Ann Surg Oncol (2019) 26:343–355
https://doi.org/10.1245/s10434-018-07095-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

The Role of the Neo-Bioscore Staging System in Guiding the Optimal Strategies for Regional Nodal Irradiation Following Neoadjuvant Treatment in Breast Cancer Patients with cN1 and ypN0–1

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ABSTRACT

Background. The role of regional nodal irradiation (RNI) in patients with cN1 breast cancer following neoadjuvant treatment (NAT) is still controversial. The Neo-Bioscore staging system has shown promising prospect in assessing individual prognosis after NAT, and we sought to evaluate the role of Neo-Bioscore in guiding RNI following NAT.

Methods. Medical records of 163 women with cN1 and ypN0–1 disease treated with NAT between 2009 and 2014 were retrospectively reviewed and a Neo-Bioscore was assigned to each patient. Survivals were calculated using the Kaplan–Meier method and compared with the log-rank test. Multivariate analysis was used to identify independent predictors by using Cox proportional hazards models.

Results. The median follow-up after surgery was 59.4 months. Of all 163 patients, 119 received RNI. At surgery, 36 patients (22.1%) had pathological complete response (pCR), while 89 patients (54.6%) achieved ypN0. In the whole cohort, RNI significantly improved distant metastasis-free survival (DMFS) on multivariable analysis. In the subgroup of patients with a Neo-Bioscore of 1–3, RNI significantly improved the 5-year DMFS rate of 97.0% versus 76.9% ($p = 0.002$), 5-year regional node recurrence-free survival rate of 95.5% versus 76.9% ($p = 0.007$), and 5-year overall survival rate of 100% versus 89.2% ($p = 0.005$). No significant difference in outcomes was found between the RNI and non-RNI groups in patients with a score of 4–6.

Conclusions. In patients with cN1 and ypN0–1, RNI was found to significantly improve DMFS following NAT. Patients with a Neo-Bioscore of 1–3 are more likely to benefit from RNI, however a large prospective study is needed to confirm this finding.

Neoadjuvant treatment (NAT) has been increasingly applied to patients with invasive breast cancer, with therapeutic purposes including downstaging primary and nodal disease in locally advanced disease, increasing the probability of breast-conserving surgery (BCS), decreasing the extent of axillary surgery, and serving as in vivo anti-tumor therapy assessment. To date, there are no results from randomized trials addressing the role of adjuvant radiotherapy following NAT, either post-mastectomy radiotherapy (PMRT) or additional regional nodal irradiation (RNI) following BCS in patients with initial cN1. Current National Comprehensive Cancer Network (NCCN) guidelines recommend that the strategy of PMRT and RNI should be based on the maximum stage in the whole course of disease.[1] To better integrate clinical and pathological stage in patients receiving NAT remains controversial.

In our previous study, we found that PMRT significantly improved locoregional recurrence-free survival (LRRFS) following NAT in patients with cT1–2N1 disease, and was more effective in the ypN0 subgroup in terms of LRRFS,

First Received: 24 August 2018;
Published Online: 5 December 2018

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distant metastasis-free survival (DMFS), and disease-free survival;[2] however, other retrospective data did not support PMRT or RNI following NAT in patients with cN1 disease.[3–7] This inconsistency implied substantial heterogeneity in recurrence risk of cN1 patients. The Neo-Bioscore staging system is a scoring system that incorporates breast cancer biomarkers in traditional anatomic staging to produce a more comprehensive prognostic system.[8] It has been proved to outperform the American Joint Committee on Cancer (AJCC) TNM staging systems by improving prognosis stratification.[8–10]

The current study explores the value of the Neo-Bioscore staging system in identifying the role of RNI in patients with cN1 and ypN0–1 breast cancer.

PATIENTS AND METHODS

Patients

The medical records of consecutive women with cN1 category (AJCC 7th edition) breast cancer who received NAT followed by mastectomy or BCS from January 2009 through December 2015 in our institution were retrospectively reviewed. Patients were excluded for the following reasons: immediate breast reconstruction, more than four positive axillary lymph nodes (LNs) at surgery, distant metastases, previous or concurrent malignancy, and bilateral breast cancer. The pretreatment clinical stage was based on clinical examination combined with imaging studies. All patients underwent ultrasonography of regional LNs and diagnostic core biopsy of the primary tumor before NAT. This study was approved by the institutional Medicine Review Board, and waiver of consent was obtained.

