Patterns of relapse and risk for new malignancies following partial breast re-irradiation

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Abstract

Purpose Repeat irradiation of the breast is not commonly used. However, among patients with prior history of breast or mantle irradiation who refuse to undergo a mastectomy, treatment of localized breast cancer (BC) has included lumpectomy + re-irradiation. This paper is an update on our experience with lumpectomy and re-irradiation for localized BC with a focus on patterns of relapse.

Methods The study includes 27 patients who had previously received radiation therapy (RT) to the involved breast. Nineteen patients had a prior history of BC treated with lumpectomy and whole breast RT via tangential fields. Eight patients with a prior history Hodgkin's disease (HD) were treated with mantle field irradiation and were subsequently diagnosed to have a second primary BC. The median time interval between diagnosis of the initial BC and recurrent/new ipsilateral BC is 94 months (range 28–211 months), and between mantle RT and diagnosis of the second primary BC is 245 months (range 68–322 months). At the diagnosis of their new breast cancer, all patients underwent lumpectomy with negative margins and received partial breast irradiation (PBI) by using interstitial low-dose rate brachytherapy. A median dose of 45 Gy was delivered over 4–5 days.

Results At a median follow up of 73 months following PBI, four (14.8 %) patients developed a local recurrence: three

patients had prior history of BC and one had prior HD. All four local relapses were salvaged by mastectomy, and these patients remain with no evidence of local or regional failure. The 5-year Kaplan–Meier mastectomy-free survival is 81 %. Three patients developed distant relapse, and three patients developed a third new primary cancer. The 5-year actuarial risk for developing subsequent non-breast primary cancer was 30 % among HD survivors and 0 % among patients with prior BC ($p=0.004$). Thus far, none of the patients with prior history of BC developed a second non-breast primary cancer.

Conclusions Our observations suggest that patients with a history of prior irradiation who are motivated towards breast conservation have an alternative to mastectomy. Our observations suggest that lumpectomy with interstitial partial breast re-irradiation did not appear to have a detrimental effect on BC-specific outcomes. However, we did observe a high prevalence for third primary malignancy among patients initially diagnosed with HD, illustrating the importance of ongoing surveillance for subsequent cancer risk.

Keywords Second malignancy · Breast cancer · Hodgkin's disease · Retreatment · Partial breast irradiation

Introduction

Since the late 1990s, there is accumulating evidence that partial breast irradiation (PBI) following lumpectomy is safe and effective for managing early stage disease [1–5]. There is currently a randomized trial [6] evaluating this treatment approach. Whether there is an opportunity to deliver therapeutically effective radiation therapy by limiting the retreatment volume using PBI in a population of patients with prior breast and mantle RT is controversial. Further, the risk of subsequent malignancies among patients undergoing

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repeat breast conservation and re-irradiation is not well studied. There are limited published data on partial breast re-irradiation for treating localized breast reoccurrence [7–13]. In prior publications, we have reported the technical feasibility and early clinical outcomes using partial breast re-irradiation [14, 31]. In this study, we sought to update clinical outcomes and evaluate the patterns of relapse and subsequent risk of cancer among breast cancer (BC) patients who had prior history of radiation therapy (RT) exposure to the breast.

Methods

This paper includes 27 patients, 19 patients with prior history of breast cancer treated with lumpectomy and external beam therapy treated on an IRB-approved study and eight patients with localized BC with prior history of mantle RT. Patient eligibility required biopsy-proven unifocal BC with negative nodes. In all cases, a multidisciplinary consultation was completed prior to obtaining informed consent that affirmed that patient refused mastectomy as the standard of care.

Table 1 summarizes the patient characteristics. The stage of initial primary breast cancer ranged from stage 0 to stage IIB. The median dose from the prior breast RT was 60 Gy. The

median time interval between the primary BC diagnosis and the second cancer event in the ipsilateral breast is 94 months (range 28–211 months). Hodgkin's disease (HD) treated with mantle + extended field RT with/without chemotherapy included stages IB, IIA, and IIB. The median radiation dose to the mantle field was 40 Gy. The median time from initial diagnosis of HD and the diagnosis of BC was 245 months (range 68–322 months). The median age at the time of the second cancer event was 54 years (46–81 years); 21 patients had an infiltrating cancer and six patients had DCIS. The median tumor size was 0.9 cm (0.4–2.0 cm). ER status is positive in 74 % of the patients. With respect to the location of the second BC, 12 patients had cancer in the same quadrant as the previous cancer, and seven patients had the cancer in a location other than the quadrant of the initial cancer. Among patients with mantle RT, the BC was located in the upper outer quadrant in five patients and in the lower inner/central quadrant in three patients.

