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Locoregional Outcomes in Clinical Stage IIB Breast Cancer After Neoadjuvant Therapy and Mastectomy With or Without Radiation

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Abstract: Low rates of locoregional recurrence (LRR) in patients with clinical stage IIB breast cancer (cT2N1 or cT3N0) who undergo neoadjuvant therapy (NAT) and mastectomy have been reported. We aimed to quantify the risk of LRR and the relationship between LRR and potential risk factors in this subset of patients.

We conducted a retrospective review of 116 patients with clinical IIB breast cancer who underwent NAT followed by mastectomy +/− postmastectomy radiotherapy (PMRT) between 2000 and 2009. We estimated the rate of LRR by cumulative incidence. The effect of prognostic factors was examined by Gray's test and Fine and Gray's test.

Median follow-up: 63 months. Median age: 49. 28.4% cT2N1 and 71.6% cT3N0. 62.1% of tumors were ER+, 22.6% HER2+, 19% triple negative (TN). All patients underwent NAT and mastectomy. The majority of patients (87%) received PMRT; 32.3% were treated to chest wall (CW) only, and 67.7% to CW plus supraclavicular (SCV) field.

Compared to cT2N1, patients with cT3N0 disease were more likely to be pN0 (60% vs 27%, $P = 0.005$). There was no significant relationship between risk of LRR and pathologic complete response (pCR), use of PMRT, RT to SCV field, or TN status, but there was higher risk of LRR in cT2N1 than cT3N0 (HR 6.03, $P = 0.015$).

LRR was more common in cT2N1 than in cT3N0 disease, emphasizing the negative prognostic implication of clinically node-positive presentation.

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Abbreviations: CW = chest wall, DM = distant metastasis, ER = estrogen receptor, LR = local recurrence, LRR = locoregional recurrence, NAT = neoadjuvant therapy, OS = overall survival, pCR = pathologic complete response, PFS = progression-free survival, PMRT = postmastectomy radiation, RR = regional recurrence, SCV = supraclavicular, TN = triple negative.

INTRODUCTION

Stage IIB breast cancer is a heterogeneous group comprised of stage T2N1 and T3N0 disease. While these 2 entities are grouped in the current AJCC staging, because of the difference in nodal status they may not have the same natural history and the optimal management may differ between the 2 subgroups. Postmastectomy radiotherapy (PMRT) has been shown to decrease locoregional recurrence (LRR) and improve overall survival (OS) for patients with high-risk breast cancer,[1–5] and national guidelines call for consideration of PMRT for both categories in the setting of up-front surgery, on the basis of node-positivity in the case of pT2N1, and on the basis of the large primary tumor in the case of pT3N0 (www.nccn.org). Despite the guidelines encouraging the use of PMRT in these patients, there remains debate regarding the underlying risk of LRR, and therefore the benefit of comprehensive PMRT in these patients, who have, by definition, either N0 disease or fewer than 4 lymph nodes positive.[6–8]

Neoadjuvant therapy (NAT), which historically had been reserved for patients with unresectable and/or stage III disease, is now increasingly used in the setting of stage II breast cancer. NAT is associated with similar outcomes to adjuvant chemotherapy, with the additional benefits of increasing the probability of breast conservation and of measuring response to therapy in vivo.[9,10] For those patients with clinical stage IIB disease who receive NAT and then undergo mastectomy, the risk of LRR is hotly debated. Pathologic complete response (pCR) to chemotherapy has been reported to correlate with lower rates of LRR.[11,12] At the same time, other data indicate that the risk of LRR is substantial even in the setting of pCR.[13,14]

Given these uncertainties in the risk of LRR in patients with clinical stage IIB breast cancer who undergo NAT and mastectomy, we queried our institutional breast cancer database to evaluate outcomes and risk factors for recurrence in this subset of patients, including T and N stage at presentation, as well as other established risk factors including receptor status, response to NAT, and use of PMRT.

MATERIALS AND METHODS

This retrospective analysis was approved by the University of Miami Institutional Review Board. We conducted a review of the medical records of patients with breast cancer who received PMRT between January 2000 and December 2009 at Jackson Memorial Hospital and at the University of Miami's Sylvester

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Comprehensive Cancer Center, and identified 116 patients with clinical stage IIB breast cancer who underwent NAT followed by mastectomy with or without PMRT.