Assessment of Tumor Biomarkers

Estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and histological grade status were obtained from diagnostic core biopsy. ER and PR status were assessed by immunohistochemistry (IHC) analysis. A positive result was considered as $\geq 1\%$ of cells staining positive, and a positive HER2 status was defined as an expression level intensity of 3 + on IHC or a gene amplification ratio > 2.2 by fluorescence in situ hybridization. Molecular subtypes were identified by ER, PR, and HER2 status according to the St Gallen international expert consensus.[11]

Systemic Treatment and Surgery

Sixty-eight patients received adjuvant chemotherapy, mostly following residual invasive tumor. All patients with hormone receptor (HR)-positive tumors were proposed for endocrine therapy, whereas trastuzumab was proposed to patients with HER2-positive tumors. The decision of surgical choice (mastectomy or BCS) was based on tumor characteristics and patient preference. All patients received axillary LN dissection.

Radiotherapy

Dose prescription to the whole breast/chest wall and regional nodes (supraclavicular, infraclavicular with or without internal mammary nodes) was 50 Gy in 25 fractions. A sequential tumor bed boost of 10 Gy in 5 fractions was delivered to patients treated with BCS. The decision for RNI was at the discretion of the radiation oncologist, and was usually based on increased pathologically positive LNs, poor response to NAT, or unfavorable biomarkers. Whole breast or chest wall irradiation was delivered using field-in-field forward-planned intensity-modulated radiotherapy (FiF-IMRT) using photons,[12] and tumor bed boost was administered using an anterior electron beam. Regional nodes were treated using an anterior mixed photon and electron beam. The volume delineation and definition were based on the Radiation Therapy Oncology Group guidelines.[13]

Statistical Analysis

The Neo-Bioscore staging points were determined for each patient according to the previously published work by Mittendorf et al.[8] A pathological complete response (pCR) was defined as no invasive cancer in the breast and regional LNs after surgery.

Locoregional recurrence (LRR) was defined as any first recurrence confirmed by histology or cytology within the ipsilateral chest wall and/or regional nodes. Any recurrences at distant sites were recorded as distant metastasis. Recurrence-free survival (RFS) was defined as the time from the date of surgery to any recurrence of tumor, or death from any cause, while overall survival (OS) was defined as the time from the date of surgery until death from any cause. Follow-up was calculated from the date of surgery to the first event or last confirmed date of breast cancer disease-free status.

Descriptive analysis was performed using proportion for categorical variables, and median and range for continuous variables. Differences between the RNI and non-RNI groups were evaluated using Pearson's Chi square statistics for categorical variables, and Wilcoxon rank-sum tests for

continuous variables. Survival curves were generated using the Kaplan–Meier method and were compared using the log-rank test.[14,15] Multivariate analysis (Cox proportional hazards models) were used to identify predictors for outcomes. With the exception of RNI (yes vs. no), all factors that showed evidence of association ($p < 0.10$) in the univariate analysis (log-rank test) were used in the multivariate analysis. All tests were two-sided and a p value < 0.05 was considered statistically significant. SPSS software version 16.0 was used for data analysis (SPSS Corporation, Chicago, IL, USA).

RESULTS

Patient and Treatment Characteristics

Patient and treatment characteristics regarding the receipt of RNI and response to NAT are detailed in Table 1. In total, 163 patients were included in this study, of whom 119 (73.0%) were treated with RNI. ypN0 was observed in 89 of 163 patients (54.6%) and pCR was observed in 36 of 163 patients (22.1%). More patients in the RNI group were younger than 40 years of age compared with the non-RNI group (22.7% vs. 9.8%, $p = 0.05$). Among 87 patients with HR-positive tumor, 78 (89. 7%) received endocrine therapy; 96.1% and 69.6% of patients in the RNI and non-RNI groups, respectively, received adjuvant endocrine therapy ($p = 0.001$). There was no significant difference in the Neo-Bioscore distribution between the two groups.

