remain elusive, such as the specific severity or number of symptoms at onset or the persistence of symptoms despite systemic treatment. Notably, between 3.8% and 65.7% of patients had not received prior systemic treatment, with the number of previous treatments ranging from one to six [11,14,17-19,23,24]. These variations in the timing of RT referrals, influenced by differences in institutional and physician practices, lead to diverse symptom presentations at the time of RT. This lack of consensus on the optimal timing of palliative RT referral underscores the need for more standardized guidelines to ensure timely and effective symptom management.

TARGET DEFINITION FOR RT

No consensus has been established on target contouring for palliative RT in patients with symptomatic breast cancer. The definitions of palliative RT targets are summarized in **Table 1** [11,14-19,23,24,26]. Some studies adopted a targeted approach, focusing radiation specifically on the gross tumor that caused the symptoms [17,19,23,24,26], while others opted for a broader scope, encompassing the entire breast or chest wall [11,15,16,18,23]. Additionally, some studies included the regional nodal area [11,15,18]. The use of a boost also varied across studies [11,18].

Determining the appropriate palliative RT field may benefit from a multidisciplinary approach. In particular, an expanded RT field is associated with increased skin toxicity (breast mass vs. breast + supraclavicular lymph node, hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.01–5.45; $p = 0.04$) [19]. By contrast, a previous study suggested that a large planning target volume (PTV) is not related to radiation-induced skin toxicity when only symptomatic breast tumor lesions are treated [17]. Therefore, personalized treatment for each patient is essential, taking into account the tumor multiplicity, tumor size, skin infiltration patterns, nodal involvement, RT techniques employed, and state of extra-breast disease, along with anticipated local control (LC). However, further research is needed to precisely define individualized approaches.

PALLIATIVE RT DOSE-FRACTIONATION SCHEMES

Palliative RT serves as a critical component in managing symptomatic breast cancer lesions, offering relief and improving the QOL of patients with advanced disease. Despite the lack of randomized trials comparing different dose-fractionation regimens, several observational studies employing various dose-fractionation regimens have shed light on the efficacy and outcomes of palliative RT in managing symptoms and lesions (**Table 1**) [11,14-19,23,24,26].

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Table 1. Summary of studies investigating palliative radiotherapy for symptomatic breast cancer

Author	Period	Design	No.	Target	Dose	Tumor response*	Local control	Overall survival	Toxicity (≥ Gr 3)	Dose-response relationship
Vempati et al. [14]	2006–2015	Retrospective	13	-	Median, 30 Gy	-	-	Mean, 4.5 months	No	≥ 30 Gy
Chia et al. [24]	2000–2010	Retrospective	35	GTV	Median, 30 Gy/10 Fx Range, 20–66 Gy with 2–6 Gy per Fx	PR†, 46%; SD†, 48%; PD†, 6%	Median, 10 months	Median, 11.7 months at 1 year, 58%	No	No
Hoeltgen et al. [17]	2012–2021	Retrospective	26	GTV	Median, 39 Gy/13 Fx Range, 9–54 Gy with 1.8–4 Gy per Fx	-	Median, 7.4 months at 6 months, 75.0% at 12 months 47.6%	Median, 10.9 months at 6 months, 60.0% at 12 months, 31.7%	No	No
Nakamura et al. [26]	2014–2016	Prospective	21	GTV	Median, 36 Gy/12 Fx Range, 30–60 Gy with 2–3 Gy per Fx	-	-	-	Grade 3 skin toxicity, n = 2	-
Singh et al. [15]	2016–2018	Prospective	30	Breast/CW+ RNI	30 Gy/10 Fx	PR, 90%; SD, 7%; PD, 3%	-	-	-	-
Choi et al. [19]	2010–2016	Retrospective	22	GTV	Range, 42.5–55 Gy with 2.5–3 Gy per Fx	PR, 82%; SD, 14%; PD, 5%	-	Median, 17.3 months at 1 year, 62.8% at 2 year, 34.5%	No	No, but showing tendency: BED (α/β = 4) ≥ 80 Gy (p = 0.06)
Kim et al. [23]	2010–2021	Retrospective	133	GTV, 81%; Breast/CW, 19%	Median, 45 Gy/15 Fx Range, 24–75 Gy with 2–8 Gy per Fx	CR, 9%; PR, 65%; SD, 19%; PD, 7%	at 2 years, 49.4%	at 2 years, 48.3%	No	EQD2 (α/β = 3.5) ≥ 63 Gy‡
Chatterjee et al. [18] (HYPORT)	2015–2017	Prospective	28	Breast + RNI	35 Gy/10 Fx	Metabolic§; CR, 30%; PR, 60%; SD, 10%	-	Median, 24 months	No	-
Chatterjee et al. [18] (HYPORT B)	2018–2020	Prospective	30	Breast + RNI + SIB	26 Gy/5 Fx with 32 Gy/5 Fx to GTV	Metabolic§; CR, 17%; PR, 65%; SD, 17%	-	Median, 32.3 months	Grade 3 acute skin toxicity, n = 2	-
Jacobson et al. [16]	2006–2016	Retrospective	53	Breast/CW	8 Gy/1 Fx, 17%; Fractionated, 83% Median, 39 Gy/13 Fx Range, 45–50 Gy with 2–3 Gy per Fx	-	-	-	Grade 3 radiation pneumonitis, n = 2 (fractionated)	No
Webb et al. [11]	2011–2020	Retrospective	109	Breast/CW± RNI ± boost	30 Gy/5 Fx, 30%; 30 Gy/5 Fx + 6 Gy/1 Fx boost to affected quadrant, 70% - qw, 43% - biw, 24% - tiw, 22% - Consecutive weekdays, 11%	CR†, 10%§; PR†, 77%§; SD†, 12%§; PD†, 1%§	Median, 23.5 months at 1 year, 75.3% at 2 years, 44.1%	Median, 11.4 months at 1 year, 47.9% at 2 years, 25.1%	Gr 3 acute skin toxicity, n = 7§ Gr 4 late skin toxicity, n = 1§	-

