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Teaching Case

Breast-Directed Quad Shot Radiation Therapy for Effective Breast Symptoms Palliation Without Interrupting or Delaying Systemic Cancer Therapy Schedule in Patients With Neglected Breast Cancer

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Introduction

Despite advances in breast cancer screening and awareness campaigns, some patients still neglect and delay breast cancer care until their neglected breast cancer (NBC) becomes an advanced disease and causes symptoms. With the locally infiltrative nature of breast cancer, patients with advanced NBC often present with ulcerative and/or fungating breast masses causing intractable pain, bleeding, malodorous discharge, and infection. Although upfront systemic cancer treatment (SCT: chemotherapy, biologic targeted therapy) is the main treatment for patients with advanced breast cancer,[1,2] these devastating breast symptoms require palliative local therapy before or during SCT. In such situations, patients prefer an effective yet short-course palliative treatment to avoid delaying or interfering with their SCT schedule.

Radiation therapy (RT) is commonly used in palliative cancer care.[3] Length of palliative RT (pRT) regimens can vary from a single day to multiple weeks. Usually, modern SCT combined with a hypofractionated pRT is administered sequentially, not simultaneously. As such, a short-course pRT would have an advantage of no (or least) interference with patient's SCT schedule. Data support that a single-fraction pRT (SF-pRT: 8 Gy in one fraction) for uncomplicated metastatic bone lesions provided similar pain response compared with longer protracted pRT.[4] However, SF-pRT was associated with a short duration of symptom relief and high rates of recurrent pain requiring repeat pRT after the initial dose.[4] In addition, the efficacy and tolerance of SF-pRT has not been extensively evaluated in nonbone malignant lesions.

A "quad shot" (QS; 14-14.8 Gy in 4 fractions, bid) is a pRT regimen consisting of only 2 consecutive days per course, which can be repeated, if needed, every 3 to 4 weeks to a total of 42 to 44.4 Gy. QS has shown rapid and durable symptoms palliation with low toxicity in patients with nonbone malignant lesions.[5-8] Thus, breast-directed

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Data are stored in an institutional repository and will be shared upon request to the corresponding author and approval from an institutional authority.

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QS (BD-QS) to patients with NBC can be a practical short-course pRT regimen offering effective symptoms palliation without delaying or interfering with their SCT schedule. However, there is very limited information regarding the effectiveness and toxicity of BD-QS in the palliative setting. In this report, authors describe the clinical courses of breast symptom palliation in 2 patients with NBC who were treated with BD-QS.

Patients

The UPMC Williamsport Institutional review board waived a board review on this report. The patients have given consent for reporting this report.

Case 1

A 74-year-old female patient visited a breast clinic with uncontrolled bleeding and pain from the right breast mass. Eight years before this visit, she had a mammogram showing a clustered microcalcification in the upper inner quadrant of the right breast. At that time, despite recommendations for biopsy or close monitoring, she was lost to follow-up. About 1 year ago, she noticed a mass in the right breast that continuously grew, broke through the breast skin, and has caused persistent bleeding and a painful open wound (Fig. 1A). Biopsy of the right breast lesion confirmed an invasive ductal carcinoma that was estrogen receptor positive (ER+), progesterone receptor positive (PR+), and human epidermal growth factor recepter-2 (HER2)+. Positron emission tomography scan revealed multiple hypermetabolic lesions in the right breast, axilla, lung, mediastinum, liver, and bone (Fig. 1B). As the result of the intractable bleeding and pain in the right breast lesion, she was referred for an urgent pRT before starting SCT. To avoid delaying her SCT schedule, BD-QS was recommended with the possibility of additional BD-QS as needed.