Radiotherapy

Overall, 111 of 145 patients received PMRT following mastectomy. Among four patients who received chest wall irradiation alone, one had pCR, two achieved ypN0, and one had cT3 disease. Twelve of 18 patients received additional RNI following BCS. At the discretion of the radiation oncologist, 53 of 119 patients in the RNI group (44.5%) received internal mammary nodes radiotherapy (IMN-RT), mainly owing to the large tumor size, increased positive LNs, and the inner or central location of the primary tumor. All patients completed radiotherapy as planned.

Patterns of Recurrence and Survival

The median follow-up time was 60 months (range 16–106), and the overall 5-year rate of LRRFS, RRFS, DMFS, RFS, and OS was 96.1%, 98.0%, 88.9%, 88.4%, and 96.2% in the whole cohort. During follow-up, six patients in the RNI group and one patient in the non-RNI group developed LRRs as the first event, including four regional recurrences (RRs; three in the RNI group and one in the non-RNI group). There were 17 distant metastases (nine in the RNI group and eight in the non-RNI group), and 11 deaths, (five in the RNI group and six in the non-RNI group). All 11 deaths were subsequent to distant metastasis from breast cancer.

Univariate and Multivariate Analysis of Outcomes

The univariate analysis is detailed in Table 2. RNI slightly improved DMFS, with a 5-year rate of 91.6% versus 81.8%; however, together with other endpoints, no significant difference in LRRFS, RRFS, DMFS, RFS, and OS was observed between the RNI and non-RNI groups. Clinical T category, clinical stage, and pathological T category were found to significantly impact LRRFS and RRFS (all $p < 0.05$). An increased number of positive LNs was significantly associated with decreased RRFS ($p = 0.03$). Pathological T category was the only predictor of DMFS ($p = 0.004$), while clinical T category, pathological T category, and pathological stage significantly influenced RFS (all $p < 0.05$). By multivariate analysis, RNI was found to be an independent predictor for increased DMFS [hazard ratio (HR) 3.20, 95% confidence interval (CI) 1.17–8.75; $p = 0.02$] (Table 3).

Benefit of Regional Nodal Irradiation According to Clinicopathological Characteristics and Neo-Bioscore

As the median value of the Neo-Bioscore was 3, the whole cohort was grouped into subgroups of patients with a Neo-Bioscore of 1–3 or 4–6 for further analysis of benefit of RNI. In total, the 5-year rate of LRRFS, RRFS, DMFS, RFS, and OS was 97.8% versus 93.9%, 98.9% versus 96.7%, 91.9% versus 85.0%, 90.8% versus 85.4%, and 97.0% versus 95.1% in the subgroup of patients with a score of 1–3 or 4–6, respectively (all $p < 0.05$). In the subgroup of patients with a score of 1–3, RNI was associated with a significant improvement in 5-year DMFS, from 76.9% to 97.0% ($p = 0.002$), 5-year RFS, from 76.9% to 95.5% ($p = 0.007$), and 5-year OS, from 89.2% to 100% ($p = 0.005$) (Fig. 1a and Table 4). However, RNI was not associated with improved therapeutic outcomes in those with a score of 4–6 (Fig. 1b and Table 4). Patients with one of the following characteristics, i.e. cT3–4, ypT3–4, clinical stage IIIA–IIIB, ER positivity, HER2 positivity, luminal subtype, three positive LNs, and absence of breast pCR, were also found to benefit from RNI in terms of improved OS, DMFS, or RFS. The subgroup analyses are detailed in Table 4.