GTV = gross tumor volume; Fx = fraction; PR = partial response; SD = stable disease; PD = progressive disease; CW = chest wall; RNI = regional nodal irradiation; BED = biologically effective dose; CR = complete response; EQD2 = equivalent dose in 2 Gy fractions; SIB = simultaneous integrated boost; qw = once weekly; biw = twice a week; tiw = three times a week.
*The response was evaluated by the Response Evaluation Criteria in Solid Tumors.
†This study did not specify the criteria for response evaluation.
‡In patients who had received second-line or lower previous systemic treatment and had stable disease burden outside of the breast.
§Among the available patients.

Median 30–39 Gy with a fraction size of 3 Gy

Vempati et al. [14] conducted a retrospective study of 13 patients treated with palliative RT for ulcerative breast lesions. Among these patients, six underwent re-RT of the same breast. The median dose administered to the entire cohort was 30 Gy delivered in 15 fractions, while the RT-naïve patients received a higher radiation dose of 32.5 Gy. The mean survival time was

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markedly short at 4.5 months; however, 46% of the patients demonstrated improvements in symptoms and wound healing after palliative RT. Although prior RT did not correlate with treatment benefits ($p = 0.81$), none of the patients who received less than 30 Gy of RT (n = 4) experienced any improvement. Consequently, the authors recommended using doses exceeding 30 Gy, regardless of the presence or absence of prior RT, and advocated hypofractionation to facilitate the immediate resumption of systemic treatment.

In another study analyzing 35 patients, subgroup analysis based on a threshold of 30 Gy showed that higher doses were unrelated to improvements in palliation duration, local progression-free survival, and OS [24]. Within a median OS of 11.7 months, which is more than twice as long as that reported by Vempati et al. [14], 94% of patients achieved symptom palliation. The median local progression-free survival times for patients with partial response, stable response, and progressive disease were 14.1, 5.2, and 1.5 months, respectively ($p < 0.05$).

An investigation using a median dose of 39 Gy delivered in 13 fractions reported the median LC and OS of 7.4 and 10.9 months, respectively [17]. The LC rate was 75% at 6 months and decreased to 48% at 12 months. The OS rates at 6 and 12 months were 60% and 32%, respectively. This study exhibited a relatively lower LC rate than that of subsequent studies. The substantial factor contributing to this trend could be the large PTV, with a median of 1206.8 cm^3 (range, 242.4–4,112.4 cm^3), despite exclusively targeting tumor lesions causing breast symptoms. Using a biologically effective dose (BED, $\alpha/\beta = 4$) cutoff value of 68.3 Gy, no significant differences were found in OS or LC, possibly owing to the relatively narrow range of dose levels. Symptom relief was achieved in 95% of the patient cohort, without an apparent association between BED and the degree of symptom palliation. Specifically, palliative RT resulted in a 29% reduction in the analgesic levels in patients, potentially minimizing the side effects associated with analgesics.

