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Treatment And Outcomes Of Female Patients Who Underwent Mastectomy For Breast Cancer At Yale New Haven Hospital From 2000-2005: Examination Of Recurrence Rates

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Treatment and Outcomes of Female Patients who underwent Mastectomy for Breast Cancer at Yale New Haven Hospital from 2000-2005: Examination of Recurrence Rates

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Abstract

Introduction: Locoregional recurrence (LRR) and distant recurrence after mastectomy are very important clinical endpoints. It is well established that postmastectomy radiation therapy (PMRT) plays an important role in the treatment of locally advanced breast cancer and in the prevention of locoregional and distant recurrence. There are also other prognostic factors such as nodal status, tumor size, and predictive factors such as hormone receptor status that are known to influence local and distant recurrence. There are varying reports on the rates of LRR after mastectomy. This variation in published rates of LRR creates a limitation in adequately assessing risk and benefits of PMRT to reduce local and distant recurrence. Given the availability of more effective chemotherapy/systemic regimens, safer methods of delivering PMRT, there is a need to further evaluate the actual rates of locoregional and systemic recurrence after mastectomy.

Aim: Our study sought to evaluate the local and distant recurrence rates in our population of patients who underwent mastectomy for breast cancer as well as the effects of various predictive and prognostic factors on local and distant recurrence. We hypothesized that the rate of local and distant recurrence in our patient population will be much lower than that stated in the published large-scale trials.

Methods: All cases of breast cancer treated with mastectomy with or without post mastectomy radiation between Jan 1, 2000 and December 31, 2004, at Yale New Haven Hospital were analyzed.

Results: A total of 443 cases were analyzed. Of the 356 cases in which local and distant recurrence status were known, 65 were non-invasive breast cancers while 291 were invasive breast cancer and invasiveness was unknown in 2 cases. Patients were followed for a mean of 79.6 months (std: 29.9). Local recurrence occurred in 2(3%) of non-invasive cancers and 5(1.7%) of invasive cancers. Distant recurrence occurred in none of the non-invasive cancers and 32(11%) of the invasive cancers. There were significant differences in distant recurrence by T stage ($p=0.016$), N stage ($p=0.022$), ER status ($p<0.001$) , PR status($p<0.001$), molecular type ($p<0.001$) and PMRT ($p=0.01$). However on multivariate analysis, only differences in nodal status ($p=0.02$) and ER status($p<0.001$) remained significant for distant recurrence.

Conclusion: Our study found lower than expected rates of local and distant recurrence.

Principal investigator: Dr Meena Moran
Manual data collection from electronic medical records: Oluwatosin Onibokun
Data Analysis and interpretation: Dr Donald Lannin and Oluwatosin Onibokun

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Introduction

Local and distant recurrence after mastectomy are very important clinical endpoints given their impact on morbidity, overall survival, as well as their devastating psychological effect. However, the reported rates of locoregional recurrence (LRR) after mastectomy range from as low as 4% to as high as 32% (Katz et al., 2000; Overgaard et al., 1997; Ragaz et al., 2005). This variation in published rates of LRR creates a limitation in adequately assessing risk benefit ratios in clinical decision-making regarding the use of prophylaxis for LRR.

There are factors such as postmastectomy radiation therapy (PMRT), hormone receptor status, nodal status and margin status that are known to influence local and distant recurrence. Of note, The American Society of Clinical Oncology (ASCO) recommends PMRT for patients with four or more positive axillary lymph nodes and those with stage III tumors (Recht et al., 2001). However, there is no standard recommendation on the use of PMRT in lower risk groups such as patients with fewer lymph nodes involved (one to three positive axillary lymph nodes) or in those without any lymph node involvement (Recht et al., 2001).

Benefits of PMRT in the prevention of locoregional and distant recurrence were publicized by large randomized controlled studies in the late 1990's and mid 2000 by two separate groups, the Danish and the British Columbians in Canada (Overgaard et al., 1997; Overgaard et al., 1999; Ragaz et al., 2005). These studies showed the benefits of PMRT in reducing rates of locoregional recurrence and improving overall survival. However, the studies are criticized for inadequate information on lymph node

involvement and thus limited staging information, as well as for the use of chemotherapy regimens that are not considered standard of care in this present time.

Specifically, one of the studies conducted by the Danish group (82b trial) that analyzed the effect of post mastectomy radiation, was conducted among 1708 high-risk premenopausal women who had all undergone mastectomy and chemotherapy with cyclophosphamide, methotrexate and fluorouracil (CMF). The result showed that at 10 years, there was a lower locoregional recurrence rate of 9% in patients who received PMRT to the chest wall and regional lymphatics versus a higher rate of 32% in patients who did not receive PMRT ($P< 0.001$). The study also found superior disease free survival (48% vs 34%, $P < 0.001$) and superior overall survival (54% vs 45%, $P < 0.001$) in patients who received PMRT versus patients who did not receive PMRT respectively. In the British Columbia study, they examined 318 high risk pre-menopausal women with breast cancer who either received adjuvant chemotherapy (CMF) and PMRT or underwent adjuvant chemotherapy (CMF) alone after mastectomy. Their study showed similar results to the Danish trial with a 20 year survival free of isolated LRR of 90% in patients who received chemotherapy and radiation versus 74% in the group that got chemotherapy alone ($P=0.002$). However, the British Columbia study did not show a statistically significant difference in the overall survival of the group that received PMRT (RR 0.74, 95% CI= 0.53 to 1.02; P= 0.07). Similarly, in trials done among 1460 post-menopausal women (Danish 82 c trial), a lower LRR of 8% was seen in high -risk women who received PMRT and tamoxifen versus a rate of 35% in patients who received tamoxifen alone without PMRT.

