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Among women who experience a recurrence after postmastectomy radiation therapy irradiation is not associated with more aggressive local recurrence or reduced survival

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Abstract

Recent pre-clinical models suggest that radiation can promote tumor aggressiveness. We hypothesized that if this were occurring clinically, locoregional recurrences (LRRs) after postmastectomy radiation therapy (PMRT) would lead to lower survival than LRR after mastectomy alone. This study used two independent data-sets to compare survival after LRR in women treated with versus without PMRT. Data from 229 LRR cases among 1,500 patients enrolled on prospective trials at the MD Anderson Cancer Center (MDA), and 66 LRR cases among 318 patients enrolled in the British Columbia Cancer Agency (BCCA) PMRT randomized trial were analyzed. In the MDA non-randomized dataset, 189/1031 had LRR after mastectomy alone and 40/469 had LRR after PMRT. In the randomized BC trial dataset, 52/158 had LRR after mastectomy alone and 14/160 had LRR after PMRT. In both datasets, survival was calculated from the time of LRR to death. Analysis of MDA data shows that in all LRR cases regardless of distant metastasis (DM), 5/10-year OS were 50/34% without PMRT and 27/19% after PMRT ($P = 0.006$). However, PMRT-treated patients had increased risk factors for DM (advanced T and N stages) and more PMRT-treated patients developed DM prior to LRR (63 vs. 34%, $P = 0.005$). Analyzing only patients with an isolated LRR (without previous or simultaneous DM), there was no OS difference between groups ($P = 0.33$). Analysis of BCCA data shows that distributions of T and N stages were similar in patients with LRR after mastectomy alone versus after PMRT. DM free survival after any LRR and after isolated LRR were similar in mastectomy alone versus PMRT-treated patients ($P = 0.75$, $P = 0.26$, respectively). Overall survival after any LRR and after isolated LRR were also similar in the two groups ($P = 0.93$, $P = 0.28$, respectively). Patients who develop LRR after mastectomy alone have high rates of DM and poor OS but these rates are not affected by the use of PMRT at the time of primary treatment. These data do not support the hypothesis that irradiation promotes biologically aggressive local recurrences.

Keywords

Postmastectomy; Locoregional recurrence; Survival; Radiation therapy; Stromal activation; Accelerated repopulation

Introduction

Radiation therapy has been demonstrated to improve locoregional control and survival in patients with high-risk breast cancer [1–8]. However, preclinical studies while inherently limited as all model systems are suggest that all cancer treatments including surgery, radiation therapy, and chemotherapy can promote tumor repopulation and aggressive disease progression when they fail to eradicate the disease [9]. In part, these changes result from changes in the normal tissue stroma surrounding malignant tumors, and the stroma–tumor interaction has been implicated as a determinant of tumor biology and response to cytotoxic treatments [10–14]. Ionizing radiation causing disruption of the physical and the functional integrity of the tumor bed stroma has been suggested to result in alteration of tumor response to radiation and chemotherapy [12]. Early studies using tumor models have also suggested that radiation-induced stromal injury can be conducive to tumor initiation and distance metastasis (DM) [13]. Irradiating mammary gland stroma with a dose of 4 Gy prior to tumor cell implantation increased the tumorigenic potential of transplanted cells when compared to those transplanted into unirradiated stroma [15]. Similarly, in an experiment of ten tumors grown subcutaneously in mice that had or had not received ionizing radiation prior to tumor cell transplantation, Milas et al. [16] reported that tumors which grew in a preirradiated environment were more necrotic and had an increased propensity to metastasize. Radiation-induced increase in vascular permeability and the prolonged period of growth of tumors in irradiated tissue were suggested as factors likely responsible for the enhancement of metastatic spread [16]. Radiation has also been shown to increase recruitment of mesenchymal stem cells into tumors via induced alterations in secreted factors [17], and more recently, normal stem cells in the peri-tumoral stroma have been described to interact directly with tumor cells to promote tumor growth [18], although the effect of radiation on this process has not been studied.

Although the phenomenon is observed in a variety of preclinical models in contexts that are significantly different from the clinical context of adjuvant therapeutic radiation, these reports may influence public opinion and engender concern despite these limitations and clinical data demonstrating a clear benefit for the use of radiation in the treatment of primary breast cancer. We hypothesized that if radiation therapy (RT) can promote aggressive recurrences in the clinical setting, then locoregional recurrences (LRRs) after postmastectomy radiation therapy (PMRT) would lead to lower survival when compared to LRRs occurring after mastectomy alone, a comparison not explicitly addressed in the current clinical trial-based literature. To address this hypothesis, we used two independent datasets to compare survival in patients with breast cancer who developed LRRs after mastectomy alone versus after mastectomy plus PMRT.