In 2018, the first prospective observational study evaluating the efficacy of palliative RT in patients with skin invasion was published [26]. Except for two patients who received 30 Gy in 10 fractions, other patients (n = 19) were treated with various dose-fractionation schemes of 36 Gy or higher. Bleeding and discharge improved after RT compared with that at baseline, and offensive odor significantly improved, especially at three months. Symptoms might have recurred at 6 months, implying the need to identify optimal palliative RT schedules for effective long-term control. Unexpectedly, the pain levels remained consistent. Although the proportion of patients who did not require pain medication increased from 48% to 88% at three months post-RT, this change was not significant. As only a few patients experienced severe pain (14% used opioid analgesics), evaluating the effectiveness of RT may be challenging. Furthermore, the lack of a significant change in the QOL score could be attributed to tumor progression outside the RT field, despite the alleviation of breast-related symptoms. Thus, expectations regarding the efficacy of palliative RT should be tailored to each patient's circumstances.

In contrast to earlier studies, a study reporting the outcomes of the common palliative regimen of 30 Gy in 10 fractions documented tumor size reduction and subjective symptom relief in 90% of patients [15].

In summary, the symptom palliation rates ranged from 45% to 95% when these regimens were used. Pain improvement was observed in 30%–40% of patients, with no significant changes observed in the QOL. The median survival time ranged from 5 to 12 months, and the median LC was 2–14 months.

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Median dose of > 40 Gy delivered in 3 Gy

Twenty-two patients with symptomatic inflammatory breast cancer underwent palliative intent hypofractionated RT at a total dose of 42.5–55 Gy delivered in 2.5–3 Gy per fraction [19]. Approximately 60% of the patients exhibited symptom improvement by more than 70% within one week after palliative RT, with the most prominent reduction observed in symptomatic pain alone. Patients who received higher doses (BED [$\alpha/\beta = 4$] ≥ 80 Gy) showed a slightly more favorable trend in symptom relief ($p = 0.06$). In contrast to a previous study, the median OS significantly increased to 17.3 months, with 82% of the patients exhibiting a partial response.

In a recently published retrospective study that analyzed the largest number of patients (n = 133), a median dose of 45 Gy in 15 fractions resulted in a 76% improvement in pain/bleeding symptoms in 51 patients with symptomatic disease [23]. Remarkably, 62% of patients underwent palliative RT due to radiological progression despite being asymptomatic, indicating a recent increase in the proportion of asymptomatic patients receiving palliative RT. Multivariate analysis revealed an association between the inferior LC and an equivalent dose of < 63 Gy in 2 Gy fractions (EQD2, $\alpha/\beta = 3.5$). The treatment outcomes are summarized in **Table 1** [11,14-19,23,24,26].

Fraction size of more than 3 Gy

In India, two consecutive prospective phase 1/2 studies have been conducted: HYPORT and HYPORT B [18]. The HYPORT study used 35 Gy delivered in 10 fractions, while the HYPORT B study used 26 Gy delivered in 5 fractions to assess the efficacy of simple palliative hypofractionated RT. Unlike other studies, this study performed positron emission tomography-computed tomography (PET-CT) scans prior to RT initiation and three months after treatment to evaluate metabolic response. Among HYPORT patients, 30% showed a complete metabolic response. Among HYPORT B patients, a complete metabolic response was only observed in 17% of patients. Furthermore, this study described the QOL assessment results in detail. The results from the physical and functional well-being tests showed improvement or stabilization in approximately 80% of the patients. Moreover, the incidence of moderate to severe psychological distress decreased by up to 26%. Within one year, only 10% of the patients experienced recurrence of local symptoms. This finding supports the clinical benefit of the regimen proposed in this study, particularly the resource-sparing regimen consisting of a 1-week, 5-fraction approach.