However, the high LRR rates in patients who did not receive PMRT published in these studies have been questioned given lower rates found in subsequent smaller studies among similar patient groups (Floyd et al., 2006; S. M. Macdonald et al., 2009; Panoff et al., 2011). PMRT is not without its disadvantages with potential long-term risks including lymphedema, brachial plexus damage, radiation pneumonitis, cardiac toxicity, and radiation-induced second cancers (Feigenberg, Price Mendenhall, Benda, & Morris, 2003; Ragaz et al., 2005; Recht et al., 2001). Therefore, the lower locoregional recurrence rates seen in more recent retrospective studies in women who did not undergo PMRT suggests a lower benefit for additional PMRT.

Hormone receptor status is another important prognostic factor for recurrence as well as response to systemic therapy (Kyndi et al., 2008; Panoff et al., 2011; Voduc et al., 2010)Negative hormone receptor status has been associated with increased risk of LRR in women with breast cancer. Specifically, negative estrogen and progesterone receptor status were associated with increased risk of LRR in women with breast cancer(Panoff et al., 2011). In the study, Her 2 positive receptor status was associated with a lower LRR rate (1.7 in Her2 +, versus 7.5 in Her2 -, P= 0.0032).

Another retrospective study analyzed the effect of molecular subtypes on recurrence among 2, 985 breast cancers in patients who underwent breast conserving surgery with radiotherapy, mastectomy alone, and mastectomy with radiation(Voduc et al., 2010). In this study, basal like tumors (ER, PR and Her2 negative tumors) were more likely to have local regional recurrence when compared to luminal A tumors (ER or PR positive, Her2 negative, Ki-67 < 14%) (Voduc et al., 2010).

In terms of surgical margins as an important prognostic factor, a study by (Abi-Raad et

al., 2011) found that those with positive or close margin status had significantly higher risk of LRR when compared with those with negative margins $P < 0.0001$.

Therefore, given the availability of more effective chemotherapy/systemic regimens, safer methods of delivering PMRT, as well as improved surgical techniques, there is a need to further evaluate the actual rates of locoregional and systemic recurrence after mastectomy. There is also a need to evaluate the effects of factors such as hormone receptor status, nodal status, and margin status on the local and distant recurrence after mastectomy in order to identify the subset of patients that could best benefit from PMRT.

Aims and Hypothesis

- To evaluate the local and distant recurrence rate in women who underwent mastectomy for breast cancer. We hypothesize that the rate of local and distant recurrence in our patient population will be much lower than that stated in the already published large-scale trials.
- To evaluate the impact of PMRT on local and distant recurrence rates in our patient population. Our hypothesis is that patients who received PMRT will have a lower rate of local and distant recurrence.
- To evaluate the impact of hormone receptor status (estrogen, progesterone, herceptin) on local and distant recurrence rates in patients who have undergone postmastectomy radiation. We hypothesize that patients with estrogen and progesterone negative hormone receptor status will have a higher rate of recurrence and thus benefit most from PMRT compared to patients with hormone receptor positive status.

- To evaluate the impact of surgical techniques (margin status, nodes examined) on the local and distant recurrence rates. We hypothesize that on average, more nodes will be examined in our study group when compared to the Danish and British Columbia clinical trials.

Methods

All breast cancer patients who underwent mastectomy with or without post mastectomy radiation at Yale New Haven Hospital between Jan 1, 2000 and December 31, 2004, were queried from the hospital cancer registry. Hospital records and pathology records of these patients were reviewed via the electronic medical records (EMR). Before review of medical records, institutional review board approval was obtained. Patients who did not meet the study criteria of having their mastectomy done at Yale New Haven Hospital during the study period were excluded. Patients with distant metastasis at time of mastectomy were also excluded. In patients with bilateral synchronous breast cancer where the two breast cancer cases occurred during the study period, the synchronous breast cancers were recorded as two separate cases. The following variables were extracted from the medical records: age at surgery, race/ethnicity, laterality of breast cancer, date of diagnosis, type of surgery, date of surgery, histology, invasive tumor size, pathologic tumor size, pathologic nodal status, total number of nodes examined, total number of positive nodes, number of sentinel lymph nodes examined, nuclear grade, histologic grade(Bloom Richardson Score), ER status, percent ER status, PR status, percent PR status, Herceptin status, Herceptin number (immunohistochemisty), FISH (for those that had it tested), surgical margin and radiation therapy, date last seen, status at

date last seen and type of recurrence. We consulted the hospital tumor registry database to obtain the following variables: radiation therapy, date last seen, recurrence status, date of local recurrence and date of distant recurrence. For patients, without adequate variable information in the EMR, we consulted the tumor registry to fill in the gaps where possible, however, deference was always given to information collected directly from the EMR.

In our study, local recurrence was defined as recurrence to the ipsilateral chest wall and axilla. Distant recurrence was defined as recurrence beyond the chest wall and axilla. We also collected information regarding use of adjuvant therapy, use of hormonal therapy, trastuzamab and other systemic therapy from the EMR when available.

The student, Oluwatosin Onibokun, worked on the design and planning of the project along with Dr Donald Lannin and Dr Meena Moran. The student, Oluwatosin Onibokun, examined and extracted all the available data relating to the breast cancer diagnosis, treatment and follow-up from the electronic medical records for all the patients who met the criteria for inclusion in this study. This included examining pathology reports, operative reports and physician notes. She worked with Dr Lannin and Dr Moran on getting data from the hospital tumor registry. She extracted data from the hospital tumor registry records. She compared data from the hospital tumor registry with data she collected from the EMR and she reconciled the two data using standard guidelines such as the American Joint Committee on Cancer (AJCC) tumor staging guidelines, 7th edition as well as in consultation with Dr Lannin. She worked jointly with her research advisor Dr Lannin on the computing and statistical analysis of the study data. She also worked with Dr Lannin on the interpretation of the study results.

