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Low locoregional recurrence rates in patients treated after 2000 with doxorubicin based chemotherapy, modified radical mastectomy, and post-mastectomy radiation

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Abstract

Purpose—To determine the rate of locoregional recurrence (LRR) associated with modern tri-modality therapy.

Methods—We retrospectively reviewed data from 291 consecutive PMRT patients treated from 1999 to 2001. These patients were compared to an historical group of 313 patients treated from 1979 to 1988 who had fluoroscopic simulation and contour-generated 2D planning. 1999–2001 spans the adoption of CT simulators for breast radiation therapy and a comparison was made between patients simulated before and after the implementation of CT simulation. Five-year actuarial rates for LRR, distal metastasis (DM), and overall survival (OS) between the pre and post CT simulation cohorts were compared as well.

Results—Compared to a 2D planned historic control, the combined contemporary patients had improved outcomes at 5 years for all endpoints studied; LRR 3.0% vs. 11.5%, DM 29.2% vs. 39.2%, and OS 79.2% vs. 70.6% ($p = 0.0004$, 0.0052, 0.0012, respectively). Significant factors in a multivariate analysis for LRR were: advanced T-stage (RR = 2.14, CI = 1.11–4.11, $p = 0.023$), and percent positive nodes (RR = 1.01, CI = 1.00–1.02, $p = 0.012$). The comparison of the pre and post CT-simulated PMRT patients (1999–2001) found no significant difference in any endpoint.

Conclusions—The rate of locoregional control for PMRT patients treated with modern radiotherapy is outstanding and has improved significantly compared to historical controls.

Keywords

PMRT; Post-mastectomy radiation therapy; Locoregional control; Locoregional recurrence; 3D treatment planning

Overall survival of breast cancer patients has steadily increased since the 1990s and numerous advances in treatment, such as the use of post-mastectomy radiation (PMRT), likely contributed to this success. Three randomized prospective studies [1–3] of patients treated in the 1980s demonstrated that the use of radiation improves the overall survival of

patients with lymph-node positive breast cancer who are treated with mastectomy and systemic therapy. In these trials, the actuarial 10-year local–regional recurrence risks were 8–13% with PMRT compared to 32–35% without radiation.

The advantage of these studies is the long follow up, but the disadvantage is that advances in imaging, staging, chemotherapy, and local therapy are not reflected in these data. In this retrospective study we report PMRT outcomes in the modern era of multimodality therapy. The time frame chosen for the cohort permits reporting of 5-year outcome data in the setting of modern therapy including but not limited to taxane based and dose dense chemotherapy regimens, sentinel lymph node biopsy in clinically node negative patients, and advanced technology for more sensitive and specific staging as well as more advanced radiotherapy targeting and delivery. We report very low rates of locoregional failure after multimodality therapy including PMRT among patients treated with contemporary therapy.

Patients and methods

Medical records of 291 consecutive patients treated from April 1999 to April, 2001 with PMRT in our department were retrospectively reviewed. Patients treated with PMRT in the setting of metastatic disease or recurrent disease were not included in this study. The institutional surveillance board approved the protocol for this retrospective study. The period of time was selected to bracket the April 2000 date when CT simulators were incorporated into the planning of PMRT, and a comparison is made of LRR before and after this change. Immediately prior to this change in April 2000, PMRT was planned with fluoroscopic-based simulation followed by a treatment planning CT and single-plane dosimetry planning on one CT slice. This era in radiation planning is referred to as two and a half dimensional (2.5D) planning as unlike historic radiation planning using only fluoroscopy to generate two-dimensional (2D) images for planning, CT images were used, but not fully integrated into the planning. After April 2000 patient's simulation and planning were fully CT-based. Dosimetry was then modeled on the full CT data set, and as such this is referred to as 3D planning throughout. Between April 1999 and April 2000, 145 patients underwent 2.5D planning and from April 2000 to April 2001, 146 underwent 3D planning.