Single fraction vs. multi-fractionation

One study compared the single (8 Gy, n = 9) and fractionated (39 Gy in 13 fractions, 45 Gy in 15 fractions, and 50 Gy in 20 fractions, n = 44) protocols [16]. All patients treated with a single fraction demonstrated poor performance, while nine patients in the fractionated group had previously undergone postoperative RT. Only 77% of the patients in the single-fraction group experienced clinical benefits, while 100% of those who received fractionated treatment showed clinical benefits. Additionally, re-irradiation was performed more frequently in patients who received a single fraction (44% vs. 18%), with a shorter time to re-irradiation (3 vs. 16 months). Overall, single-fraction RT proved less effective compared with fractionated RT. Nonetheless, single-fraction treatment is a viable option for patients with poor performance status or those needing minimal interruptions in systemic treatment. Single-fraction RT remains useful and can be safely repeated, thereby reducing the burden on patients and their families. In this study, no correlation emerged between a threshold dose of 39 or 30 Gy and response.

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Once weekly vs. accelerated schedule

One study compared palliative RT administered at 1–3 sessions per week with the conventional treatment schedule of 5 consecutive days [11]. Patients in the study received 30 or 36 Gy delivered in 6 Gy per fraction. Among these patients, 43% were treated once a week, 24% twice a week, and 22% three times a week. Additionally, 11% of the patients were treated on consecutive weekdays to minimize systemic treatment interruptions, ensure patient convenience, and address rapidly progressive disease. No significant differences were observed in the objective response rate (81% vs. 91%), time to local progression (median, 23.5 vs. 19.0 months), or toxicity (any grade, 76% vs. 74%; and grade 3, 7% vs. 8%) between the once weekly group and accelerated group. However, the group that received consecutive daily RT experienced a higher incidence of late toxicity, including the development of grade 4 skin radionecrosis. Therefore, this regimen is not recommended. Instead, the twice-weekly regimen was found to be a safe and appealing alternative to the once-weekly approach.

Alternative strategy

A case report described the implementation of breast-directed quad-shot (BD-QS) RT in two patients with neglected breast cancer [20]. The BD-QS regimen comprised 14 Gy administered in four fractions, delivered twice daily at 6-hour intervals over two consecutive days. After three months, the response to BD-QS was assessed, and BD-QS was repeated up to a total dose of 42 Gy, when necessary. This approach provides rapid and long-lasting symptom relief without causing skin toxicity or disrupting systemic treatment.

RISK FACTORS AFFECTING TREATMENT OUTCOMES

Several studies have identified factors influencing symptom relief and LC following palliative RT [19,23]. The presence of a single symptom or multiple symptoms significantly affects the degree of symptom relief [19]. According to a univariate analysis of 22 patients, those with a single symptom experienced greater symptom relief than those with a combination of symptoms (HR, 3.57; 95% CI, 1.87–49.08; $p = 0.02$). Breast tumor pathology, a history of systemic treatment, and tumor response did not serve as prognostic indicators of symptom relief [19].

One study investigated the prognostic factors of LC using a multivariate analysis [23]. Among the baseline patient, tumor, and treatment characteristics, a history of more than two lines of systemic treatment (HR, 2.84; 95% CI, 1.50–5.36; $p = 0.001$) and disease burden outside the breast (progressive disease or mixed responses, HR, 2.20; 95% CI, 1.15–4.20; $p = 0.009$) were associated with poorer LC. Risk group stratification was performed using the two aforementioned risk factors. As the number of risk factors increased, the 2-year LC rates decreased to 63.9%, 43.2%, and 0.0% and the 2-year OS rates declined to 72.8%, 35.8%, and 6.8%. In the group without risk factors, a substantial improvement in LC was observed with an EQD2 ($\alpha/\beta = 3.5$) of ≥ 63 Gy. In patients with a single risk factor, a borderline significant difference ($p = 0.055$) was found. However, in patients with two risk factors, no discernible benefit from a higher dose was noted.

TOXICITY PROFILES DURING AND AFTER PALLIATIVE RT

Acceptable levels of toxicity were observed in studies on palliative RT (**Table 1**) [11,14-19,23,24,26]. One study reported no RT-related toxicity [14], while another reported a low

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incidence of grade 2 skin toxicity (5%) [26]. Generally, nearly all patients experienced grade 1–2 acute toxicity (37%–100%), with most presenting skin-related side effects or occasional fatigue [11,16-19]. Grade 3 acute skin toxicity occurred in approximately 10% of the patients [11,18,26].

In terms of late toxicity, grade 3 radiation pneumonitis developed in two (5%) patients and was managed with oral steroids [16]. One patient (2%) developed grade 4 skin radionecrosis [11]. Other side effects included breast distortion/asymmetry, skin thickening/fibrosis/induration, telangiectasia, breast edema, skin dryness, and rib pain without fracture [11]. A few studies have indicated the absence of chronic toxicity, which can be attributed to short follow-up and survival periods [14,17,19].