Case 2

A 54-year-old female patient was hospitalized to manage progressively worsening dyspnea, cough, and pain in the left breast, chest wall, and back. During hospitalization, she was found to have a fungating erythematous mass in the left breast (Fig. 2A) and multiple firm nodules in the left axilla. She admitted that she ignored the mass in the left breast for the past 2 years because of the coronavirus disease 2019 pandemic. Biopsy of the left axillary node confirmed a metastatic invasive ductal carcinoma which was estrogen receptor positive, progesterone

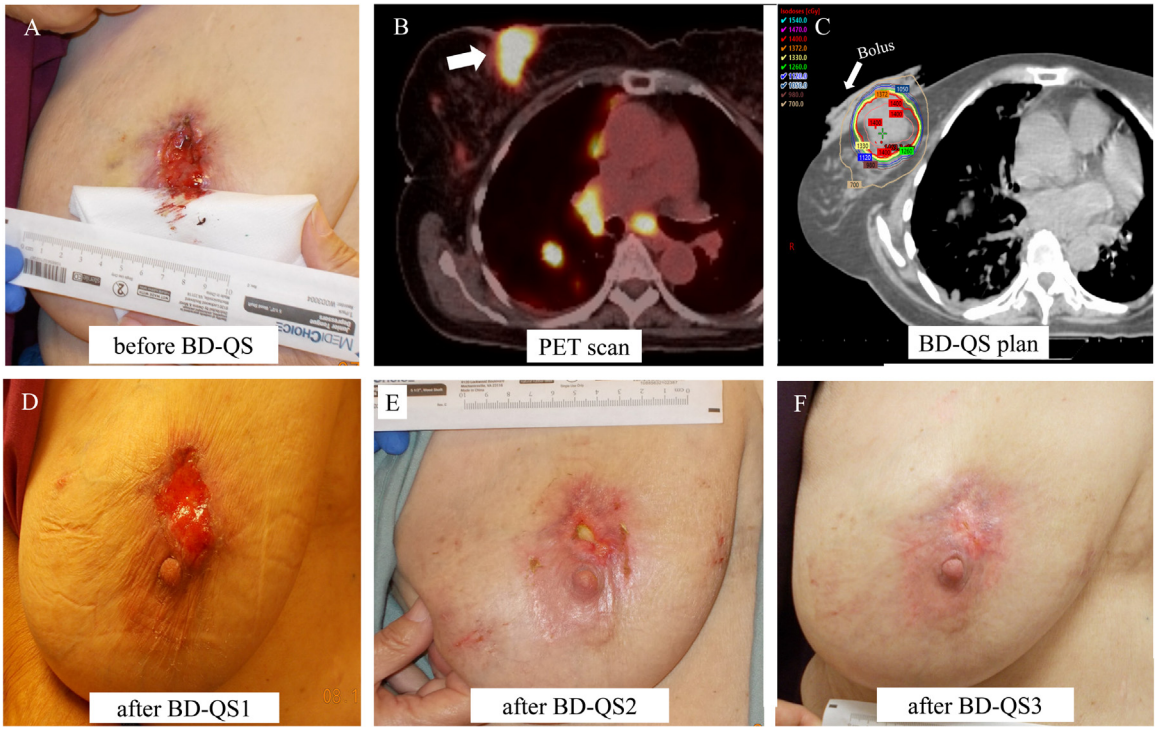

Figure 1 (A) A skin infiltrating breast cancer in right breast causing intractable bleeding and pain in case 1. (B) Multiple hypermetabolic lesions in thorax and right breast (white arrow), which is well correlating with her right breast bleeding and pain. (C) Radiation therapy plan for BD-QS1. (D-F) Right breast lesion at 3 weeks after BD-QS1, BD-QS2, and BD-QS3, respectively. *Abbreviations:* BD-QS = breast-directed quad shot; PET = positron emission tomography.