TABLE 1 Patient and treatment characteristics

Patient characteristics	All patients		RNI		Non-RNI		*p* Value
	N = 163	%	*N* = 119	%	*N* = 44	%	
Age, years							
Median (range)	50 (23–87)		49 (23–75)		52 (36–87)		0.14
≤ 40	31	19.0	27	22.7	4	9.1	0.05
> 40	132	81.0	92	77.3	40	90.9	
Menopausal status							
Pre/peri-menopausal	89	54.6	69	58.0	20	45.5	0.15
Menopausal	74	45.4	50	42.0	24	54.5	
Histological grade							
1–2	52	31.9	39	32.7	13	29.6	0.70
3	111	68.1	80	67.2	31	70.5	
ER status							
Negative	76	46.6	55	46.2	21	47.7	0.86
Positive	87	53.4	64	53.8	23	52.3	
PR status							
Negative	117	71.8	84	70.6	33	75.0	0.58
Positive	46	28.2	35	29.4	11	25.0	
HER2 status							
Negative	102	62.6	72	60.5	30	68.2	0.37
Positive	61	37.4	47	39.5	14	31.8	
Molecular subtype							
Luminal	87	53.4	64	53.8	23	52.3	0.94
Triple-negative	42	25.8	31	26.1	11	25.0	
HER2 overexpressing	34	20.9	24	20.2	10	22.7	
Neo-Bioscore							
Median (range)	3 (1–6)		3 (1–6)		3 (1–6)		
1	10	6.1	7	5.9	3	6.8	0.97
2	31	19.0	22	18.5	9	20.5	
3	51	31.3	40	33.6	11	25.0	
4	53	32.5	35	29.4	18	40.9	
5	16	9.8	14	11.8	2	4.5	
6	2	1.2	1	0.8	1	2.3	
NAT regimen							
Taxanes	25	15.3	22	18.5	3	6.8	0.03
Anthracycline	21	12.9	16	13.4	5	11.4	
Taxanes + anthracycline	115	70.6	81	68.1	34	77.3	
Others	2	1.2	0	0	2	4.5	
Histology							
IDC	143	83.7	102	85.7	41	93.2	0.38
ILC	4	2.5	3	2.5	1	2.3	
Others	16	13.8	14	11.8	2	4.5	
Clinical T category							
T0	2	1.2	2	1.7	0	0	0.80
T1	27	16.6	19	16.0	8	18.2	
T2	101	62.0	72	60.5	29	65.9	
T3	17	10.4	13	10.9	4	9.1	
T4	16	9.8	13	10.9	3	6.8	

TABLE 1 continued

Patient characteristics	All patients		RNI		Non-RNI		*p* Value
	N = 163	%	*N* = 119	%	*N* = 44	%	
Clinical TNM stage							
IIA	29	17.8	21	17.6	8	18.2	0.85
IIB	101	62.0	72	60.5	29	65.9	
IIIA	17	10.4	13	10.9	4	9.1	
IIIB	16	9.8	13	10.9	3	6.8	
Surgery type							
Mastectomy	145	89.0	107	89.9	38	86.4	0.58
Breast-conserving	18	11.0	12	10.1	6	13.6	
Axillary surgery							
ALND	159	97.5	116	97.5	43	97.7	1.00
SLNB alone	4	2.5	3	2.5	1	2.3	
Number of sampled LNs [median (range)]	15 (2–39)		15 (5–39)		14 (2–26)		0.15
pCR							
No	127	77.9	96	80.7	31	70.5	0.16
Yes	36	22.1	23	19.3	13	29.5	
ypT Category							
T0	43	26.4	28	23.5	15	34.1	0.46
T1	71	43.6	55	46.2	16	36.4	
T2	38	23.3	27	22.7	11	25.0	
T3	7	4.3	5	4.2	2	4.5	
T4	4	2.5	4	3.4	0	0	
Number of positive LNs							
0	89	54.6	61	51.3	28	63.6	0.14
1	33	20.2	23	19.3	10	22.7	
2	21	12.9	18	15.1	3	6.8	
3	20	12.3	17	14.3	3	6.8	
Adjuvant chemotherapy							
No	95	58.3	70	58.8	25	56.8	0.82
Yes	68	41.7	49	41.2	19	43.2	
Endocrine therapy in HR + (n = 87)							
No	9	10.3	2	3.1	7	30.4	0.001
Yes	78	89.7	62	96.9	16	69.6	