Studies analyzing patients previously treated with breast RT showed that re-irradiation did not significantly increase treatment-associated toxicity, contrary to concerns [14,16,17]. This outcome was attributed to the long interval between initial and palliative RT [14,17]. Therefore, palliative re-RT for ulcerative breast lesions remains a viable option [14]. Although generally acceptable, it is important to acknowledge the potential for increased late toxicity with hypofractionated regimens, particularly in patients who underwent prior RT. Careful patient selection and monitoring are required in such cases.

Univariate analysis revealed that elevated serum C-reactive protein (CRP) levels during palliative RT predicted a higher incidence of skin toxicity [19]. The CRP level can reflect systemic inflammation and skin irritation; however, it can also fluctuate due to various reasons, such as infection. Nonetheless, considering the various factors in this study, CRP levels were associated with the occurrence of skin toxicity. Although further validation is necessary, the careful monitoring of CRP levels and the provision of appropriate supportive care may be warranted.

STEREOTACTIC BODY RADIOTHERAPY (SBRT) FOR UNRESECTABLE BREAST TUMORS BEYOND PALLIATION

Even when primary breast cancer is resectable, some patients refuse to undergo surgery or are medically inoperable, particularly older adults who are frail or have severe comorbidities that contraindicate surgery [27,28]. In these situations, identifying noninvasive treatment strategies that can serve as alternatives to surgical resection represents a significant unmet clinical need.

SBRT is a highly conformal RT technique that uses large fraction sizes. It has demonstrated treatment outcomes comparable to those of surgery for several types of primary cancer, including early-stage non-small-cell lung cancer, making it an attractive and promising treatment option for patients with unresectable breast cancer [29,30]. SBRT has the advantage of shorter treatment duration, thus minimizing interruptions to systemic treatment.

Several recent studies, both prospective and retrospective, have examined SBRT for unresectable breast cancer, albeit with small patient cohorts (**Table 2**) [27,28,31,32]. These studies primarily defined the PTV by assigning an appropriate margin to the gross tumor volume [27,28,31,32]. However, some studies have also explored the irradiation of the entire breast and/or elective nodal areas [27,32]. All patients received a five-fraction regimen,

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Table 2. Summary of studies investigating stereotactic body radiotherapy for unresected breast cancer

Author	Period	Design	No.	Target	Dose	Tumor response*	Local control	Overall survival	Toxicity (≥ Gr 3)
Moore-Palhares et al. [27]	2014–2021	Retrospective	57 (61 course)	GTV, 67%; Breast ± SIB, 33%; ± RNI	35 Gy/5 Fx, 65%; 40 Gy/5 Fx, 35% to GTV (Breast, median 25 Gy/5 Fx; range, 20–40 Gy with 4–8 Gy per Fx) - qw, 26% - biw, 36% - EOD, 18% - Consecutive weekdays, 20%	CR, 8%†; PR, 46%†; SD, 36%†; PD, 10%†	Median, 18.2 months at 1 year, 100% at 2 years, 88.6%	Median, 31 months at 1 year, 75.2% at 2 years, 51.8% at 3 years, 38.8% at 4 years, 28.4%	Grade 3 skin toxicity, n = 8 Grade 4 skin toxicity, n = 1
Ippolito et al. [31]	2019–2021	Prospective	10	GTV	40 Gy/5 Fx (EOD)	CR, 50%; PR, 30%; SD, 20%	at 1 year, 100%	7 patients alive (median follow-up, 13 months)	No
Zabrocka et al. [28]	2015–2022	Retrospective + Prospective	21 (23 course)	GTV	40 Gy/5 Fx (EOD)	-	at 6 months, 100% at 1–3 years, 93.3%	at 6 months, 85.7% at 1 year, 69.6% at 2–3 years, 63.8%	Grade 3 skin toxicity, n = 2
Lee et al. [32]	2017–2022	Retrospective	27	GTV, 15%; Breast, 7%; Breast + SIB, 78%	30 Gy/5 Fx, 56%; 35 Gy/5 Fx, 40%; 40 Gy/5 Fx, 4% to GTV (Breast, median 26 Gy/5 Fx, range 20–30 Gy with 4–6 Gy per Fx) - Consecutive weekdays, 66.7% - EOD, 33.3%	CR, 22%; PR, 59%; SD, 19%	at 1 year, 83% at 2 years, 77%	at 2 years, 78%	No