Statistical Analysis

We used the SPSS version 19 to perform statistical analysis. We used the Chi- square method in our bivariate analysis to compare the effect of various factors on recurrence. Linear regression using the backward method was used for multivariate analysis.

Results

Of the 443 patients that met our study criteria, there were 359 (81.1%) cases where the local and distant recurrence was known and 84 (18.9%) cases where the local and distant recurrence was not known.

We compared cases where the recurrence outcome was known with those where the recurrence was unknown. As seen in table 1, cases with invasive cancers tended to have more cases with known recurrence status when compared with cases with non-invasive cancers ($p= 0.006$). This is likely because patients who undergo a mastectomy for DCIS are usually not given any other local or systemic treatment, so they tend to be followed by their home town primary care physician rather than returning to the cancer center. There was no difference between cases with known and unknown recurrence based on age, race, nodal status or receipt of post-mastectomy radiation. Patients were followed for a mean of 79.7 months(min: 0.2, max: 138, std deviation: 29.9). We focused our analysis on 359 cases where the local and distant recurrence status was known.

Table 1: Comparison of patients with known and unknown recurrence status

	Recurrence unknown	**Recurrence known**	**P value (Chi square)**
Total	84 (100%)	359 (100%)	
Age			0.739
<50	28 (33.35%)	132 (36.7%)	
>50	56 (66.6%)	226 (62.9%)	
Unknown	0 (0%)	1 (0/3%)	
Race			0.539
White	69 (82.14%)	294 (81.8%)	
Black	10 (11.9%)	39 (10.9%)	
Hispanic	1 (1.2%)	10 (2.8%)	
Asian	1 (1.2%)	3 (0.8%)	
Other	1 (1.2%)	5 (1.4%)	
Unknown	2 (2.4%)	8 (2.2%)	
T stage			0.03
Insitu	26 (30.9%)	65 (18.1%)	
1	27 (32.1%)	144 (40.1%)	
2	18 (21.4%)	109 (30.3%)	
3	8 (9.5%)	22 (6.1%)	
4	2 (2.4%)	16 (4.4%)	
Unknown	3 (3.6%)	3 (0.8%)	
N stage			0.707
0	40 (47.6%)	213 (59.3%)	
1	17 (20.2%)	75 (20.9%)	
2	5 (5.9%)	25 (7%)	
3	4 (4.75)	11 (3%)	
Unknown	18 (21.4%)	35 (9.7%)	
PMRT			0.360
No	72 (85.7%)	299 (83.2%)	
Yes	8 (9.5%)	48 (13.3%)	
Unknown	4 (4.8%)	12 (3.3%)	
Invasiveness			
Non-invasive	26 (31%)	65 (18.1%)	0.006
Invasive	55 (65.4%)	291 (81%)	
Unknown	3 (3.6%)	3 (0.8%)	

Table 2: Patient and tumor characteristics for invasive and non-invasive tumors

	Non-invasive	Invasive
Total	65 (100%)	291 (100%)
Age		
<50 years old	26 (40%)	106 (36.4%)
>50 years old	39 (60%)	185 (63.5%)
Race		
White	54 (83%)	237 (81.4%)
Black	7(10.7%)	32 (10.9%)
Asian	0 (0%)	3 (1%)
Hispanic	2 (3%)	8 (2.7%)
Other/ Unknown	2(3%)	11 (3.7%)
Laterality		
Right	21 (32.3%)	133 (45.7%)
Left	40(61.5%)	140 (48.1%)
Unknown	4 (6.1%)	18 (6.1%)
Tumor Histology		
Infiltrating ductal	0	188 (64.6%)
Infiltrating lobular	0	37 (12.7%)
Infiltrating lobular and ductal	0	20 (6.9%)
Mucinous (Colloid)	0	5 (1.7%)
Intraductal with focal invasion	0	8 (0.03%)
Intraductal	61 (93.8%)	0 (0%)
Other / Unknown	4 (6.1%)	33 (11.3%)
T stage		
Insitu	65(100%)	0
1	0	144(49.5%)
2	0	109(37.5%)
3	0	22(7.6%)
4	0	16(5.5%)
Unknown	0	0
N stage		
0	49 (75.3%)	163 (56%)
1	0 (0%)	75 (25.7%)
2	0 (0%)	25 (8.6%)
3	0 (0%)	11 (3.7%)
Unknown	16 (24.6%)	17 (5.8%)
Grade		
1	7 (10.7%)	41 (14.1%)
2	24 (36.9%)	102 (35.0%
3	22 (33.8%)	108 (37.1%)
Unknown	12 (18.4%)	40 (13.7%)
ER status		
Negative	6 (9.2%)	55 (18.9%)
Positive	8 (12.3%)	189 (64.9%)
Not determined/ Unknown	51 (78.4%)	47 (16.1%)
PR status		
Negative	6 (9.2%)	81 (27.8%)
Positive	7 (10.7%)	165 (56.7%)
Not determined / Unknown	52 (80%)	45 (15.4%)
HER 2 status		
Negative	1 (1.5%)	178 (61.1%)
Positive	2(3.07%)	47 (16.15%)
Indeterminate	0 (0%)	16 (5.55)
Not determined / Unknown	62 (95.3%)	50 (17.2%)

Patients and tumor characteristics

Of the 359 cases in which local and distant recurrence rates were known, 65 were non-invasive breast cancers while 291 were invasive breast cancers. Invasiveness was unknown in 3 cases; thus a total of 356 cases were analyzed.