Clinical breast cancer stage was determined by physical examination and imaging. Patients did not undergo sentinel lymph node biopsy before they received NAT, and fine-needle aspiration of clinically suspicious axillary lymph nodes also was not standard during the treatment period assessed but was performed in selected patients. Clinically suspicious lymph nodes that were negative on fine-needle aspiration were staged as negative (cN0). Staging was determined per the American Joint committee of Cancer TNM classification, 6th edition.

Follow-up was determined from the date of diagnosis. The date of progression was selected as the date of first event including LRR, distant metastasis (DM), or death. Local recurrence (LR) was defined as tumor recurrence in the ipsilateral chest wall (CW). Regional recurrence (RR) was defined as recurrence in the axilla, internal mammary nodes or supraclavicular (SCV) fossa. Local recurrence and RR were defined together as LRR. Progression-free survival (PFS) was defined as the elapsed time from the date of diagnosis to earliest occurrence of LRR, DM, or death from any cause. Progression-free patients were censored at most recent date of documented progression-free status. OS was defined as the time from diagnosis to death from any cause with surviving patients censored at date of last contact. PFS and OS were estimated by the Kaplan–Meier method.

The rate of LRR with or without synchronous distant failure was estimated by the method of cumulative incidence as described by Gray using the cuminc procedure in the R statistical package cmprsk,[15] with death as a competing risk. The effect of potential prognostic factors was examined by Gray's test, which compares cumulative incidence curves, or the test of Fine and Gray,[16] based on the competing risk Cox proportional hazards regression method implemented in the crr procedure in the cmprsk package. Statistical analyses were conducted using SAS software version 9.3 (SAS Institute, Inc., Cary, NC) and R software version 2.15.0.

RESULTS

Patient and Disease Characteristics—Entire Cohort

Patient demographics and tumor characteristics are shown in Table 1. Among the entire cohort, median age at diagnosis was 49 years, and 57.8% were pre- or perimenopausal. Fifteen point five percent were black, and 79.3% were Hispanic.

Tumor histology was ductal in 82% of the patients, lobular 11% and other histologies in 7%. Clinical stage was cT2N1 in 28.4% and cT3N0 in 71.6%. Estrogen receptor (ER) status was positive in 62.1%, HER-2 was positive in 22.4%, and 19.8% had triple negative (TN) tumors.

Treatment Characteristics—Entire Cohort

The NAT regimen consisted of a combination of platinum, anthracyclin, and taxane in 40.5% of patients, anthracyclin and taxane without platinum in 17.2%, hormonal therapy in 8.6%, and a trastuzumab-containing regimen in 21.6% (25 of 26 patients with HER2-overexpressing tumors).

All patients had mastectomy and axillary node dissection. The median number of lymph nodes removed was 17.

One hundred one patients (87.1%) received PMRT to the CW with or without SCV treatment, and 15 patients did not receive any form of radiotherapy. There was no significant difference in patient characteristics between those patients who received radiotherapy and those who did not, and the decision to treat was based on the recommendation of the multidisciplinary breast cancer team. Among those that received radiotherapy, 67.7% received radiotherapy to CW and SCV field and 32.3% received radiotherapy to CW only; 95% received CW boost. Median CW dose was 50.4 Gy, SCV dose 45 Gy, and CW boost dose 10 Gy.

Comparison of Patients With T3N0 vs T2N1 Disease

Table 1 shows a comparison of demographics and disease characteristics by stage. Patients with T3N0 were similar to those with T2N1 disease with respect to age, menopausal status, and tumor receptor status. Black patients more commonly presented with T2N1 disease ($P = 0.012$) while Hispanic patients were more commonly T3N0 ($P = 0.009$). The mean clinical breast tumor size was 6.7 cm for T3N0 and 3.8 cm for T2N1 ($P < 0.001$).