GTV = gross tumor volume; SIB = simultaneous integrated boost; RNI = regional nodal irradiation; Fx = fraction; qw = once weekly; biw = twice a week; EOD = every other day; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
*The response was evaluated by the Response Evaluation Criteria in Solid Tumors.
†Among the available patients.

delivering 30–40 Gy to the gross lesion, while the breast received a median dose of either 25 Gy or 26 Gy [27,28,31,32]. The majority of treatments were administered either daily or every other day [27,28,31,32]. However, in the study by Moore-Palhares et al. [27], additional treatments were scheduled twice weekly (36%) and once weekly (26%). The objective response rates ranged from 54% to 81% [27,31,32]. The 1- and 2-year LC rates were 83%–100% and 77%–93.3%, respectively [27,28,31,32]. According to the analysis of failure patterns, in-field local progression was noted in 30% of the patients, while distant progression was reported in 67% [32]. The 1-year OS rates ranged from 69.6% to 75.2%, while the 2-year OS rates ranged from 51.8% to 78% [27,28,32]. Among the 115 patients from four studies, grade 3 toxicity occurred in 10 patients, while grade 4 toxicity was observed in one patient [27,28,31,32]. At baseline, 30% to 67% of the patients exhibited clinical symptoms, and all patients showed complete or partial resolution of pre-RT symptoms [27,31,32]. For patients who experienced complete symptom relief, a median time of 6.6 months was required [27].

PALLIATIVE RT IN THE ERA OF TARGETING AND IMMUNOMODULATORY AGENTS

Systemic treatment is commonly used to manage inoperable primary breast cancer [9,10]. In approximately one-fourth of patients, palliative RT was administered concurrently with chemotherapy, while one in three patients received hormonal therapy [16,26]. In addition to

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traditional systemic treatments, novel therapies such as targeted therapy and immunotherapy are increasingly being used in these patients. Following these advancements, palliative breast RT is primarily considered or delayed in patients with persistent/progressive disease [17,33]. Among patients receiving palliative RT, anti-human epidermal growth factor receptor 2 therapy was concurrently used with palliative RT in only 8% of patients [23], while immunotherapy was used in only 4% of patients [17]. The limited number of patients receiving treatment with innovative agents may account for the lack of observed differences in LC rates between treatment eras (2010–2015 vs. 2016–2021) [23].

Specifically, the combination of palliative thoracic RT and these novel therapies in patients with stage IV non-small cell lung cancer has proven effective for symptom management without significantly increasing the incidence of severe side effects [34,35]. This suggests that combining palliative RT with novel agents for symptomatic breast lesions could yield significant beneficial effects and minimal toxicity. In addition, the efficacy of palliative RT relies significantly on timing, advocating for the early consideration of symptomatic RT in palliative care, especially for patients with limited life expectancies [17]. According to an international multidisciplinary consensus on combining RT with new systemic agents for breast cancer treatment, cyclin-dependent kinase 4/6 inhibitors may be considered in a palliative setting [36]. However, the concomitant use of phosphoinositide 3-kinase and mammalian target of rapamycin inhibitors with RT has been advised [36]. Additionally, the integration of newer tyrosine kinase inhibitors, poly (ADP-ribose) polymerase inhibitors, and immunotherapy with RT is only recommended in clinical trials [36]. Therefore, there is a pressing need for active research combining new systemic treatments with palliative RT. Moreover, potential concerns related to the increased toxicity of these combinations must be addressed, emphasizing the need for careful patient selection to ensure safety and efficacy.

CONCLUSION

Despite several limitations such as the paucity of literature and the small sample sizes in most studies, palliative RT remains a vital tool for managing symptomatic advanced breast cancer. It effectively alleviates symptoms and ultimately enhances the patients' QOL. The evolving landscape in this field highlights the need for well-defined treatment protocols that balance optimal efficacy with minimal toxicity. A trend toward increased tumor control was observed with increasing total radiation doses. Similar to the importance of a multidisciplinary approach during the initial radical treatment, such an approach remains crucial in palliative settings. Future research endeavors and integration with novel therapeutic approaches offer promising potential for the further refinement and optimization of this crucial treatment modality. These advances have paved the way for more comprehensive and tailored treatment strategies, ultimately benefiting patients with advanced breast cancer.

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