Table 2 highlights the patient and tumor characteristics of the cases. As can be seen, 40% (26/65) of the non-invasive cases were below 50 years old (pre-menopausal) while 60% (39/65) were above 50 years old (menopausal). Similarly for invasive cancers, 36.4% (106/291) were below 50 years old while 63.5% (185/291) were above 50 years old. Of the invasive cancers, 81.4% occurred among white, 10.9% among black, 2.7% among Hispanic and 1% among Asian women. The same trend in racial distribution was seen for non-invasive cancer. There was left sided laterality in both invasive and non-invasive cancer with the highest left to right sided predominance seen in the non-invasive cancers (61.5% on the left and 32.3% for non-invasive cancers versus 48.1% on the left and 45.7% on the right for invasive cancers). For the invasive cancers, 64.6% were infiltrating ductal, 12.7% infiltrating lobular, 6.9% infiltrating ductal and lobular, 7% mucinous (colloid), and 0.03% intraductal with focal invasion. Of the invasive cancers, a majority, 49.5% were 2cm or less (T1), 37.5% were greater than 2cm but less than or equal to 5cm (T2), 7.6% were greater than 5cm (T3) while 5.5% had dermal involvement (T4). More than half of the invasive cases were node negative (56%), 25.7% had 1-3 positive nodes (N1), 8.6% had 4-9 positive nodes (N2) and 3.7% had greater than 9 positive lymph nodes involved.

Of the invasive cancers, 14.1% were low grade (grade 1), 35% grade 2 and 37.1% were

grade 3. Similarly for the non- invasive cancers, 10.7% were grade 1, 36.9% grade 2 while 33.8% were grade 3. It was more likely that grade was unknown in the non-invasive cancers when compared to invasive cancers (18.4% versus 13.7% respectively). Most of the invasive cancers were ER positive 189 (64.9%), 55(18.9%) were known to be ER negative while ER receptor status was unknown or undetermined in 47 cases (16.1%). The ER status was not determined for most of the non-invasive cancers (78.4%).

In the invasive cancers, HER 2 status was negative in 178 (61%), positive in 47 (16%) and indeterminate in 16 (5.5%). HER 2 was deemed indeterminate when the Immunohistochemistry (IHC) result was 2+ but the FISH was not determined. The HER 2 status was not determined in most of the non-invasive cases, as expected. In terms of molecular type for invasive cancers, 139 (47.8%) were either ER or PR positive, and HER 2 negative (Luminal A); 32(11%) were either ER or PR positive and HER 2 positive (Luminal HER 2+); 13(4.4%) were ER and PR negative and HER 2 positive, and 32(11%) were ER and PR negative and HER 2 negative (triple negative, basal like).

Overall treatment characteristics

As can be seen in table 3, 151 (51.9%) cases underwent modified radical mastectomy, 82 (28.2%) cases underwent total mastectomy with negative sentinel lymph node biopsy and 45 (15.4%) cases underwent total mastectomy.

An average of 8.96 nodes were examined for the invasive cancers alone (std deviation 7). Almost all the non-invasive cases, 63 (96.9%) did not receive post mastectomy radiation, while status of PMRT was unknown in 2 cases. Of the invasive cases, 234 (80.4%) of

cases did not receive PMRT, 47 (16.2%) received PMRT while status of PMRT was unknown in 10 (3.4%) of cases. Surgical margins were close (2mm or less) in 24 (82%) of invasive cases.

Our study showed that higher risk patients tended to get PMRT. As seen in table 4, a higher percentage of patients under 50 years old received PMRT when compared to those over 50 years of age (16.9% versus 10.7% respectively, P= 0.007). None of the patients with breast carcinoma in situ received PMRT. For the invasive cases, a higher percentage of tumors with larger sizes received PMRT when compared to those with smaller sizes (4.8%, 22.8%, 40%, 46.7% for T1, T2, T3 and T4 tumors respectively, P<0.001). Finally, this same trend was seen by N stage. Those with more positive nodes were more likely to receive PMRT when compared to those with fewer positive nodes (2.8%, 25.3%, 44.8%, 69.3% for N0, N1, N2 and N3 respectively P< 0.001).

There was very limited information on adjuvant chemotherapy in the EMR. Out of the 291 invasive cases, 21 were known to have not received adjuvant chemotherapy, 89 were

Table 3: Treatment characteristics for invasive and non-invasive tumors

	Non-invasive	Invasive
Surgery		
Modified radical mastectomy	6 (9.2%)	151 (51.9%)
Total mastectomy (with negative SLNB)	27 (41.55)	82 (28.2%)
Total mastectomy	29 (44.6%)	45 (15.4%)
Other	1 (1.5%)	2 (0.7%)
Unknown	2 (3.1%)	11 (3.7%)
Nodes Examined		
8 or less nodes	38 (58.4%)	135 (46.4%)
> 8 nodes	3 (4.6%)	131 (45%)
No nodes examined	10 (15.35)	6 (2%)
Unknown	14 (21.5%)	19 (6.5%)
Margin status		
Negative	47 (72.3%)	195 (67%)
Close(2mm or < 2mm)	2 (3%)	24 (8.2%)
Positive	0 (0%)	16 (5.5%)
Equivocal	0 (0%)	1 (0.3%)
Unknown	16 (24.6%)	55 (18.9%)
Post-mastectomy radiation		
No	63 (96.9%)	234 (80.4%)
Yes	0 (0%)	47 (16.2%)
Unknown	2 (3.1%)	10 (3.4%)

SLNB= Sentinel lymph node biopsy

known to have received adjuvant chemotherapy, and chemotherapy status was unknown in 181 cases. Similarly for hormone therapy, of the 291 invasive cases, 90 were known to have received adjuvant hormone therapy, 10 were known to have not received it, while adjuvant hormone therapy status was not known in 191 invasive cancer cases.