Materials and methods

Data from patients who developed LRR after mastectomy with and without PMRT were analyzed using two independent datasets from The University of Texas M.D. Anderson Cancer Center (MDA) and the British Columbia Cancer Agency (BCCA).

MDA dataset

From 1975 to 1994, 1,500 patients with stages II and III breast cancer treated with mastectomy and level I/II axillary lymph node dissection with and without PMRT were enrolled in sequential prospective trials of doxorubicin-based chemotherapy at the MDACC [19, 20]. Decisions for PMRT use were individualized by the treating radiation oncologist. The MDA study cohort comprised 229 patients who developed LRR, 184 after mastectomy alone, and 45 after mastectomy plus PMRT.

BCCA dataset

From 1979 to 1986, 318 premenopausal women with stages II and III breast cancer, who were referred to the BCCA after modified radical mastectomy and axillary dissection, were enrolled on a randomized trial of PMRT or no additional treatment. All patients received cyclophosphamide, methotrexate, and 5-fluoro-uracil chemotherapy [3, 4]. The BCCA study cohort comprised 66 patients who developed postmastectomy LRR. To address the current hypothesis, data analysis in the BCCA study cohort was based on treatment received, not intention to treat. Among 318 patients enrolled, 160 patients underwent PMRT and 158 patients had mastectomy without PMRT. Of these, 14/160 patients had LRR after PMRT and 52/158 patients had LRR after mastectomy alone.

LRR and survival outcomes

In both datasets, all LRR events occurring before or after distant recurrence (DR) were captured and were defined as recurrence involving the chest wall (local) and/or axillary, supraclavicular or infraclavicular, and internal mammary nodes (regional).

In the BCCA dataset, LRR was defined as LRR occurring as the first site of recurrence without simultaneous DM or DM within 1 month from the LRR event. Isolated LRR was defined in the MDA dataset as the first site of recurrence without simultaneous DM or DM within 3 months from the LRR event (a more conservative definition was used here since additional analyses in this non-randomized dataset were performed to examine the competing risk of distant metastases).

In both datasets, overall survival after LRR was defined as the interval between the date of LRR diagnosis and the date of death from any cause.

Statistical analysis

Analyses of the two independent datasets were performed separately. In each dataset, patient and tumor characteristics were compared between subjects with LRR after mastectomy alone versus mastectomy plus PMRT using Chi-square and Fisher's exact tests. The tumor factors analyzed were: age at diagnosis, pathologic T stage, nuclear grade, lymphovascular

invasion (LVI), estrogen receptor (ER) status, number of positive nodes, number of excised nodes, and positive/excised nodal ratios. Survival was calculated using Kaplan–Meier methods. Statistical significance of survival differences was tested using log-rank statistics.

All statistical tests were two-sided with statistical significance established at $P < 0.05$. All analyses were performed using Statistical Package for the Social Sciences (SPSS) software, version 15.0; SPSS Inc, Chicago, Illinois.

Results

The characteristics of patients who developed LRR after mastectomy with versus without PMRT in the MDA and BCCA datasets are summarized in Tables 1 and 2, respectively.

MDA dataset

In the MDA dataset, the median follow-up time among living patients was 192 months. The distributions of age, LVI, and nodal ratios were similar in the two cohorts (all $P > 0.05$). Patients who received PMRT had larger primary tumors, higher grade primaries, less ER-positive disease, and more involved lymph nodes (all $P < 0.05$) (Table 1).

Time intervals from initial breast cancer diagnosis to local and distant recurrence and from LRR to death are summarized in Table 3. The median time from diagnosis to LRR was 2.9 years in patients treated with PMRT and 2.8 years in patients treated with mastectomy alone ($P = 0.16$). The median time from LRR to death from any cause was 2.4 and 1.3 years in patients with LRR after PMRT and after mastectomy, respectively ($P = 0.01$). As expected given the imbalance in poor prognostic features in patients selected for PMRT, DM free survival after any LRR event (Fig. 1a) and overall survival after any LRR event (Fig. 1b) were lower in the PMRT cohort. When examining only patients with an isolated LRR (reducing the competing risk of DM which is higher in the PMRT cohort) there was no difference in DM free survival after isolated LRR (Fig. 2a) or in overall survival after an isolated LRR event (Fig. 2b). The 5- and 10-year overall survival estimates after an isolated LRR event were 67 and 46% in patients with LRR after mastectomy alone and 63 and 38% in patients with LRR after mastectomy plus PMRT, ($P = 0.33$). In a separate analysis of all patients who developed metastatic disease ($N = 387$ no PMRT, 233 after PMRT) revealed no difference in 5- or 10-year OS after DM (18/6% without PMRT vs. 14/9% after PMRT, $P = 0.2$)