RNI regional nodal irradiation, *NAT* neoadjuvant treatment, *pCR* pathological complete response, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *ALND* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *LNs* lymph nodes, *HR* + hormone receptor-positive

DISCUSSION

To our knowledge, this is the first study to evaluate the role of the Neo-Bioscore staging system in the therapeutic benefit of radiotherapy following NAT. In our study, the overall LRR rate was low and the major recurrence pattern was distant metastasis. RNI was found to be significantly associated with a decreased risk of distant metastasis in patient with cN1 and ypN0–1. RNI significantly improved DMFS, RFS, and OS in patients with better prognosis, defined as a low Neo-Bioscore of 1–3, but not in those with a score of 4–6.

Breast cancer patients with cN1 receiving NAT remains the population in which the role of radiotherapy is not clearly defined. The pooled analysis of the B-18 and B-27 trials examined the patterns of LRR as a first event in 3088 patients with cT1–3N0–1 disease who were treated with NAT without PMRT or RNI following BCS.[16] Pathological nodal status was found to be an independent predictor for LRR, with 10-year LRR varying from 0% to 12.4% in

TABLE 2 Univariate analysis of outcomes according to clinical and pathological factors

Patient characteristics	No. of patients	LRRFS		RRFS		DMFS		RFS		OS	
		5-year rate (%)	*p* Value	5-year rate (%)	*p* Value	5-year rate (%)	*p* Value	5-year rate (%)	*p* Value	5-year rate (%)	*p* Value
All patients	163	96.1		98.0		88.9		88.4		96.2	
RNI											
Yes	119	95.5	0.41	98.0	0.87	91.6	0.06	90.9	0.15	98.0	0.10
No	44	97.7		97.7		81.8		81.8		91.9	
IMN-RT											
Yes	53	100	0.28	100	0.73	92.0	0.38	92.0	0.50	97.8	0.76
No	110	94.2		96.9		87.3		86.5		95.4	
Age, years											
≤ 40	31	93.5	0.48	96.8	0.72	86.0	0.61	83.1	0.35	92.7	0.92
> 40	132	96.7		98.2		89.6		89.6		97.1	
Menopausal status											
Pre/peri-menopausal	89	96.6	0.49	98.9	0.19	89.7	0.80	88.8	0.77	95.9	0.34
Menopausal	74	95.4		96.7		87.9		87.9		96.8	
Clinical T category											
T0–2	130	98.2	< 0.001	99.0	0.005	90.9	0.07	90.1	0.04	96.1	0.20
T3–4	33	87.9		93.9		80.9		81.7		96.9	
Clinical TNM stage											
IIA	29	96.6	0.004	100	0.04	96.6	0.16	93.1	0.08	100	0.47
IIB	101	98.8		98.8		89.3		89.3		95.0	
IIIA	17	88.2		94.1		74.9		76.5		94.1	
IIIB	16	87.5		93.8		87.5		87.5		100	
Surgery type											
Mastectomy	145	95.6	0.34	97.7	0.48	88.2	0.49	87.6	0.41	96.6	0.74
Breast-conserving	18	100		100		94.4		94.4		92.9	
Tumor quadrant											
Centrally or medially	52	100	0.06	100	0.16	89.8	0.82	89.8	0.88	95.6	0.91
Others	110	94.3		97.0		88.3		87.5		96.4	
ypT Category											
T0–2	152	97.4	< 0.001	98.7	0.001	91.4	0.004	90.9	< 0.001	96.6	0.74
T3–4	11	79.5		87.5		57.3		57.3		90.9	
Number of positive LNs											
0–2	143	96.3	0.21	98.4	0.03	88.0	0.38	87.4	0.74	95.6	0.56
3	20	95.0		95.0		95.0		95.0		100	
ypTNM stage											
0–IIA	133	97.0	0.11	98.5	0.12	91.9	0.09	91.3	0.047	97.0	0.94
IIB–IIIB	30	92.3		95.5		77.4		77.4		93.3	
Tumor pCR											
No	120	96.7	0.49	97.3	0.24	87.2	0.17	87.3	0.30	96.0	0.63
Yes	43	97.6		100		93.9		91.5		96.9	
Node pCR											
No	74	95.9	0.49	98.6	0.81	92.2	0.11	85.1	0.11	95.4	0.25
Yes	89	96.3		97.5		85.2		91.4		96.9	