We hypothesized that better visualization of treatment targets using 3D planning resulted in fewer LRR than 2.5D planning. Patient, tumor, and treatment characteristics are presented for each planning method in Table 1. The median age for all 291 patients was 51 years (interquartile range, 44–58 years), and the median follow-up time for surviving patients was 79 months. The PMRT targets and dose prescriptions were similar in the two groups. However, in the 2.5D + 3D group CT data was used to verify that the dose covered the intended target (coverage was approved by the treating physician. CT contouring was not routinely performed). Intensity modulated radiation therapy was not used. Patients received treatment to the chest wall, internal mammary lymph nodes, axillary apex, and supraclavicular fossa to a dose of 50 Gy in 2 Gy fractions followed by a 10 Gy boost to the chest wall (median total chest wall dose 60 Gy, range 60–66 Gy). Patients treated for an inflammatory breast cancer typically received 51 Gy in 1.5 Gy fractions given twice daily to the primary fields followed by a 15 Gy in 10 fraction chest wall boost. The chest wall was treated with tangent photon fields or appositional electron fields matched to an appositional internal mammary lymph node electron field. The supraclavicular fossa/axillary apex was treated with appositional photons. Radiation target volumes have not changed over time. All patients underwent a modified radical mastectomy (MRM), and had been treated with doxorubicin-based systemic therapy (either neoadjuvant or adjuvant) with or without taxanes or hormonal therapy. No patient received trastuzumab as part of their primary therapy.

Based on the unexpectedly low rates of LRR found in these groups and reported below, subsequent to this comparison between 2.5D and 3D planning, these patients treated in 1999–2001 (2.5D + 3D) were compared to an historic group of 313 patients treated with PMRT on institutional protocols [4–10] from 1979 to 1988. These patients underwent fluoroscopic simulation and had contour-generated two-dimensional treatment planning (2D) without the use of CT. These patients received either adjuvant [11] or neoadjuvant [12] doxorubicin-based systemic therapy, and their outcomes have been previously reported [11,12]. Patient, tumor, and treatment characteristics for the 2D planned group are presented in Table 2. No patient in the 2D group received taxanes.

Surgical approach did not change significantly between the 2D and 2.5D + 3D groups. The patients were not sentinel lymph node candidates. Number of nodes dissected remained the same over the years. Margins have been defined consistently for the entire time. Pathology for each patient was reviewed at M.D. Anderson Cancer Center before treatment, and information concerning pathologic findings was obtained from these reports. The histologic type of the primary tumor was defined according to the World Health Organization system [13]. Tumor grade was defined according to a modification of Black's nuclear grading system [14].

Endpoints and statistical analysis

The distributions of patient and tumor characteristics were compared between groups using the Chi-square test. Analysis of variance was used to compare time from surgery to first radiation treatment. Five-year actuarial rates were calculated according to the Kaplan–Meier method with comparisons among groups performed using two-sided log-rank tests [15]. The endpoints were LRR, DM, and OS. LRR was defined as any LRR independent of the timing of distant metastases. Multivariate analysis was performed using Cox logistic regression analysis [15]. All *p* values were two-tailed, with a value of ≤ 0.05 considered to be significant. Calculations were performed using SPSS 11.5 for windows, Chicago IL, USA.

Results

Patient and primary tumor data for CT-planned patients (2.5 vs. 3D)

The two groups of CT-planned patients were balanced with respect to tumor size, nodal status, estrogen receptor status, chemotherapy use and lymph-vascular space invasion ($p = \text{NS}$, Table 1). The patient's median ages were 50 and 51 years-old respectively at the time of diagnosis. As expected, most patients had locally advanced disease; most commonly stage III (78.8% and 80.0% in 2.5D and 3D respectively) with T3 or T4 tumor size and positive lymph nodes. The histology was primarily ductal carcinoma (84.9% and 81.4% in 2.5D and 3D respectively), and more than half were poorly differentiated. Lymphovascular space invasion (LVSI) was common (43.8% and 33.8% in 2.5D and 3D respectively) with a trend towards more LVSI in 2.5D patients ($p = 0.079$). Inflammatory disease was prevalent at 11.0% for 2.5D and 6.9% for 3D ($p = 0.224$). Hormonal therapy and neoadjuvant chemotherapy were used similarly between the groups. There was no difference in clinical outcomes between the two groups. The 5-year actuarial rate for LRR for fluoroscopy-simulated patients and CT-simulated patients was 3.7% and 2.2% respectively ($p = 0.335$, Fig. 1A). A comparison of the 5-year actuarial rate for DM was also statistically similar for fluoroscopy-simulated (28.5%) and CT-simulated (29.9%) patients ($p = 0.414$, Fig. 1B). Additionally, OS at 5 years was 79.9% for fluoroscopy-simulated and 78.5% for CT-simulated patients ($p = 0.623$, Fig. 1C).