Table 4: Characteristics of patients who received PMRT

	No	Yes	P value
Age			0.007
<50	128(83.1%)	26(16.9%)	
>50	24(89.3%)	29(10.7%)	
unknown	0	1(100%)	
T stage			<0.001
insitu	89(100%)	0	
1	157(95.2%)	8(4.8%)	
2	95(77.2%)	28(22.8%)	
3	18(60%)	12(40%)	
4	8(53.3%)	7(46.7%)	
N stage			<0.001
0	240(97.2%)	7(2.8%)	
1	65(74.7%)	22(25.3%)	
2	16(55.2%)	13(44.8%)	
3	4(30.8%)	9(69.2%)	

Local and Distant Recurrence Rates.

As can be seen in table 5, a low overall rate of both local and distant recurrence was found in our study. Local recurrence occurred in 2(3%) of non-invasive cancers and 5(1.7%) of invasive cancers. Distant recurrence did not occur in any of the non-invasive cancers, while 32 (11%) of the invasive cancers had distant recurrence.

Table 5: Overall local and distant recurrence

	Local recurrence		Distant recurrence	
	Non-invasive	**Invasive**	**Non-invasive**	**Invasive**
No	63 (96.9%)	286 (98.2%)	65 (100%)	259 (89%)
Yes	2 (3%)	5 (1.7%)	0 (0%)	32 (11%)
Total	65 (100%)	291 (100%)	65	291 (100%)

Prognostic factors for recurrence for invasive cancers

The relationship of a number of tumor and biological characteristics to local recurrence is shown in Table 6. None of these factors were statistically significant, probably because of the low incidence of local recurrence, and because a large percentage of the high-risk patients received radiation therapy. On bivariate analyses of invasive cases using chi-square, differences in tumor size ($p=0.016$), nodal status ($p=0.022$), ER status ($p<0.001$), PR status ($p< 0.001$) , and molecular subtype ($p <0.001$) , were significantly related to distant recurrence (table 7). Differences in age, grade, and HER 2 status were not statistically significant for distant recurrence. However on multivariate analysis using linear regression model, only differences in nodal status ($p=0.02$) and ER status ($p<0.001$) remained significant for distant recurrence.

Table 6: Local Recurrence in relation to PMRT

	Invasive cancer		Non-invasive cancer
	PMRT+	**PMRT-**	**PMRT-**
T stage			
insitu	-	-	2/63 (3.2%)
1	0/7 (0%)	1/134 (0.7%)	-
2	0/25 (0%)	2/80 (2.5%)	-
3	0/9 (0%)	1/13 (7.7%)	-
4	1/6 (17%)	0/7 (0%)	-
N stage			
0	1/7 (14%)	2/152 (1.3%)	2/47 (4.3%)
1	0/20 (0%)	2/53 (3.8%)	-
2	0/12 (0%)	0/12 (0%)	-
3	0/7 (0%)	0/2 (0%)	-
Grade			
1	0/3 (0%)	2/37 (5.4%)	0/6 (0%)
2	0/17 (0%)	2/83 (2.4%)	1/23 (4.3%)
3	1/22 (4.5%)	0/81 (0%)	1/22 (4.5%)
Surgical Margins			
Negative	1/30 (3.3%)	2/159 (1.3%)	2/45 (4.4%)
Close	0/7 (0%)	1/16 (6.3%)	0/2 (0%)
Positive	0/4 (0%)	1/10 (10%)	-
Equivocal	-	0/1 (0%)	-
ER status			
Negative	1/11 (9%)	1/42 (2.3%)	1/6 (16.7%)
Positive	0/33 (0%)	3/151 (2%)	0/8 (0%)
Not determined	0/2 (0%)	0/23 (0%)	1/44 (2.2%)
PR status			
Negative	1/14 (7.1%)	1/62 (1.6%)	1/6 (16.7%)
Positive	0/30 (0%)	3/132 (2.3%)	0/7 (0%)
Not determined	0/2 (0%)	0/23 (0%)	1/45 (2.2%)
HER 2			
Negative	1/35 (2.8%)	2/35 (5.7%)	0/1 (0%)
Positive	0/7 (0%)	0/14 (0%)	0/2 (0%)
Indeterminate	0/2 (0%)	0/18 (0%)	1/48 (2%)
Molecular type			
ER/PR+, Her2 -	0/26 (0%)	2/111 (1.8%)	0/1 (0%)
ER/ PR+, Her2 +	0/4 (0%)	1/25 (4%)	-
ER/ PR-, Her 2 +	0/2 (0%)	1/9 (11.1%)	0/1 (0%)
Triple negative (ER-, PR-, Her2-)	1/8 (12.5%)	0/24 (0%)	-
Indeterminate	0/7 (0%)	0/65 (0%)	2/61 (3.3%)

Table 7: Bivariate analysis of factors influencing distant recurrence for invasive cancers

	Distant recurrence	P value (Chi square)
Age		
<50	14/106 (13.2%)	0.361
>50	18/185 (9.7%)	
T stage		0.016
1	10/144 (6.9%)	
2	13/109 (11.9%)	
3	4/22 (18.2%)	
4	5/16 (31.3%)	
N stage		
0	12/163 (7.4%)	0.022
1	10/75 (13.3%)	
2	6/25 (24%)	
3	3/11 (27.3%)	
Grade		
1	1/41 (2.4%)	0.109
2	13/102 (12.7%)	
3	16/108 (14.8%)	
Surgical margin		0.029
Negative	20/195 (10.3%)	
Close (< 2mm)	5/24 (20.8%)	
Positive	1/16 (6.3%)	
Misc/Equivocal	1/1 (100%)	
ER status		
Negative	15/55 (27.3%)	<0.001
Positive	15/189 (7.9%)	
Not determined	1/26 (3.8%)	
PR status		
Negative	19/81 (23.5%)	<0.001
Positive	12/165 (7.3%)	
Unknown	1/26 (3.8%)	
HER 2 Neu		
Positive	23/178 (12.9%)	0.733
Negative	4/47 (8.5%)	
Indeterminate	1/16 (6.3%)	
Molecular type		
ER/PR+, Her2 -	11/139 (7.9%)	<0.001
ER/ PR+, Her2 +	1/32 (3.1%)	
ER/ PR negative, Her 2 +	3/13 (23.1%)	
Triple negative (ER-, PR-, Her2-)	11/32 (34.4%)	
Unknown	6/75 (8%)	
PMRT		
No	20/234 (8.5%)	0.01
Yes	10/47 (21.3%)	

Table 8:Local recurrence for invasive cancer cases in pre-menopausal women who did not receive PMRT (comparison with Wallgren et al, 2003).