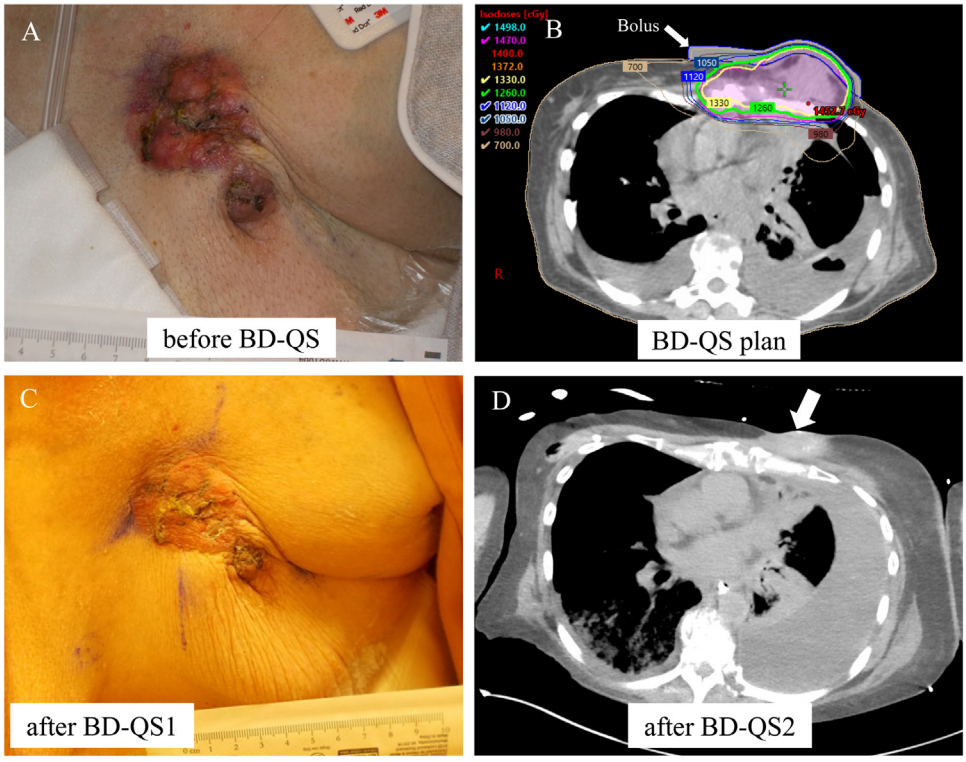

Figure 2 (A) Fungating mass from neglected breast cancer in left breast causing intractable pain whenever she breath or cough in case 2; (B) Radiation therapy plan for BD-QS1; (C) left breast lesion at 3 weeks after BD-QS1; (D) Computed tomography scan of the chest showing left breast lesion at 2 months after BD-QS1 (white arrow). *Abbreviation:* BD-QS = breast-directed quad shot.

receptor positive, and HER2−. Positron emission tomography scan demonstrated widespread hypermetabolic lesions in the left breast infiltrating into the chest wall and sternum, axilla, lung, liver, and bones. As the result of her frail condition, sepsis from empyema, and intractable pain from the left breast lesion, she was referred for urgent pRT before considering SCT. During radiation oncology consultation, she expressed "severe" pain in the left breast mass radiating into chest wall and sternum whenever she breathed or coughed. For rapid pain relief, a BD-QS was recommended to her.

Procedures and Treatment

Patients underwent computed tomography simulation scans for planning a BD-QS. A clinical target volume included symptomatic gross tumors in the breast (Fig. 1C: 53.6 cc, Fig. 2B: 239.9 cc) in concordance with the diagnostic images and physical examination. A 0.5- to 1.0-cm margin was added to the clinical target volume to create a planning target volume (PTV: 115.7 cc and 426.4 cc for case 1 and case 2, respectively). For each BD-QS, 14 Gy in 4 fractions, twice daily, at 6-hour intervals, for 2 consecutive days, was prescribed to PTV. Intensity-modulated RT planning objectives required the PTV coverage of 95% to 110%. A 1.0-cm bolus was applied on top of the gross tumors in the breast to deliver a full prescription dose to the surface of the tumors (Fig. 1C and Fig. 2B). For organs at risk such as the heart and ipsilateral lung, the radiation dose constraints were "as low as reasonably achievable" and followed suggestions from published recommendations.[8] At 3 weeks after BD-QS, patients were re-evaluated and new pRT plans for additional BD-QS, as needed, were created with repeat CT-simulation scans to consider tumor response from previous BD-QS.

Palliative Response From BD-QS

Case 1

Within a week after the first BD-QS (BD-QS1), the patient noticed less pain and bleeding cessation in the right breast lesion (Fig. 1D). Compared with their status at consultation, hemoglobin and hematocrit were elevated at 3 weeks after BD-QS1 (11.0 g/dL and 36.9% vs 12.2 g/dL and 39%, respectively). Subsequently, the patient was able to begin SCT using Taxol (paclitaxel; weekly) and dual HER2 blockage (pertuzumab and trastuzumab, every 3 weeks) as planned. Although bleeding

from the right breast had stopped after BD-QS1, the open wet wound in the tumor bed (Fig. 1D) adhered to her undergarments, causing persistent abrasion, inflammation, and discomfort. To close this cancer-related open wet wound in the right breast, she elected to pursue additional BD-QS. To avoid interrupting her scheduled SCT, the next BD-QS was given between SCT cycles. The open wet wound in the right breast near completely closed with less discharge after BD-QS2 (Fig. 1E) and completely closed after BD-QS3 (Fig. 1F). She remained free of breast symptoms at her last clinical visit (6 months after BD-QS1).