Patient and primary tumor data for contemporary vs. historic patients treated with multimodality therapy including PMRT

Given the statistically similar patient characteristics and outcomes of the contemporary groups and the low rates of LRR, we combined the 2.5D and 3D groups to examine the outcomes for PMRT patients for whom CT was used in any component of treatment planning (2.5D + 3D). The median age for whole group of 604 patients was 51 years (range, 18–79 years). Characteristics of this study population are characterized in Table 2. Both groups of patients most commonly presented with advanced disease, stage III 77.3%, 2D and 79.4%, 2.5D + 3D. There was a trend towards more T4 disease in the 2.5D + 3D group (24.3%, 2D vs. 29.6%, 2.5D + 3D, $p = 0.063$), and 2.5D + 3D patients had significantly more N3 disease (4.2% vs. 10%, $p < 0.001$, likely a reflection of increasing use of ultrasound to stage the regional lymph nodes). LVSI was similar between the groups. Both groups presented predominantly with ductal carcinoma, and the statistical difference in histology ($p < 0.001$) was driven by the larger number of unknowns in the 2D planned group. While the grade was also unknown in a large percentage of the 2D group, the 2.5D + 3D group did have a significantly higher proportion of poorly differentiated disease (25.2% vs. 54.6%). The 2.5D + 3D group also had more inflammatory disease (2.6% vs. 8.9%, $p = 0.001$). During treatment the 2.5D + 3D group was more likely to receive hormonal therapy ($p < 0.001$) or neoadjuvant chemotherapy ($p < 0.001$). No patient in the 2D group received taxanes, while over two-thirds of 2.5D + 3D patients did receive taxanes. Time from date of surgery to the beginning of radiation among 302 patients with available data (excluding those who received neoadjuvant chemotherapy) reveals longer time from surgery to radiation among the contemporary cohort consistent with the use of taxanes (5 vs. 7.2 months, $p < 0.0001$ ANOVA). Examining total radiation treatment time reveals only 5/224 contemporary patients and 4/291 historic cohort patient with available data had radiation therapy duration of greater than 49 days.

Correlation between treatment era and LRR, DM, or OS

Comparing outcomes directly between the contemporary cohort described above and an historic cohort of 313 patients treated with pre-CT PMRT planning and treatment on institutional protocols [4–10] from 1979 to 1988, the 5-year actuarial rate for LRR was significantly better for the 2.5D + 3D patients compared to the 2D patients (3.0% vs. 11.5%, $p = 0.0004$, Fig. 2A). Five-year actuarial rates for DM were also more favorable in the 2.5D + 3D patients compared to 2D planned patients (29.2% vs. 39.2%, $p = 0.0052$, Fig. 2B). Overall survival at 5 years was also improved in the 2.5D + 3D group compared to 2D group of patients (79.2% vs. 70.6%, $p = 0.0012$, Fig. 2C).

On univariate analysis for LRR, 2D planning (a surrogate for era), T-stage, N-stage, LVSI, and percent positive nodes were associated with significantly increased risk of LRR (Table 3). Taxol and hormonal therapy decreased the risk of LRR (Table 3). On multivariate analysis, T-stage, and percent positive nodes were risk factors of LRR, while other factors dropped out (Table 4). 2D planning, was associated with an increased relative risk of LRR, however this did not reach statistical significance, $p = 0.08$.

Discussion

Evidence suggests that for appropriately selected patients, PMRT improves overall survival by eradicating persistent foci of disease and reducing subsequent local–regional recurrence [16]. Accordingly, advances in local–regional therapies should have their major goal being in minimizing the risk of local–regional recurrence. Historically, the rates of local–regional recurrence after PMRT have been 1–2% per year or between 10% and 20% at 10-years. In this study, we demonstrated that in a more modern cohort of patients, the risk of local–

regional recurrence after PMRT has decreased. Our data indicated that a contemporary cohort of patients with locally advanced breast cancer treated with modern surgery, chemotherapy and CT planned radiation therapy had a 5-year local–regional recurrence risk under of 3%. This risk of local–regional recurrence was significantly lower than that seen in a cohort of patients treated in the 1970s and 1980s.

No difference was found in LRR among patients treated with either 2.5D or 3D radiation treatment planning, however the low rate of events makes this comparison of contemporary cohorts underpowered to detect a difference in this sample size. Although this study did not show a clear advantage to 3D simulation compared to 2.5D planning in improved local control, this does not suggest this approach should be abandoned. CT treatment planning allows for optimized visualization of 3D targets, improves the understanding of dose distributions within the irradiated volume, and permits anatomy based modulation of dose within the treatment fields [17,18]. Better visualization of patient anatomy makes it easier to avoid normal tissue toxicity and give adequate dose to the target. It also plays a critical role in treatment planning of patients with difficult anatomy [19] and residual disease. The advantages of reduced toxicity may be more evident with IMRT [20], which remains to be studied.