BCCA dataset

To minimize the limitations of the retrospective dataset and validate the findings, the same questions were examined in the randomized dataset from the BCCA. The median follow-up time among living patients was 235 months. In the comparison of clinical characteristics of patients who developed LRR after mastectomy with versus without PMRT, the distributions of age, T stage, nuclear grade, LVI, ER status, number of positive and excised nodes, and nodal ratios were similar in the two cohorts (all $P > 0.05$) (Table 2).

Time intervals from initial breast cancer diagnosis to local and distant recurrence and from LRR to death are summarized in Table 3. The median time from diagnosis to LRR was 2.2

years in patients treated with PMRT and 2.5 years in patients treated with mastectomy alone ($P = 0.27$). The median time from LRR to death from any cause was 2.0 and 1.9 years in patients with LRR after PMRT and after mastectomy alone, respectively ($P = 0.94$).

The rates of developing DM after LRR were similar in patients with LRR after mastectomy with versus without PMRT (93 and 96%, respectively, $P = 0.60$). DM free survival after any LRR event (Fig. 3a) and after isolated LRR (Fig. 3b) were similar in the two cohorts. Overall survival after any LRR event (Fig. 4a) and after isolated LRR (Fig. 4b) were also comparable in the two cohorts. The 5- and 10-year overall survival estimates after any LRR event were 21 and 8% in patients with LRR after mastectomy alone and 23 and 12% in patients with LRR after mastectomy plus PMRT, $P = 0.93$). Comparison of OS in patients who experienced any event (local, regional, or distant) also found no differences between cohorts treated with versus without PMRT (log-rank $P = 0.24$).

Discussion

While the aim of local and systemic therapy is to eradicate the primary tumor and sterilize subclinical disease, and randomized trials clearly demonstrate the benefit of radiation therapy to overall survival for patients with breast cancer [1–8], researchers using experimental tumor models have reported the observation that surgery, radiation therapy, and chemotherapy can stimulate tumor progression and metastasis [9–18, 21–26]. The phenomenon of local RT to a primary tumor triggering metastatic progression was initially described six decades ago by Kaplan and Murphy [21] who conducted an experiment in which mammary tumor was implanted in mice, 96 of which underwent local RT and 85 served as controls. Lung metastasis subsequently developed at a higher rate among irradiated when compared to nonirradiated mice (44 vs. 10%, $P < 0.0001$) [18]. Other investigators subsequently reported similar observations with experimental tumor models in which animals with local recurrence after RT were found to have higher rates of DM when compared to unirradiated counterparts [22–24]. Camphausen et al. reported that RT to a primary Lewis lung carcinoma (LLL–LCM) led to accelerated growth of previously dormant metastasis. However, administration of recombinant angiostatin prevented the growth of the metastases. These data suggest that a subset of patients may be at increased risk for DM after radiotherapy to their primary tumor and that there may be benefits with combining an angiogenesis inhibitor with conventional treatment [25]. In another recent pre-clinical study using a transgenic model of metastatic breast cancer, Biswas et al. [26] reported that the administration of ionizing radiation or doxorubicin chemotherapy caused increased plasma levels of TGF- β and increased circulating tumor cells and DM. While these tumor model-based data are intriguing, they are limited by the flaws inherent in all model systems, and often did not intend to examine definitive radiation strategies comparable to clinical radiation therapy treatment. The question of whether clinically appropriate definitive doses of RT can potentially promote biologically aggressive local recurrences and stimulate distant disease progression in the clinical setting remains unknown.

The current analysis using two independent datasets of patients prospectively enrolled on clinical trials after mastectomy focused on survival comparisons between patients with LRRs after mastectomy with and without PMRT. In the non-randomized MDA dataset,

when all LRR cases regardless of DM were analyzed, overall survival after LRR was lower in the cohort treated with PMRT. However, PMRT-treated patients had increased risk factors for DM, including more advanced T and N stages. More PMRT-treated patients also developed DM prior to LRR. Removing the competing risk of DM by studying only isolated LRR, we found no survival difference after LRR in the PMRT setting.