Table 2 shows a comparison of treatment characteristics and response to treatment by stage. A greater proportion of patients with cT3N0 received a platinum-containing chemotherapy regimen compared to those in the cT2N1 group ($P = 0.028$), but there was no significant difference in the proportion of patients receiving radiotherapy ($P = 0.358$) or the number that received SCV radiotherapy ($P = 0.053$). There was no significant difference in the pathological tumor size for those patients who were cT3N0 vs cT2N1 (2.9 vs 2.3 cm, $P = 0.231$), or the rates of pathological complete response in the breast and axilla between groups (20.5% vs 15.2%, $P = 0.509$). There was a significant difference in the number of positive lymph nodes, with more cT2N1 patients having positive lymph nodes at the time of final dissection compared to cT3N0 ($P = 0.005$).

Clinical Outcomes—Entire Cohort

The median follow-up was 63 months. Eighty-eight percent were alive at the last follow-up and 81% had no progression at the time of last follow-up.

The estimated cumulative incidence of LRR at 5 and 9 years was 2.9 (95%CI: 0.8, 7.5) and 5.7% (95%CI: 1.5, 14.3), respectively (Figure 1, left panel). There were 5 LRR in the entire cohort, all of which occurred in the group that received radiotherapy. Two LRR were local-only and 3 regional-only. One out of the 3 regional failures occurred in patients who did not receive radiation to SCV nodes. There were a total of 17 distant failures (14.7%), 5 were cT2N1 and 12 were cT3N0 (Table 3). Two cT3N0 patients had LRR after distant failure, one as local failure after 5.1 months and the other as regional failure after 6.4 months. Five-year PFS was 83.2% (95%CI: 74.3, 89.3) and OS 90.5% (95%CI: 82.4, 95.0).

Clinical Outcomes—T3N0 vs T2N1 Disease

Three of the patients with LRR were cT2N1 and 2 were cT3N0. The 3 LRRs in cT2N1 disease occurred between 2 and 3 years from diagnosis at times 25.9, 27.9, and 32 months. The 2 LRRs in cT3N0 disease occurred more than 6 years from diagnosis at times 89.5 and 141.4 months. The effect of stage was significant ($P = 0.020$ by Gray's test, hazard ratio for cT2N1 vs cT3N0 of 6.03 [95%CI: 1.41, 25.8], $P = 0.015$ by Fine and Gray's test) (Table 4). The estimated curves for cumulative incidence of LRR in T3N0 disease and in T2N1

TABLE 1. Demographics and Disease Characteristics by Clinical TN Stage

Variable	Total		T2N1		T3N0		*P* Value*
	N	%	N	%	N	%	
Total patients	116	100.0	33	100.0	83	100.0	
Age at diagnosis in years							
≤50	66	56.9	17	51.5	49	59.0	0.461
>50	50	43.1	16	48.5	34	41.0	
Mean (SD)	49.6 (9.8)		50.5 (10.6)		49.2 (9.5)		
Median (min, max)	49 (26, 78)		50 (30, 69)		49 (26, 78)		
Race							
White	92	79.3	23	69.7	69	83.1	0.012
Black	18	15.5	10	30.3	8	9.6	
Asian/other	6	5.2	—	—	6	7.2	
Ethnicity							
Hispanic	92	79.3	21	63.6	71	85.5	0.009
Non-Hispanic	24	20.7	12	36.4	12	14.5	
Menopausal status							
Premenopausal/perimenopausal	67	57.8	19	57.6	48	57.8	0.980
Postmenopausal	49	42.2	14	42.4	35	42.2	
Histology of tumor							
Ductal	92	82.1	31	93.9	61	77.2	0.139
Lobular	12	10.7	1	3.0	11	13.9	
Other	8	7.1	1	3.0	7	8.9	
Total	112	100.0	33	100.0	79	100.0	
Clinical tumor size in cm, n = 115							
Mean (SD)	5.9 (2.6)		3.8 (1.0)		6.7 (2.6)		<0.001
Medium (min, max)	6.0 (1.5, 17.0)		4 (2, 7)		6.0 (1.5, 17)		
Number of lymph node removed, n = 113							
Mean (SD)	18.2 (7.7)		16.9 (7.4)		18.6 (7.8)		0.290
Medium (min, max)	17.0 (1.0, 40.0)		17.0 (2.0, 36.0)		17.5 (1.0, 40.0)		
ER							
Positive	72	62.1	21	63.6	51	61.4	0.826
Negative	44	37.9	12	36.4	32	38.6	
PR							
Positive	32	45.7	11	55.0	21	42.0	0.324
Negative	38	54.3	9	45.0	29	58.0	
Total	70	100.0	20	100.0	50	100.0	
HER2							
Positive	26	22.4	7	21.2	19	22.9	0.845
Negative	90	77.6	26	78.8	64	77.1	
Total	116	100.0	33	100.0	83	100.0	
Triple negative							
Not triple negative	93	80.2	27	81.8	66	79.5	0.779
Triple negative	23	19.8	6	18.2	17	20.5	