There are a number of potential reasons for the excellent local–regional recurrence rates in contemporary vs. historic cohorts. Although the limitations of retrospective comparisons (discussed below) temper conclusions, improvements in radiation techniques have developed concurrently with other important changes that all may incrementally help minimize the risk of local–regional recurrence. For example, it is possible that taxanes had a significant positive effect on local control. Since taxanes were only given to patients in the modern treatment group, this study could not separate their potential benefit from the contribution of other advances. The local control benefit of paclitaxel has been demonstrated for patients undergoing breast conservation therapy by the Cancer and Leukemia Group B (CALGB) 9344 study [21]. A subset analysis of this CALGB study also suggested at a possible local control benefit for mastectomy patients but did not reach significance, and the subset was underpowered to draw conclusions. Differences in sequencing and dosing regimens between contemporary and historical may also play a role. The retrospective nature of this study has inherent limitations, and biases between groups cannot fully be accounted for. In particular, the historical cohort, while a surrogate for 2D radiation treatment planning, is also a surrogate for era and many unknown changes over time that may affect outcome. Although we have attempted to control for known factors through multivariate analysis, numerous well-described limitations impact comparisons to historical controls [22,23].

In conclusion, patients receiving PMRT with modern techniques have outstanding local control, and these data should impact statistical considerations in developing future trials. The rates of LRR reported here are consistent with rates of LRR after breast conserving treatment for early stage breast cancer detected in trials with sample sizes well over 1,000 patients. Distant recurrence rates and overall survival are also improving over time. It is likely that multiple incremental improvements across disciplines contribute to this phenomenon.

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Fig. 1. Kaplan–Meier outcome curves for contemporary patients treated with PMRT planned using 2.5D vs. 3D simulation show no difference in (A) locoregional recurrence, (B) distant metastasis, or (C) overall survival.

Fig. 2.

Kaplan–Meier outcome curves for contemporary patients treated with PMRT planned using 2.5D + 3D vs. 2D simulation show significant difference in (A) locoregional recurrence, (B) distant metastasis, or (C) overall survival.

Table 1

CT planned patient, tumor, and treatment characteristics.

Characteristic	2.5D		3D		<i>p</i> [*]
	No.	%	No.	%	
Age					0.679
Median	50		51		
Interquartile	42–58		45–59		
≤35	12	8.2	8	5.5	
36–50	63	43.2	60	41.4	
51–60	46	31.5	46	31.7	
>60	25	17.1	31	21.4	
Stage					0.187
I	0	0	4	2.8	
II	29	19.9	24	16.6	
III	115	78.8	116	80.0	
Unknown	2	1.4	1	0.7	
Tumor Stage					0.575
T1	21	14.4	14	9.7	
T2	45	30.8	45	31.0	
T3	33	22.6	32	22.1	
T4	43	29.5	43	29.7	
TX	4	2.7	2	1.4	
Nodal Stage					0.747
N0	13	8.9	16	11.0	
N1	100	68.5	92	63.4	
N2	20	13.7	18	12.4	
N3	12	8.2	17	11.7	
NX	1	0.7	2	1.4	
No. of involved nodes					0.880
Median	3		3.5		
Interquartile	1–7		1–8		

Characteristic	2.5D		3D		p [*]
	No.	%	No.	%	
0	28	19.2	33	22.8	
1-3	45	30.8	45	31.0	
4-9	43	29.5	40	27.6	
≥ 10	30	20.5	27	18.6	
Histology					0.189
Ductal/mixed	124	84.9	118	81.4	
Lobular	13	8.9	20	13.8	
Other	9	6.2	5	3.4	
Unknown	0	0	2	1.4	
Grade					0.361
Well differentiated	8	5.5	6	4.1	
Moderately differentiated	48	32.9	59	40.7	
Poorly differentiated	82	56.2	77	53.1	
Other	1	0.7	1	0.7	
Unknown	7	4.8	2	1.4	
Inflammatory					0.224
Yes	16	11.0	10	6.9	
No	130	89.0	135	93.1	
LVI present					0.079
Yes	64	43.8	49	33.8	
No	82	56.2	96	66.2	
Hormonal therapy					0.210
Yes	96	65.8	85	58.6	
No	50	34.2	60	41.4	
Taxanes					0.333
Yes	103	70.5	96	66.2	
No	42	28.8	50	34.5	
Neoadj. chemotherapy					0.126
Yes	85	58.2	97	66.9	
No	61	41.8	48	33.1	

Characteristic	2.5D		3D		<i>p</i> [*]
	No.	%	No.	%	
Totals	146	100	145	100	

Abbreviations: No., number; NS, not significant.