Analysis of the BCCA randomized PMRT trial confirmed that survival was similar among women who developed LRR, irrespective of PMRT use. In the randomized dataset, the distributions of patient and tumor characteristics were similar between cohorts with LRR after mastectomy alone when compared to mastectomy plus PMRT. The rates of DM after LRR were also comparable in the two groups.

Consistent with the current findings of a lack of survival differences after LRR in women initially treated with mastectomy with and without PMRT, in an analysis of the Danish Breast Cooperative Group (DBCG) 82 b and c PMRT trials, in which 535/3083 patients experienced LRR alone as the first site of failure, Nielsen et al. [7] reported that the probabilities of subsequent DM were similar in women with LRR, irrespective of PMRT use. Survival rates after LRR in women enrolled in the DBCG studies were also similar, irrespective of initial randomization group [7].

Insight into the full impact of adjuvant RT on not only locoregional control but also survival can only be gained with long-term follow-up. In a report of 20-year results of the BCCA randomized trial, Ragaz et al. [4] demonstrated that PMRT used in conjunction with systemic therapy significantly reduced the rates of LRR and DM and improved survival in women with high-risk breast cancer. The clinical evidence that PMRT reduces the rate of systemic recurrence supports the principle that RT, even though delivered locoregionally, can ultimately exert a positive effect on systemic disease control and challenges the traditional belief that RT only reduces LRR but not systemic relapse [4].

The analysis of randomized data from BCCA supports the findings in the non-randomized MDA dataset. While we acknowledge that unintended analyses of randomized trial data may be influenced by hidden biases, the similarity in the findings between the two independent datasets make this less likely. A more significant limitation is the inclusion criteria for patients entered into these prospective trials. We cannot rule out radiation-induced tumor progression as a rare event, or an event typical of patients not included in these trials including patients with inflammatory breast cancer. Unusual cases of patients with aggressive or inflammatory skin recurrence coincident with radiation for a DM, extensive recurrence bounded in extent by the prior radiation field, or progression at the field edge during a therapeutic radiation course still merit further biological investigation.

Conclusions

Decades of randomized data have demonstrated that PMRT reduces LRR and improves survival. In the non-randomized dataset, removing the competing risk of DM by studying only isolated LRR, we found no survival difference after LRR in the PMRT setting. Analysis of the randomized trial confirmed that survival was similar among women who

developed LRR, irrespective of PMRT use. These data do not support the hypothesis that irradiation promotes biologically aggressive local recurrences.

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Fig. 1. MDA non-randomized trial dataset: **a** Kaplan-Meier DM free survival and **b** overall survival in patients with any LRR, after mastectomy with versus without PMRT

Fig. 2. MDA non-randomized trial dataset: **a** Kaplan-Meier DM free survival and **b** overall survival in patients with isolated LRR, after mastectomy with versus without PMRT

Fig. 3. BCCA randomized trial dataset: Kaplan–Meier DM free survival in patients with **a** any LRR and **b** isolated LRR, after mastectomy with versus without PMRT

Fig. 4. BCCA randomized trial dataset: Kaplan–Meier overall survival in patients with **a** any LRR and **b** isolated LRR, after mastectomy with versus without PMRT

Table 1

Patient and tumor characteristics of subjects with locoregional recurrence after mastectomy alone versus mastectomy plus radiation therapy (MDA non-randomized dataset)