All patients underwent lumpectomy + axillary staging, with the surgical margins microscopically assessed to be negative prior to performing the brachytherapy procedure. The technique of Ir-192 multi-catheter interstitial low-dose rate (LDR) brachytherapy used has been described in a prior publication [14]. For catheter placement, standard free-hand insertion technique was used. In cases where catheters were placed during the lumpectomy procedure, the catheter placement was guided by direct vision. For close cavity cases, the placement of catheters was guided by breast ultrasound. The target volume (TV) was the lumpectomy cavity identified by clips plus 1–2 cm margin. The prescription isodose encompassed the TV. The skin dose was maintained at ≤ 20 Gy. Additional measures to spare skin toxicity included special attention during catheter insertion such that the entry and exit points of the catheters were beyond the target volume and the Ir-192 seeds at the ends of the ribbon were positioned well within the breast tissue, creating a 1–2-cm dead space between the Ir-192 seed and the skin. Patients received a median dose of 45 Gy.

Although other breast brachytherapy techniques, i.e., high-dose rate (HDR) interstitial brachytherapy, single catheter HDR brachytherapy, and IORT became more prevalent during the course of this study; the brachytherapy technique in the protocol was not changed so as to avoid confounding variables in assessing the clinical outcomes. For treating the BC, when recommended, systemic therapy was started after a minimum of 2 weeks after removal of brachytherapy catheters. Forty eight percent received hormonal therapy and 11 % received systemic therapy. All patients have been followed by a multidisciplinary team. Physical examination and imaging at regular intervals or as clinically indicated was performed.

Statistical considerations

Data were analyzed using the STATA system for data analysis v11 (StataCorp 2011, Stata Statistical Software: Release

Table 1 Patient characteristics

Median age (range)	54 years (45–81 years)
Prior cancer history	
Breast cancer	19
Lymphoma	8
Prior cancer stage	
Breast cancer	0–II
Hodgkin's disease	IB–IIA/B
Median breast dose from prior RT	
Breast RT	60 Gy
Outer quad breast dose mantle RT	40 Gy
Time interval between initial cancer and second breast cancer	
All patients: median (range)	111.9 months (28–322 months)
Initial breast cancer: median (range)	94 months (28–211 months)
Initial Hodgkin's disease: median (range)	242 months (68–322 months)
Histology	
Invasive ductal ca.	21
Ductal ca. in situ	6
Median tumor size (range)	0.9 cm (0.4–2.0 cm)
Site of cancer recurrence	
Prior lump + RT	
true	12
elsewhere	7
Prior mantle RT	
outer quad	5
central/lower inner quad	3

12, StataCorp LP, College Station, TX). Univariate factors were analyzed using the chi-square and Fisher's exact tests for categorical variables. Survival curves were computed using the Kaplan–Meier survival estimates.

Results

At a median follow up of 73 months, four patients (14.8 %) developed a local recurrence; among these, three patients had a prior history of BC, and the remaining one patient had been diagnosed of HD. All four patients underwent a salvage mastectomy and remain free of local regional relapse. The 5-year overall survival was 77 %, and the 5-year mastectomy-free survival was 81 % (Fig. 1). In the follow-up, we observed only 2/27 patients develop a contralateral metachronous second BC. Three of the eight HD patients diagnosed with second primary BC after mantle RT developed a third non-breast primary cancer, i.e., pancreas, renal, and lung primary on the contralateral side relative to the treated BC. None of the BC survivors developed another non-breast primary cancer. Review of the medical history of the patients that developed the third primary cancer notes that all three patients received combined modality therapy for HD, chemotherapy followed by mantle and para-aortic RT. None of the three patients received adjuvant chemotherapy for BC. Metastatic disease from the third primary cancer was the cause of death in all three patients. The 5-year actuarial risk for developing subsequent non-breast primary cancer was 30 % among HD survivors and 0 % among patients with prior BC ($p=0.004$) (Fig. 2).