TABLE 2 continued

Patient characteristics	No. of patients	LRRFS		RRFS		DMFS		RFS		OS	
		5-year rate (%)	*p* Value	5-year rate (%)	*p* Value	5-year rate (%)	*p* Value	5-year rate (%)	*p* Value	5-year rate (%)	*p* Value
pCR											
No	127	95.8	0.64	97.4	0.30	87.0	0.11	87.1	0.24	95.2	0.36
Yes	36	97.1		100		96.2		93.3		100	
Histological grade											
1–2	52	96.1	0.82	100	0.15	91.7	0.38	89.7	0.52	100	0.58
3	111	96.1		97.0		87.4		87.7		94.2	
ER status											
Negative	76	94.2	0.53	98.2	0.41	88.4	0.83	87.1	0.81	95.3	0.42
Positive	87	97.7		97.7		89.4		89.6		97.0	
HER2 status											
Negative	107	97.2	0.53	99.1	0.39	90.4	0.69	90.4	0.56	96.4	0.84
Positive	56	94.0		95.8		86.3		84.9		95.9	
Molecular subtype											
Luminal	87	97.7	0.77	97.7	0.48	89.4	0.92	89.6	0.96	97.0	0.72
Triple-negative	42	95.2		100		86.8		86.8		93.9	
HER2 overexpressing	34	92.9		96.0		90.2		87.2		97.1	
Neo-Bioscore											
1–3	92	97.8	0.14	98.9	0.22	91.9	0.19	90.8	0.21	97.0	0.97
4–6	71	93.9		96.7		85.0		85.4		95.1	
Trastuzumab therapy in HER2+											
No	22	90.9	0.82	90.9	0.55	80.7	0.59	81.0	0.72	94.7	0.89
Yes	37	93.5		96.3		91.0		88.2		97.3	
Unknown	2	100		100		100		100		100	
Adjuvant chemotherapy											
No	95	97.4	0.16	97.4	0.98	91.1	0.27	91.1	0.12	94.6	0.40
Yes	68	94.1		98.5		86.2		84.8		98.3	
Endocrine therapy											
No	81	94.6	0.66	98.3	0.33	86.7	0.14	85.2	0.80	92.1	0.09
Yes	82	97.6		97.6		91.2		94.1		100	

LRRFS locoregional recurrence-free survival, *RRFS* regional recurrence-free survival, *RFS* recurrence-free survival, *DMFS* distant metastasis-free survival, *OS* overall survival, *IMN-RT* internal mammary nodes radiotherapy, *RNI* regional nodal irradiation, *pCR* pathological complete response, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *LNs* lymph nodes

ypN0, and sustained above 10% in ypN1. These data indirectly implied that if LRR is to be taken as the therapeutic endpoint, patients with ypN1 might be good candidates for RNI. However, in our study, RNI was found to improve DMFS without significant benefit in lowering LRR and RR, regardless of pathological nodal status and pCR. With a 5-year rate of 3.9%, the LRR risk in our study is much lower than that in the B-18 and B-27 trials, which might attribute to better systemic therapy[17–19] and overall lower risk in our cohorts (the majority of patients had cT1–2 and more than half had ypN0). Similar to our results, a number of recent published studies also found no significant locoregional control difference with or without RNI following NAT in patients with cN1 disease.[7,20–22] A significant characteristic in prospective trials evaluating the role of RNI with modern systemic therapy is a significant amelioration in DMFS that is not always in proportion with a reduction in LRR.[23–25] In such a context, the endpoint of therapeutic benefit to decide the role of RNI should not be limited by LRR but rather distant disease control. The clinical benefit of RNI observed in our study is more consistent with modern studies and therapeutic expectations.