* Chi-square test or Fisher's exact test.

disease are shown in Figure 1, right panel. Five-year PFS was 84.8% (95%CI: 74.1, 91.4) for T3N0 vs 79.1% (95%CI: 59, 90.1) for T2N1 (log-rank test $P = 0.201$); and 5-year OS was 91.2% (95%CI: 81.4, 96.0) for T3N0 vs 88.6 (95%CI: 68.5, 96.2) for T2N1 (log-rank test $P = 0.357$).

Predictors of Locoregional Failure

Univariate analysis was performed to assess the effect of selected variables on the risk of LRR (Table 4). Significant prognostic factors found on prior series were included as follows: pCR,[11] the use of radiotherapy,[17] radiotherapy to SCV nodes,[18] receptor status and clinical stage at presentation.[11] Only clinical stage T2N1 vs T3N0 was found to be a significant predictor factor of LRR ($P = 0.015$), with a hazard ratio for LRR of 6.03 (95%CI 1.41–25.8). Given the low number of events, we were not able to perform a multivariate analysis.

DISCUSSION

We identified a significantly higher probability of LRR in patients with clinical T2N1 breast cancer compared to those with cT3N0 disease. These data highlight the strong prognostic influence of clinical axillary nodal status, which appears in our series to be a stronger factor than primary tumor size. We have previously shown that axillary status is an important prognostic factor for LRR[18] and prior series have also shown that nodal status is a better indicator of clinical outcome compared to the response of the primary tumor.[19]

The higher risk of LRR in patients with cT2N1 compared to cT3N0 disease reported in this series differs from the results

TABLE 2. Treatment Characteristics and Response to NAT by Clinical TN Stage

Variable	Total		T2N1		T3N0		*P* Value*
	N	%	N	%	N	%	
Total patients	116	100.0	33	100.0	83	100.0	
Neoadjuvant chemotherapy regimen							
Platinum anthracycline and taxane containing	47	40.5	8	24.2	39	47.0	0.028
Anthracycline and taxane containing	20	17.2	9	27.3	11	13.3	
Herceptin containing	25	21.6	6	18.2	19	22.9	
Hormonal therapy	10	8.6	6	18.2	4	4.8	
Other or unknown	14	12.1	4	12.1	10	12.0	
Pathological tumor size in cm							
≤2	73	64.6	21	65.6	52	64.2	0.292
>2–4	21	18.6	8	25.0	13	16.0	
>4	19	16.8	3	9.4	16	19.8	
Total patients	113	100.0	32	100.0	81	100.0	
Among pathological tumor size in cm >0, n = 82							
Mean (SD)	2.7 (2.5)		2.3 (1.7)		2.9 (2.7)		0.231
Median (min, max)	2.0 (0.1, 16.0)		2.2 (0.1, 5.8)		2.0 (0.1, 16.0)		
Positive lymph nodes							
0	59	50.9	9	27.3	50	60.2	0.005
1–3	35	30.2	14	42.4	21	25.3	
4+	22	19.0	10	30.3	12	14.5	
pCR in breast and axilla							
pCR	22	19.0	5	15.2	17	20.5	0.509
No pCR	94	81.0	28	84.8	66	79.5	
pCR in axilla							
pCR	59	50.9	50	49.5	9	60.0	0.448
No pCR	57	49.1	51	50.5	6	40.0	
pCR in breast only							
pCR	9	7.8	5	15.2	4	4.8	0.116
No pCR	107	92.2	28	84.8	79	95.2	
Radiation therapy							
RT	101	87.1	27	81.8	74	89.2	0.358
No RT	15	12.9	6	18.2	9	10.8	
RT-SCV field							
SCV	67	58.8	24	72.7	43	53.1	0.053
No SCV	47	41.2	9	27.3	38	46.9	
Total patients	114	100.0	33	100.0	81	100.0	

* Chi-square test or Fisher's exact test.