Due to small differences in rounding numbers, percentages do not always equal 100%.

* Chi-squared test for quality of distribution in the fluoroscopy and CT-simulated groups.

Table 2

2D and combined 2.5D + 3D patient, tumor, and treatment characteristics.

Characteristic	2D planned		2.5D + 3D planned		<i>p</i> [*]
	No.	%	No.	%	
Age					0.143
Median	51		51		
Interquartile	42.5–59		44–58		
≤35	38	12.1	20	6.9	
36–50	118	37.7	123	42.3	
51–60	93	29.7	92	31.6	
>60	64	20.4	56	19.2	
Stage					0.129
I	2	0.6	4	1.4	
II	57	18.2	53	18.2	
III	242	77.3	231	79.4	
Unknown	12	3.8	3	1.03	
Tumor stage					0.063
T1	25	8.0	35	12.0	
T2	109	34.8	99	34.0	
T3	89	28.4	65	22.3	
T4	76	24.3	86	29.6	
TX	14	4.5	6	2.1	
Nodal stage					<0.001
N0	37	11.8	29	10.0	
N1	176	56.2	192	66.0	
N2	84	26.8	38	13.1	
N3	13	4.2	29	10.0	
NX	3	0.96	3	1.0	
No. of involved nodes					0.773
Median	4		3		
Interquartile	1–8		1–8		

Characteristic	2D planned		2.5D + 3D planned		<i>p</i> [*]
	No.	%	No.	%	
0	59	16.3	61	21.0	
1-3	91	29.1	90	30.9	
4-9	100	31.9	83	28.5	
≥ 10	63	20.1	57	19.6	
Histology					<0.001
Ductal/mixed	248	79.2	242	83.1	
Lobular	26	8.3	33	11.3	
Other	3	1.0	14	4.8	
Unknown	36	11.5	2	0.7	
Grade					<0.001
Well differentiated	9	2.9	14	4.8	
Moderately differentiated	108	34.5	107	36.8	
Poorly differentiated	79	25.2	159	54.6	
Other	0	0	2	0.7	
Unknown	117	37.4	9	3.1	
Inflammatory					0.001
Yes	8	2.6	26	8.9	
No	305	97.4	265	91.1	
LVSI present					0.541
Yes	114	36.4	113	38.8	
No	199	63.6	178	61.1	
Hormonal therapy					<0.001
Yes	63	20.1	181	62.2	
No	250	79.9	110	37.8	
Taxanes					<0.001
Yes	0	0	199	68.4	
No	313	100	92	31.6	
Neoadj. chemotherapy					<0.001
Yes	150	47.9	182	62.5	
No	163	52.1	109	37.5	

Characteristic	2D planned		2.5D + 3D planned		<i>p</i> [*]
	No.	%	No.	%	
Totals	313	100	291	100	

Abbreviations: No., number; NS, not significant.

Due to small differences in rounding numbers, percentages do not always equal 100%.

* Chi-squared test for quality of distribution in the fluoroscopy and CT-simulated groups.

Table 3

Univariate analysis of factors associated with LRR for 2D, 2.5D, and 3D groups of patients.

Factor	HR	CI	p-value
2D planning	5.38	1.63–17.8	0.006
N-stage	3.00	1.60–5.62	0.001
T-stage	2.30	1.23–4.31	0.009
LVSI	1.95	1.04–3.65	0.038
Percent pos. nodes	1.02	1.01–1.02	0.002
Taxanes	0.34	0.14–0.82	0.017
Hormonal therapy	0.30	0.13–0.68	0.004

Table 4

Multivariate analysis of factors associated with LRR for 2D, 2.5D, and 3D groups of patients.

Factor	HR	CI	<i>p</i> -value
2D planning	3.96	0.85–18.5	0.080
T-stage	2.14	1.11–4.11	0.023
% pos nodes	1.01	1.00–1.02	0.012