Premenopausal (<50)

	Wallgren 10 year Recurrence (%)	Wallgren #	Yale 5 year recurrence (%)	Yale 10 year recurrence (%)	Yale #	P value**
T1	18	219/1209	0	7	1/45	0.006
T2	25	373/1510	5	5	1/22	0.03
T3	31	56/178	17	17	1/5	--
T4	--	--	0	0*	0/3*	--
N0	14	92/641	2	2	1/44	0.02
N1	20	267/1356	4	12	2/28	0.10
N2	30	186/628	0	0*	0/3*	--
N3	38	103/272	--	--	--	--

*No 10 year survivors
** 10 year Yale recurrence vs. 10 year Wallgren recurrence

Table 9:L**ocal recurrence for invasive cancer cases in post-menopausal women who did not receive PMRT (comparison with Wallgren et al, 2003).**

Postmenopausal (>50)

	Wallgren 10 year Recurrence (%)	Wallgren #	Yale 5 year recurrence (%)	Yale 10 year recurrence (%)	Yale #	P value**
T1	16	152/970	0	0	0/77	<0.001
T2	22	261/1181	0	3	1/56	<0.001
T3	32	33/104	0	0*	0/7*	--
T4	--	--	0	0*	0/4*	--
N0	12	64/551	2	2	1/108	<0.001
N1	16	159/986	0	0	0/25	0.03
N2	29	146/498	0	0*	0/9*	--
N3	35	77/220	0	0*	0/2*	--

*No 10 year survivors
** 10 year Yale recurrence vs. 10 year Wallgren recurrence

Case Studies of Patients with Local Recurrence

Given the low rate of local recurrence in our study sample, it was interesting to further focus on the 7 patients with local recurrences.

Case 1

HB was diagnosed with left breast cancer at the age of 48 years old.

Initial lumpectomy revealed a 5cm tumor with positive margins. Her definitive mastectomy took place 8 months later where she underwent modified radical mastectomy with reconstruction for infiltrative ductal and lobular carcinoma. She had multifocal tumor with the size of the largest foci of invasive tumor size of 1.8 x 0.9 cm. The size of the other invasive foci was 1.1cm. Her tumor was nuclear grade 3 and histology grade 2, ER/PR negative and HER 2 positive.

Sentinel lymph node biopsy was done with 1 out of 2 nodes positive. 5 extra nodes were excised and 0/5 were positive. Tumor margins were negative. Pt declined traditional adjuvant chemotherapy in pursuit of alternative therapy. She had 6 weekly doses of Herceptin and declined further treatment with Herceptin. She did not receive post mastectomy radiation.

Local recurrence: Her local recurrence was diagnosed on routine follow up as a palpable nodule in her axilla 10 months after her mastectomy. Pathology revealed 2/3 axillary lymph nodes positive. Recurrence was similar in morphology to primary tumor and was ER negative, PR negative and Her 2 positive like the primary tumor. Staging at time of recurrence was negative.

Case 2

HA is a white woman diagnosed with left breast cancer at the age of 37 years. She underwent modified radical mastectomy about one month after diagnosis with reconstruction. She had infiltrative ductal carcinoma with the invasive component size of 1.2 x 0.8cm. Tumor was nuclear grade 2, histologic grade 1, ER positive, PR positive and Her 2 negative. One of 3 sentinel nodes were positive for micrometastasis. The resection margin was close (2mm or less). She had adjuvant chemotherapy with Doxorubicin, cyclophosphamide and paclitaxel (ACT) and tamoxifen for 5 years. She declined post mastectomy radiation.

Local recurrence: She developed a palpable nodule in the left area of her left chest 8 years and 4 months after her mastectomy. Her recurrence was found to be well differentiated infiltrative ductal carcinoma that was ER positive, PR positive and HER 2 negative, similar to her primary tumor in tumor and biologic characteristics. Staging at time of recurrence was negative and she received radiation.

Case 3

QN is a white woman diagnosed with left breast cancer at the age of 70 years. She had infiltrating ductal carcinoma that was 0.9 cm at biopsy and residual 1.5cm at mastectomy. 0/1 nodes were positive. Tumor was T2N0 , nuclear and histologic grade 2. Her surgical margins were positive. Her tumor was ER positive, PR positive and HER 2 negative. She did not have post-mastectomy radiation. There is no information on adjuvant therapy on

logician.

Local recurrence: She had recurrence in nodule in left axilla diagnosed 6 years and 3 months after mastectomy. Her recurrence was found to be poorly differentiated adenocarcinoma that was ER positive, PR positive and HER 2 negative, similar to her primary tumor.

Case 4

RP is an African American woman diagnosed with left breast cancer at the age of 34 years. Pt had lumpectomy 3 months before mastectomy. Pt had modified radical mastectomy with reconstruction. Her tumor was mucinous carcinoma, 2.2cm in size Bloom-Richardson grade 1, ER positive and PR positive. HER 2 was negative for infiltrative component but positive for intraductal component. None of the 15 nodes examined were positive (T2N0). Surgical margins were negative. There is no information on adjuvant systemic therapy on the EMR. She did not have postmastectomy radiation.

Local recurrence: She developed local recurrence 8 months after mastectomy. There is no additional information on recurrence on the electronic medical records or in the hospital tumor registry database.