Case 2

At 1 week after BD-QS1 (Fig. 2B), she reported notably decreased pain in the left breast. The "severe" pain with breath or cough at consultation became "mild" at 3 weeks after BD-QS1. The fungating mass in her left breast became smaller, flatter, and less erythematous (Fig. 2C) compared with its state before BD-QS1 (Fig. 2A). With improved pain and general condition after BD-QS1, she was able to start SCT using palbociclib and pursed BD-QS2 for residual pain relief. At 4 weeks after palbociclib (2 months after BD-QS1), however, she was placed in hospice care due to disease progression, including uncontrolled malignant pleural effusion, although the fungating mass in the left breast was continuously regressed after BD-QS (white arrow in Fig. 2D).

Discussion

Emotional and physical distress caused by skin-infiltrative and/or fungating breast cancer can lead patients with NBC to low self-esteem, depression, and social isolation, resulting in a vicious cycle of further delaying or nonadherence to cancer care, disease progression, and worsening or developing new symptoms, all of which are negatively affecting treatment outcome as well as the patient's quality of life (QoL). For these patients, an effective timely local palliative therapy can improve not only their QoL but also their adherence to other breast cancer treatments.

Although the effectiveness of RT in palliative cancer care is well known,[3-8] there is no consensus regarding the optimal dose/fractionation in breast-directed pRT. Empirically, the same pRT regimens for other disease sites have been employed for breast lesion. Table 1 shows the palliative responses and side effects from various breast-directed pRT.[9-13] Given the low α/β ratio (2-4) of breast cancer,[9,14] the biologic effective dose (BED) and equivalent dose in 2 Gy fraction (EQD2) were calculated with the α/β ratio of 3.3 for breast cancer and 3 for the breast tissue.

A SF-pRT can be a convenient palliative option because it would take only 1 day for treatment.[3,4] Likewise SF-pRT to metastatic bone lesions[4]; however, high rate of recurring breast symptoms after breast-directed SF-pRT resulted in 57% of patients requiring repeat pRT.[10] Relatively low BED (27.39 $Gy_{3.3}$) and EQD2 (17.06 Gy) with SF-pRT can be responsible for such short-term palliation and a high rate of recurring symptoms. Because modern SCT improves survival in patients with advanced breast cancer,[1,2] durable symptom palliation became one of the most important considerations in choosing pRT for these patients.

Protracted pRT regimens with high BED (57.27-96.67 $Gy_{3.3}$) and EQD2 (40.17-60.19 Gy) have shown higher and longer breast symptom relief than SF-pRT.[10,13,15] However, these protracted pRT have shown an association with increased pRT-related toxicities, including grade 2 and 3 dermatitis in 70% to 90% and 10% of patients, respectively.[10,13,15] Minimizing pRT-related toxicity is paramount in palliative setting. In addition, longer overall treatment time with protracted pRT can delay or interfere with the SCT schedule for patients with advanced NBC, which can have a negative effect on their treatment outcomes.

Compared with other pRT regimens, a QS delivers a larger dose (3.5-3.7 Gy) per fraction on an accelerated schedule (bid, 2-consecutive day), which has shown rapid regression in cancers resulting in earlier symptom relief with lower toxicity.[5-8] Consistent with these data, BD-QS experiences in this case report also showed rapid symptom palliation in patients with NBC. All patients noticed less pain and bleeding cessation (Fig. 1D and 2C) within a week after BD-QS1. That no pRT-related dermatitis was observed during or after BD-QS in all patients is promising. There have been suggestions that adaptive nature of subsequent QS and normal tissue recovery during the 3 to 4 weeks interval between QS may be associated with low toxicity.