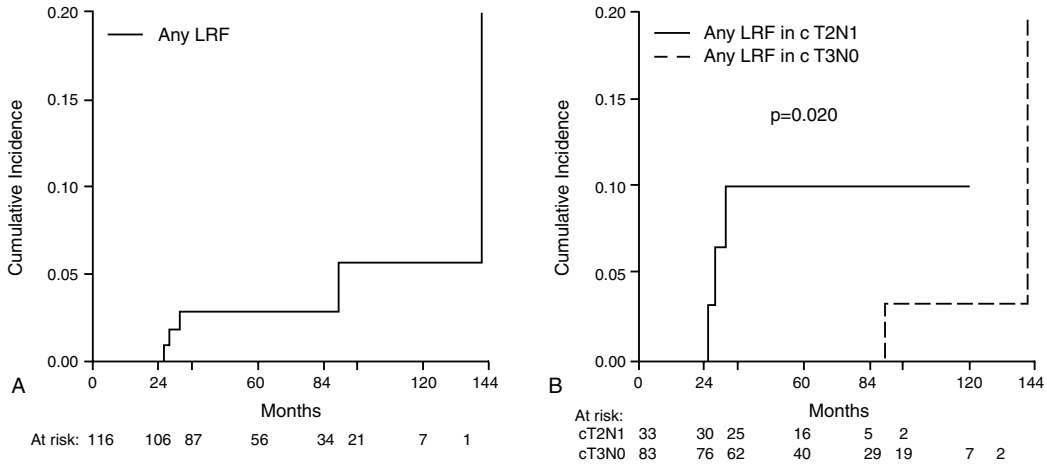
of a series reported by Garg et al,[20] which assessed patients with stage I and II breast cancer who underwent NAT and mastectomy without radiation, and showed a higher rate of LRR in patients with cT3 disease at presentation and/or 4 or more pathologic lymph nodes at the time of final dissection compared to other clinical stage I and II patients. The finding that patients with cT3 tumors had a higher rate of LRR in that series likely relates to the fact that the node-positive patients in their comparison cohort included patients with cT1N1 disease, who are often have fewer pathologically positive lymph nodes than cT2N1 disease.[15,21] There was also a higher percentage of patients with clinically node-negative disease who were found to have pathologically positive lymph nodes at the time of surgery in our series as compared to the series by Garg et al (39.8% vs 17%). These findings likely reflect a higher-risk population overall in the current series.

Another study reported by Nagar et al[22] specifically assessed outcomes in patients with cT3N0 disease who received NAT and mastectomy with or without radiation, and found a similar percent of patients with pathologically positive nodes at surgery as reported in our series, 39.8% vs 45%, reflecting a more similar patient population to the current series. That study identified the omission of PMRT as a significant predictor of LRR (4% vs 24%), as well as positive nodes after NAT.

The effect of radiotherapy on the risk of LRR could not be demonstrated in this cohort since all of the failures occurred in patients who had received PMRT. The use of radiotherapy in this cohort was based on clinician discretion, as there were no clear guidelines to delineate the use of PMRT in this population, particularly during the period assessed. Overall, 87% of the patients received PMRT. Although there were no significant differences identified between those who were treated with PMRT compared to those who did not, it is possible that those who received PMRT had additional risk factors not captured in this review that rendered them at a higher risk of recurrence.

The use of SCV radiotherapy was also not found to be a significant predictor of LRF in this series. However, given the small size of our cohort and the low number of events, we do not feel that this study is powered to draw conclusions regarding the impact of nodal RT. Sixty percent of the LRR were regional and two-thirds of those patients with regional failure (2 out of the 3 patients) did not receive SCV radiotherapy. One of these patients had a pCR to chemotherapy and received CW-only radiotherapy and was found 2 years later to have synchronous RF and DF.