Case 5

SG is a Hispanic woman diagnosed with right breast cancer at the age of 52 years when she presented with bloody nipple discharge. Her primary tumor was DCIS. She

underwent simple mastectomy with reconstruction for DCIS. The DCIS was grade 3, 2.3 cm in size, ER negative, PR negative with 0/4 nodes positive (TisN0). There were isolated tumor cells present. Surgical margins were negative. Her 2 status of her primary tumor was not on record. She did not receive PMRT.

Local recurrence: A nodule in her right lower axilla was palpated on routine exam 4 years and 3 months after mastectomy. Pt had re-excision of right chest wall recurrence that showed infiltrating ductal nuclear grade 3, ER/PR/HER 2 negative(triple negative).

Case 6

SS is a white woman who underwent mastectomy for ductal carcinoma insitu on ther left breast at the age of 53 years. Of note, patient had a history of a T2N1 right breast tumor 18 years prior for which she underwent mastectomy. Then 13 years prior to her mastectomy, she developed an infiltrative ductal carcinoma in a left breast which she underwent lumpectomy and chemotherapy with CMF and a 10 year use of tamoxifen. At the time of her most recent left sided breast cancer, she underwent simple mastectomy with negative SLNB with reconstruction for DCIS. Size of DCIS was 1.6mm and there was no residual invasive component at mastectomy. She had 0/1 nodes positive and negative surgical margins. Her tumor was nuclear grade 2. ER/PR /HER 2 status unknown. Pt did not have PMRT.

Local recurrence: Pt had a recurrence in left excision scar 2 years and 6 months after mastectomy that revealed ductal carcinoma insitu.

Case 7

RD is a white woman who was diagnosed with inflammatory breast cancer with palpable axillary adenopathy at the age of 45. She was treated with Adriamycin/Taxotere on an

every 3-week schedule for 6 cycles. She then underwent a modified radical mastectomy. Tumor pathology showed positive margins. Her tumor was ER positive, PR negative, and HER 2 negative and there was no evidence of metastases. She had adjuvant CMF for 5 cycles after which she received PMRT. She was then started on tamoxifen therapy, but she was found to have malignant right pleural effusion 9 months after mastectomy.

Local recurrence: Pt was clinically found to have recurrence of inflammatory breast cancer 1 year after mastectomy (3 months after distant metastasis was diagnosed) on her right chest wall, including nodularity. She received Taxotere and recurrence appeared to respond given reduced nodularity on physical examination.

Discussion.

Our study showed a low rate of local and distant recurrence with only 7 cases of local recurrence and 32 cases of distant recurrence.

As hypothesized, our study showed differences in distant recurrence based on differences in ER status, PR status and molecular subtypes and tumor size. As can be seen in table 7, distant recurrence was higher among ER negative, PR negative, basal like tumors and tumors with higher sizes. This result is consistent with previous studies ((Kyndi et al., 2008; Voduc et al., 2010). In a sub-group analysis of the Danish Breast Cancer Cooperative Group (BDCG) protocol 82 b and c trials, within the sub-group of 996 patients, ER negative, PR negative was associated with increased LRR and distant metastasis on univariate analysis (Kyndi et al., 2008). PR status remained significant on multivariate analysis for LRR (P=0.02) while HER 2 negative and PR status remained significant on multivariate analysis for distant metastasis. And triple negative tumor was associated with increased overall mortality (p=0.02), LRR(p=0.01) and distant

metastasis (p= 0.02) on univariate analysis while overall mortality and LRR but not distant metastasis were significant on multivariate analysis. In further sub-group analysis of patients who did not receive PMRT in the study by Kyndi et al, increased mortality, LRR and distant metastasis was seen in patients with triple negative tumors while in those randomized to PMRT (486), triple negative, was associated with increased LRR (P=0.004) but not overall mortality (P=0.7) or distant metastasis (p=0.99) . Our study did not show any significant effects of tumor size or nodal status on local recurrence. This is most likely due to the fact that as seen in our results in table 4, patients with higher T and N stages were more likely to get PMRT in the first place.

Patients who received PMRT were more likely to develop distance recurrence (p=0.01). However this is most likely due to the fact that patients who were more likely to receive PMRT were those with worse prognostic factors and higher risk for recurrence. This most likely explains why PMRT dropped off as a significant factor on multivariate analysis.

Our recurrence rates were lower than expected when compared with a widely cited study that evaluated the risk of loco-regional recurrence among women with breast cancer who underwent mastectomy and systemic therapy (if indicated) without radiation therapy (Wallgren et al., 2003).

In the study by Wallgren et al, 5, 352 women treated with modified radical mastectomy were enrolled in one of seven international breast cancer study groups. As can be seen in table 8, in the premenopausal patients who did not receive PMRT for invasive cancers, 18% (219/1209) of T1 tumors had local recurrence with or without distant recurrence at 10 years when compared to a lower 7 % (1/45) at 10 years in our study. For T2 tumors, the local recurrence rate was 5% at 10 years (1/22) lower, when compared to 25%

(3733/1510) at 10 years in the Wallgren et al study. For T3 tumors, the 10 year recurrence rate was 17% (1/5) lower when compared to the 31% (56/178) in the Wallgren et al study. Similarly when comparing by nodal status, the local recurrence rates at 10 years were 2% (1/44) and 12% (2/28) for N0 and N1 tumors in the Yale study, when compared to a much higher 14% (92/641) and 20% (267/1356) for N0 and N1 tumors respectively in the Wallgren study.

The same trends were seen in postmenopausal women as can be seen in table 9. A lower 10 year local recurrence rate of 3% (1/56) was seen in T2 tumors when compared to 22% (261/1181) in Wallgren et al. Similarly, the local recurrence rate at 10 years was 2% (1/108) for N0 tumors and 0% (0.25) for N1 tumors, lower than 12% (64/551) and 16 % (159/986) in N0 and N1 tumors respectively in Wallgren et al.