	All LRR cases (N = 229) N (%)	LRR after mastectomy alone (N = 189) N (%)	LRR after mastectomy plus PMRT (N = 40) N (%)	P value
Age (years)				
Mean (range)	50 (25-74)	51 (25-72)	47 (26-74)	0.08
40	45 (19.7)	32 (17)	13 (33)	
41-19	60 (26.2)	51 (27)	9 (23)	
50	124 (54)	106 (56)	18 (45)	
T stage				0.02
T1	47 (21)	44 (23)	3 (8)	
T2	108 (47)	89 (47)	19 (48)	
T3	42 (18)	35 (19)	7 (18)	
T4	2 (1)	1 (1)	1 (1)	
Unknown	30 (13)	20 (11)	10 (25)	
Nuclear grade				<0.001
I	12 (5)	5 (3)	7 (18)	
II	79 (35)	73 (39)	6 (15)	
III	62 (27)	56 (30)	6 (15)	
Unknown	76 (33)	55 (29)	21 (53)	
Lymphovascular invasion				0.46
Negative	110 (48)	93 (49)	17 (43)	
Positive	105 (46)	86 (46)	19 (48)	
Unknown	14 (6)	10 (5)	4 (10)	
Estrogen receptor status				<0.001
Negative	83 (36)	70 (37)	13 (33)	
Positive	93 (41)	85 (45)	8 (20)	
Unknown	53 (23)	34 (18)	19 (48)	
# Positive nodes				0.002
0	2 (1)	0 (0)	2 (5)	
1-3	70 (32)	64 (34)	6 (15)	
4	146 (66)	116 (61)	30 (75)	
Unknown	11 (7)	9 (5)	2 (5)	
# Excised nodes				0.01
10	29 (13)	19 (10)	5 (5)	
>10	198 (87)	165 (87)	33 (13)	
Unknown	2 (1)	5 (3)	2 (83)	
Nodal ratio				0.08
0.20	75 (33)	68 (36)	7 (18)	
>0.20	145 (63)	114 (60)	31 (78)	
Unknown	9 (4)	7 (4)	2 (5)	

Table 2

Patient and tumor characteristics of subjects with locoregional recurrence after mastectomy alone versus mastectomy plus radiation therapy (BCCA randomized dataset)

	All LRR cases (<i>N</i> = 66) <i>N</i> (%)	LRR after mastectomy alone (<i>N</i> = 52) <i>N</i> (%)	LRR after mastectomy plus PMRT (<i>N</i> = 14) <i>N</i> (%)	<i>P</i> value
Age (years)				
Mean (range)	43 (28-53)	43 (28-53)	44 (32-53)	0.67
40	22 (33)	19 (37)	3 (21)	0.54
41-19	39 (59)	29 (56)	10 (71)	
50	5 (8)	4 (8)	1 (7)	
T stage				
T1	15 (23)	13 (25)	2 (14)	0.35
T2	38 (58)	29 (56)	9 (64)	
T3	5 (8)	5 (10)	0 (0)	
Unknown	8 (12)	5 (10)	3 (21)	
Nuclear grade				
I	11 (17)	8 (15)	3 (21)	0.81
II	18 (27)	15 (29)	3 (21)	
III	19 (29)	14 (27)	5 (36)	
Unknown	18 (27)	15 (29)	3 (21)	
Lymphovascular invasion				
Negative	9 (14)	6 (12)	3 (21)	0.41
Positive	46 (70)	36 (69)	10 (71)	
Unknown	11 (17)	10 (19)	1 (7)	
Estrogen receptor status				0.64
Negative	8 (12)	6 (12)	2 (14)	
Positive	48 (73)	37 (71)	11 (79)	
Unknown	10 (15)	9 (17)	1 (7)	
# Positive nodes				
1-3	33 (50)	25 (48)	8 (57)	0.40
4	27 (41)	21 (40)	6 (43)	
Unknown	6 (9)	6 (12)	0 (0)	
# Excised nodes				0.49
10	29 (44)	21 (40)	8 (57)	
>10	28 (42)	23 (44)	5 (36)	
Unknown	9 (14)	8 (15)	1 (7)	
Nodal ratio				0.55
0.20	13 (20)	11 (21)	2 (14)	
>0.20	44 (67)	33 (63)	11 (79)	
Unknown	9 (14)	8 (15)	1 (7)	

Table 3

Time to event in subjects with locoregional recurrence after mastectomy alone versus mastectomy plus PMRT (BCCA and MDA datasets)

	Years from diagnosis to locoregional recurrence	Years from diagnosis to distant recurrence	Years from locoregional recurrence to death
BCCA			
No PMRT			
Mean	4.8	6.3	3.3
SD	4.8	5.7	4.0
Median	2.5	3.9	1.9
Range	0.4-19.9	0.5-19.9	0.1-19.1
PMRT			
Mean	3.3	5.9	3.4
SD	3.0	5.8	3.8
Median	2.2	4.3	2.0
Range	0.2-8.4	0.7-20.3	0.6-12.9
p	0.27	0.82	0.94
MDA			
No PMRT			
Mean	4.2	6.9	4.4
SD	3.9	6.0	4.7
Median	2.8	4.3	2.4
Range	0.3-19.5	0.5-24.8	0-22.9
PMRT			
Mean	3.3	4.5	2.3
SD	2.5	4.6	3.8
Median	2.9	3.0	1.3
Range	0.5-12.6	0.8-25	0.1-21.7
p	0.16	0.016	0.01