Late complications included grade 1 skin pigmentation at the catheter entry and exit site in three patients; one patient developed grade 3 fibrosis at the lumpectomy

Fig. 1 Overall mastectomy-free survival

Fig. 2 Actuarial risk for new non-breast primary cancers. Red line, HD survivors; blue line, BC survivors; $p=0.004$

site. There was no incidence of necrosis or skin breakdown. No patient has undergone a mastectomy for brachytherapy-related complications. Eight patients treated for the second primary breast cancer had excellent symmetry and cosmetic result. Breast asymmetry was present in the 19 patients who underwent a second lumpectomy prior to brachytherapy. In the follow-up, the one patient with grade 3 fibrosis showed progressive changes in breast asymmetry. Among the other 18 patients, the baseline breast contour and asymmetry remained stable (Figs. 3 and 4). All patients remain satisfied with their decision for breast conservation. None of the patients have pursued any additional surgery for cosmesis.

Discussion

With breast conservation therapy widely accepted, the incidence of local recurrence or new BC in a previously irradiated breast is not an uncommon clinical occurrence [15–17]. Specific to HD, with improved outcomes, the

Fig. 3 Stable breast asymmetry. **a** Reference. **b** 42-month interval

Fig. 4 Stable breast asymmetry. **a** Reference. **b** 12-month interval

prevalence of second primary malignancies including BC in long-term survivors is known [18–20]. This category of patients, with history of prior breast or mantle RT, is generally considered ineligible for breast-conserving therapy, and risk of re-irradiation is usually cited as a contraindication for re-irradiation. In particular, prior whole breast RT for BC and mantle RT for HD that exposes breast tissue to varying RT dose depending on the relative location and shape of the lung blocks used during treatment [21–23] steers BC treatment recommendations towards mastectomy.

The volume of normal tissue exposed to radiation therapy directly impacts the total RT dose that can be safely administered. It is generally accepted that by limiting the target volume, in areas not close to critical structures, it is feasible to exceed the traditionally accepted RT dose threshold. PBI provides the opportunity to deliver a conformal dose tailored to a volume at risk while sparing adjacent organs, as well as breast tissue remote from the lumpectomy cavity. Furthermore, in reviewing patterns of relapse among early-stage primary BC, it has been noted that the highest risk for local failures is in the index quadrant [24, 25]. This evidence has provided the rationale for limiting the re-irradiation volume and studying the role of partial breast re-irradiation among patients with prior history of radiation therapy (Table 2) [7–14]. Similar to results noted in other publications, we

Table 2 Locoregional control with partial breast irradiation after second lumpectomy among patients with prior history of breast cancer

Author	Re-irradiation technique	Overall survival (%)	Local control (%)	Disease-free survival (%)
Hannoun-Levi et al. [7]	LDR brachy	91.8 ^a	77.4 ^a	68.9 ^a
Kauer-Dorner et al. [10]	PDR brachy ± ERT	87 ^a	93 ^a	77 ^a
Deutsch [11]	ERT	77.9 ^a	–	68.5 ^a
Guix et al. [9]	HDR brachy	96 ^b	89.4 ^b	64.4 ^b
Current study	LDR brachy	77 ^a	89.4 ^a	79 ^a

^a At 5 years

^b At 10 years

Table 3 Incidence of third (non-breast) primary cancers

Author	Overall survival at 5 years (%)	Third non-breast primary malignancy (n)
Haberer et al. [34] <i>n</i> =72	Any nodal stage: 74.5	13
Cutuli et al. [32] <i>n</i> =119	Any nodal stage: 65.1 Node negative only: 91	7
Milano et al. [33] <i>n</i> =298	Localized breast cancer: 48 ^a	28
Current study <i>n</i> =8	Node negative only: 77	3

^a Overall survival at 15 years

observed excellent local regional control and high rate of mastectomy-free survival with repeat RT using interstitial partial breast re-irradiation. Furthermore, we noted that salvage mastectomy was very effective for achieving sustained local control in patients that relapsed after re-irradiation. Currently, there is an ongoing RTOG phase II breast re-irradiation trial for patients with history of prior BC (<http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1005>). The protocol RT schema is a hyperfractionated regimen of 1.5 Gy twice daily for a total dose of 45 Gy delivered in 30 treatments over 15 days using the 3-D-conformal PBI. Data from this study will contribute to the clinical experience with this approach.