We must note that there was longer follow up in the study by Wallgren et al (median follow up 12 to 11.5 years) compared to an average follow up of just below 7 years in our study. There is a possibility that recurrences might occur later down the road among our patient population by the 10 year mark. However, most of the local recurrences in the study by Wallgren et al occurred within the first 7 years of the study, thus covering the time span that we have follow up information on the patients in our study. In a study by (Woodward et al., 2010) that examined 295 patients with known local regional recurrence to see if they were at increased risk for distant metastasis, it was found that the median time for local regional recurrence to be diagnosed was 2.2 years and 2.5 years in patients who got post mastectomy radiation and mastectomy alone. Patients in the study by Wallgren et al were recruited from older clinical trials as far back as 1978, when older chemotherapy regimens were used. This may account for the higher recurrence rates

seen in their study when compared to our study. Lower rates of recurrence have also been seen in other retrospective studies performed in recent times (Floyd et al., 2006; S. Macdonald et al., 2009; Panoff et al., 2011). A retrospective study showed a lower 10 year LRR rate of 11% in patients with 1 to 3 positive lymph nodes versus 17% seen in women with similar nodal status's in the Danish 82b trial (MacDonald et al, 2009). Also, a relatively low LRR rate of 7.6% was found in a retrospective study of patients with node negative breast tumors 5cm or greater in size, who did not receive radiation after mastectomy (Floyd, 2006). The low recurrence rates in more recent studies are probably as a result of improvements in treatment such as chemotherapy regimen, surgical techniques and use of adjuvant hormone therapy. Improved surgical techniques could result in an increase in the number of axillary lymph nodes examined and could help to better classify patients. The average number of nodes excised in the Yale cases with invasive cancers alone was 9, compared to an average of 7 lymph nodes in the Danish trial, which is thought to be low for level I and II axillary dissection (Lee & Jagsi, 2007). Our study found low rates of local recurrence among patients with DCIS alone, 2/65 (3%) . The low rate of local recurrence with DCIS seen in our study is similar to a retrospective study that examined 207 patients who underwent mastectomy for DCIS where they found a very low rate of loco-regional recurrence 2(0.9%) after a median follow up of 4.6 years. (Chadha, Portenoy, Boolbol, Gillego, & Harrison, 2012) .The effect of post mastectomy radiation on local recurrence in their sample could not be analyzed given the low rate of recurrence.

Local recurrence: Discussion of Case studies

Most of the cases of local recurrence were palpable which underscores the importance of thorough physical exam during routine follow up visits. In addition, only one of the patients received post mastectomy radiation. Most of the patients with local recurrence were lower risk patients (except the patient in case 1 with a T 3 tumor and the patient in case 7 with inflammatory breast cancer- T4). In addition, the patient in case 6 was complicated given that she had previously been diagnosed with infiltrating ductal carcinoma for which she underwent lumpectomy several years prior, and she eventually underwent mastectomy for non-invasive cancer in the same breast. Apart from the exceptional cases stated above, most of the patients with local recurrence would not have qualified for PMRT to prevent LRR if PMRT were limited to patients with tumor sizes greater than 5cm or more than 3 positive axillary lymph nodes.

Of note, the patient in case 1 highlights some of the challenges to pathologic tumor staging. HB in case one initially had a lumpectomy for a 5cm mass with positive margins at an outside hospital. She had a 1.8cm tumor at mastectomy, making her overall tumor size 6.8cm (T3 tumor). However, in a few cases, the size of a tumor at biopsy (especially if done at an outside hospital or clinic) is not added to the size of the tumor at mastectomy creating an underestimation of the size by the hospital tumor registry. This was partially the case in HB, as her tumor size was staged by the tumor registry as a T1N1 tumor (considering the tumor size of 1.8cm at mastectomy) as opposed to a T3 tumor. Fortunately in this case though, the tumor registry assigned an overall American

Joint Committee on Cancer (AJCC) staging guidelines score of 3 to the patient, thus taking into account the size of the tumor at outside biopsy. However, the T stage still remained inaccurate on their record. Therefore in our study, great effort was made to ensure correct estimation of tumor size and nodal staging by taking into account data from pathology reports found on the EMR, hospital tumor registry, as well as clinician notes that commented on tumor size and other tumor variables.

Also, the case of HB (case 1) who refused traditional adjuvant therapy is very interesting example that sheds light on the issue where some patients choose alternative therapy over traditional therapy for their breast cancer which could negatively impact their outcomes. Although, not as common in the United States, patronage of alternative medicine over traditionally known therapies for breast cancer leading to delayed presentation and delayed time to receiving definitive treatment is a big problem in developing countries and is quoted as one of the reasons for the high mortality rate from breast cancer, especially in sub-Saharan Africa(El Saghir et al., 2011; Ezeome, 2010; Sankaranarayanan, 2011; Sankaranarayanan et al., 2010).

Limitations of Study

Our study is limited by the number of patients for whom we have no follow up information. There was no information on status of local recurrence and distant recurrence in 84/443 (18.9%) cases. However as stated earlier, our comparison between the groups with known and unknown recurrence did not show any significant difference between the two groups except by degree of invasiveness where cases with unknown

recurrence status were proportionately more in the non-invasive cases. This suggests that if anything, we might be overestimating our recurrence rate.

Our study is limited by need for longer follow-up time, especially to detect distant recurrences.

Our study attempted to collect chemotherapy and hormonal therapy treatment information on patients; however there was limited availability of this information both in the electronic medical records as well as in the tumor registry database.

Conclusion

This study shows lower than expected rates of local and distant recurrence in patients who have undergone mastectomy for breast cancer in our Yale New Haven Hospital patient population. This needs to be considered when making decisions regarding post-mastectomy radiation therapy.

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