The needs for additional BD-QS can be decided depending on the patients' general condition, palliative response from previous BD-QS, and/or upcoming SCT schedule. Although additional QS has shown further and longer symptom relief, one QS can still offer substantially durable palliation.[5-8] In fact, one patient whose metastatic breast cancer continuously progressed after various salvage SCT was treated with a QS to the left chest wall, neck, and axillar nodes (Fig. E1 A-C) in this clinic. A week after a QS, she reported notably less pain in the left neck and anterior chest wall, and decreased edema and paresthesia in the left arm (Fig. E1 D,E). After such rapid symptom relief with a QS, she began another SCT as planned without delay. Although further pRT was not pursued, a computed tomography scan of the chest/abdomen done at 2 months after a QS showed "significantly decreased mass/lymphadenopathy in the left neck, supraclavicular, and axillary regions" (Fig. E1F) and disease

Table 1 Review of breast-directed palliative radiation therapy regimens

RT regimen	Overall RT time	Breast cancer (α/β ratio 3.3) BED	Breast cancer (α/β ratio 3.3) EQD2	Breast tissue (α/β ratio 3.0) BED	Breast tissue (α/β ratio 3.0) EQD2	Response	RT-related breast dermatitis
8 Gy × 1[9] vs	1 d	27.39	17.06	29.33	17.60	85% less symptoms 57% repeat pRT to same site	Grade 1: 100%
3 Gy × 13 3 Gy × 15 2 Gy × 25	17 d 19 d 33 d	74.45 85.91 83.30	46.36 53.49 50.00	78.00 90.00 83.33	46.80 54.00 50.00	100% less symptoms 15% repeat pRT to same site	Grade 2: 90% Grade 3: 1 patient
2.14 Gy × 14[10] (previous breast RT) vs	18 d	49.45	30.79	51.40	30.84	No symptom response	N/A
3.25 Gy × 10 (no previous breast RT)	12 days	64.51	40.17	67.71	40.63	66% less symptoms	N/A
3 Gy × 10[9]	12 days	57.27	35.66	60.00	46.60	94% less symptoms 46% partial response 48% stable disease	Grade 3-4: None
3 Gy × 12[10]	16 days	68.73	42.79	72.00	43.20	Bleeding: none or on contact only at 3 months after RT. Rebleeding 6 months after RT. No pain relief.	Grade 3: 10%
2.5 Gy × 22[11]	30 days	96.67	60.19	100.83	60.50	59.1% less symptoms at 1week after RT. 81.8% tumor response	Grade 2: 72.7%
Current report							
BD-QS1	2 days	30.76	19.15	32.40	19.44	100% less symptoms	No dermatitis
BD-QS2		57.70*	35.92*	60.67*	36.40*		
BD-QS3		86.55†	53.89†	91.00†	54.60†		

Abbreviations: BD-QS = breast-directed quad shot, cyclical hypofractionated RT to deliver 14∼14.8 gray (Gy) in 4 fractions, given twice a day, 6 hours apart, for 2 consecutive days, repeated every 3∼4 weeks up-to 3 times; BED = biologically effective dose; EQD2 = equivalent dose in 2 Gy fractions; N/A = data not available; pRT = palliative radiation therapy; RT = radiation therapy.

* Accumulated doses (BED and EQD2) with second cycle of BD-QS (BD-QS2).

† Accumulated doses (BED and EQD2) with BD-QS3.

Overall RT time indicates days required to complete planned RT, assuming RT begins on Monday and no treatment breaks; BED or EQD2 calculation using α/β ratio to be 3.3 Gy for breast cancer; Gy_3, BED or EQD2 calculation using α/β ratio to be 3 Gy for breast tissue.

progression in nonirradiated metastatic lesions. She had maintained symptom palliation in the left neck and arm until she passed away at 5 months after a QS. This flexibility of pursuing an additional QS coupled with such durable symptom palliation after one QS can reduce the treatment burden on patients with advanced breast cancer.

As with any palliative treatment, careful selection of patients for BD-QS is important. Projected life expectancy, patients' expectation and preference on pRT, and schedules for other cancer treatments are some of the important clinical factors to be considered before offering BD-QS to patients with advanced breast cancer. Further study with large numbers of selected patients treated with BD-QS is warranted.

In conclusion, all patients with advanced NBC who were treated with BD-QS in this report successfully achieved rapid and durable symptom relief without skin toxicity, which improved their QoL and allowed them to receive their scheduled SCT without interruption or delay.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101229.

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