Among patients with HD, the risk of second malignancies is well recognized [20, 26–30]. However, there are very few studies that report on the pattern of ongoing risk for third new non-breast primary cancers [32–34]. Table 3 summarizes data from studies that have reported on observing a third non-breast primary cancer after initial diagnosis of HD followed by second primary breast cancer. Cutuli et al. [32] described third primary tumors in 7/119 patients with HD and second primary BC. Milano et al. [33] noted that 28/298 HD survivors diagnosed with BC died of third non-breast primary cancer. Further, they reported a sevenfold increased risk of death from other cancers among patients with second primary BC among HD survivors when compared to

Table 4 Incidence of contralateral breast cancer among patients with prior Hodgkin's disease

Author	Contralateral breast cancer (%)
Haberer et al. [34] <i>n</i> =72	14
Milano et al. [33] <i>n</i> =298	18
Wolden et al. [27] <i>n</i> =61	9.8
Elkin et al. [36] <i>n</i> =253	18
Cutuli et al. [32] <i>n</i> =119	11.7
Alm El-Din et al. [37] <i>n</i> =39	38

patients that present with BC as the first primary cancer. Haberer et al. [34] observed an 18 % risk of non-breast carcinoma third primary cancer among a population of HD survivors that developed second primary BC; 2/13 died of non-breast primary cancer. Munker et al. [35] in the Munich HD registry between 1974–1994 observed 85 second malignancies, and five patients had a diagnosis of a third primary cancer.

The risk of contralateral breast cancer in HD survivors is also higher than the sporadic primary BC patient population and is described to be in the range of 9–38 % (Table 4). Milano et al. [33] also described a higher although not statistically significant ($p=0.07$) risk of contralateral breast cancer among the HD survivors with BC (18 %) compared to patients with diagnosis of primary BC only (8 %). Similar observations were also reported by Elkin et al. [36] where 18 % of incidence of metachronous contralateral BC was 18 % among HD survivors compared to an incidence of 8 % in the sporadic BC population. Among BC survivors, subsequent risk of synchronous and metachronous cancers described ranges from 1–3 % and 7–12 %, respectively. Curtis et al. [31] reported prevalence of second cancers among 322,863 women with sporadic breast cancer. They reported that an overall estimate of second cancer risk varies widely with O/E ratios ranging from 1.0 to 2.4. In their review, specifically after the exclusion of breast cancers, the risk of non-breast second malignancies decreased significantly to near unity with an O/E ratio of 1.01. In our study, at the time of this writing, 2/19 patients with history of prior BC developed a contralateral breast cancer, and the prevalence of a third non-breast primary malignancy was noted only among HD survivors treated for a second primary BC. None of the BC patients undergoing partial breast re-irradiation developed a non-breast primary cancer. The incidence of contralateral BC observed in this study is lower than that noted in some of the earlier reviews in the literature. This observation may be a result of prescribed systemic therapy for the initial cancer, when indicated, and then again use of systemic therapy among 63 % ($n=12/19$) of the BC patients treated following localized recurrence of BC.

One of the major limitations of our study is that it includes only a small number of patients. Nevertheless, our observations as well as outcomes described in the literature suggest that an evaluation of therapy options for localized BC among patients with prior history of RT should include a consideration of competing risks. Particularly for patients motivated towards breast conservation and who do not carry a BRCA mutation, repeat breast conservation with lumpectomy and re-irradiation can be considered. For such patients, mastectomy may not be the only treatment option.

Conclusion

In summary, for selected patients with prior history of RT, breast-conserving surgery and partial breast brachytherapy may be alternative to mastectomy. Patterns of relapse following BC suggest that lumpectomy and partial breast re-irradiation did not have a detrimental effect on breast cancer-specific outcomes. We observed a high rate of local control and freedom from mastectomy. Further, our observations highlight the need for careful ongoing surveillance for risk of subsequent primary cancer in this patient population. Additional studies on patterns of relapse and the risk of new non-breast primary cancers would improve our understanding on competing risks in this select category of patients.

Conflict of interest There is no conflict of interest.

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