Other historically described prognostic factors for LRR including pCR[11,18] and receptor status[18,20,23,24] were also not found to be significant prognostic factors in this cohort, likely



	Time Interval	Cumulative Incidence of sny LRF Rate (95% CI)
5 events of Any LRF	36 to <89.5 months	2.9% (0.8, 7.5)
	89.5 to <141.4 months	5.7% (1.5, 14.3)
	141.4 months	78.5% (0,100)
cT2N1: 3 any LRFs between 24 to <36 months	36 to 96 months	9.9% (0.8,7.5)
cT3N0: 2 any LRFs at 89.5 and 141.4 months	83.1 to <141.4 months	3.4% (0.2, 15.0)
	141.4 months	81.2% (0, 100)

FIGURE 1. Cumulative incidence of locoregional recurrence: (A) Overall and by (B) clinical stage.

secondary to the low number of events. A very low risk of LRR has been described in patients with clinical stage IIB and pCR to NAT.[11,17,22] In the current series, 1 of 5 LRR was in the setting of a pCR, in a patient whose additional risks factors included TN disease and young age (39 years).

It is also notable in our series that while there was no difference in LRR by race, black patients were more likely to present with node-positive disease. SEER analysis demonstrates that black patients are more likely to present with more advanced disease compared to whites,[25] so this finding of more node-positivity in blacks is in line with the literature, but requires further investigation.

Thus, in this small series of patients with clinically staged IIB breast cancer who underwent NAT followed by mastectomy,

TABLE 3. Failures by Clinical TN Stage

	Total		T2N1		T3N0	
Variable	N	%	N	%	N	%
Total patients	116	100.0	33	100.0	83	100.0
Vital status						
Dead	14	12.1	5	15.2	9	10.8
Alive	102	87.9	28	84.8	74	89.2
Progression						
Progressed	22	19.0	8	24.2	14	16.9
No progression	94	81.0	25	75.8	69	83.1
Local regional failures						
Yes	5	4.3	3	9.1	2	2.4
No	111	95.7	30	90.9	81	97.6
Site of local regional failures						
LF	2	1.7	1	3.0	1	1.2
RF	3	2.6	2	6.1	1	1.2
Distant failures						
Yes	17	14.7	5	15.2	12	14.5
No	99	85.3	28	84.8	71	85.5

TABLE 4. Univariate Analysis: Effect of Selected Variables on Risk of Any LRF

Prognostic Factor	Any LRF, HR (95%CI)*	*P* Value*	*P* Value†
T2N1 vs T3N0	6.03 (1.41, 25.8)	0.015	0.020
pCR vs no pCR breast and axilla	1.39 (0.15, 13.0)	0.772	0.774
pCR vs no pCR axilla	0.29 (0.03, 2.73)	0.276	0.251
ER negative vs positive	1.62 (0.29, 9.17)	0.585	0.538
Her2-negative vs positive	0.87 (0.10, 7.86)	0.902	0.860
TN vs no TN	1.54 (0.18, 13.3)	0.693	0.649
RT vs no RT	NE (all 5 LRR in RT group)	NE	0.527
RT to SCV vs no RT to SCV	2.10 (0.23, 19.1)	0.508	0.544

pCR = pathologic complete response, RT to SCV = radiation to supraclavicular field, TN = triple negative.
* HR (95%CI): Hazard ratio, corresponding 95% confidence interval and *P* value, using univariate regression models by the Fine and Gray's method for competing risks analysis, with distant alone or death as competing risks for any LRF.
† *P* value from Gray's test comparing cumulative incidence curves for 2 or more groups, taking into account competing risks.

only clinical nodal status at presentation was predictive of LRR. While the study does not elucidate novel risk factors, it highlights the strong prognostic influence of clinical axillary nodal status, which appears in our series to be a stronger factor than primary tumor size.

Our findings are limited by the retrospective nature of the study and the limited number of patients included in this cohort. Further prospective studies are required to address the role of PMRT and regional nodal radiation in patients with clinical stage IIB disease, especially in those with pathologically negative lymph nodes after NAT. Enrollment on the 2 cooperative group trials that are currently open to this population, Alliance A011202 and NRG B-51, should be strongly encouraged for all patients meeting eligibility criteria.

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