The Neo-Bioscore staging system was developed to use the ER, HER2 status and histological grade biomarkers, in combination with pre-treatment clinical and post-treatment pathological anatomical stage, to predict outcomes following NAT.[8] Compared with anatomic stage alone, the

TABLE 3 Multivariate analysis of outcomes

Patient characteristics	LRRFS			RRFS			DMFS			RFS			OS		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
RNI (yes vs. no)	1.57	0.18–13.80	0.68	1.63	0.18–14.62	0.66	3.20	1.17–8.75	0.02	2.62	1.00–6.88	0.05	2.33	0.70–7.71	0.17
cT Category (T0–2 vs. T3–4)	6.63	1.06–41.32	0.04	6.75	1.08–42.01	0.04	1.89	0.63–5.70	0.26	1.84	0.64–5.24	0.26			
ypT Category (T0–2 vs. T3–4)	3.59	0.66–19.72	0.14	3.88	0.62–24.31	0.15	4.31	1.23–15.10	0.02	4.90	1.53–15.67	0.007			
Number of positive LNs (0–2 vs. 3)				1.22	0.18–8.24	0.84							2.66	0.71–10.23	0.15
Endocrine therapy (yes vs. no)															

LRRFS locoregional recurrence-free survival, *RRFS* regional recurrence-free survival, *RFS* recurrence-free survival, *DMFS* distant metastasis-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *RNI* regional nodal irradiation, *LNs* lymph nodes

FIG. 1 Kaplan–Meier survival curve of LRRFS, RRFS, DMFS, RFS, and OS according to receipt of RNI. Outcomes in patients with a Neo-Bioscore of (**a**) 1–3 and (**b**) 4–6 (statistical comparison between the survival curves was made using the log-rank test). *LRRFS* locoregional recurrence-free survival, *RRFS* regional recurrence-free survival, *DMFS* distant metastasis-free survival, *RFS* recurrence-free survival, *OS* overall survival, *RNI* regional nodal irradiation, *CI* confidence interval ▶

Neo-Bioscore staging system was found to be more powerful in separating outcomes in a cohort of 2377 breast cancer patients treated with NAT at the MD Anderson Cancer Center, and further validated in a cohort of 43,320 patients obtained through the National Cancer Database (NCDB).[8–10] Based on these findings, we explored whether the Neo-Bioscore staging system can also serve to better define the role of post-surgical radiotherapy in patients with cN1 receiving NAT. With this study, we found that the Neo-Bioscore staging system did have the potential to individualize the therapeutic benefit of RNI following NAT. RNI was found to significantly improve DMFS by multivariate analysis in the whole population of patients with cN1 and ypN0–1. For patients with a Neo-Bioscore of 1–3, RNI significantly improved DMFS, RFS, and OS, and reduced the risk of RR with borderline significance. It seems that patients with 'good' rather than 'poor' prognosis benefit more from RNI. This finding reminds us of the results of the re-analysis of 3083 breast cancer patients in the Danish Breast Cancer Cooperative Group (DBCG) 82b and 82c trials.[20] After a median follow-up of 17 years, PMRT resulted in the smallest (11%) absolute reduction of 5-year LRR in the 'good' prognosis group, and the largest absolute reduction in the 'poor' prognosis group (36%), which also resulted in the biggest (11%) 15-year absolute reduction of breast cancer mortality in the 'good' prognosis group, but a 0% reduction in the 'poor' prognosis group. Similar to the Neo-Bioscore staging system, their prognostic definition combined the T/N category with histological grade, and HR and HER2 status. Our previous study also found that PMRT was more effective in patients with better response to NAT in terms of LRRFS, DMFS, and RFS.[2] A possible explanation for this was that the benefit of radiotherapy to eradicate the metastatic potential can be better exerted in tumors with good prognosis, while in patients with a co-existing high risk of distant micrometastases, the therapeutic potential of locoregional radiotherapy would be less optimistic. The study population in the MA.20 and EORTC 22922/10925 trials are at lower risk compared with previous studies of PMRT, however the therapeutic benefit in reducing breast recurrence was significant.[23,24] The hypothesis that the therapeutic benefit of radiotherapy is beyond locoregional control has also been proposed in its effect for decreasing

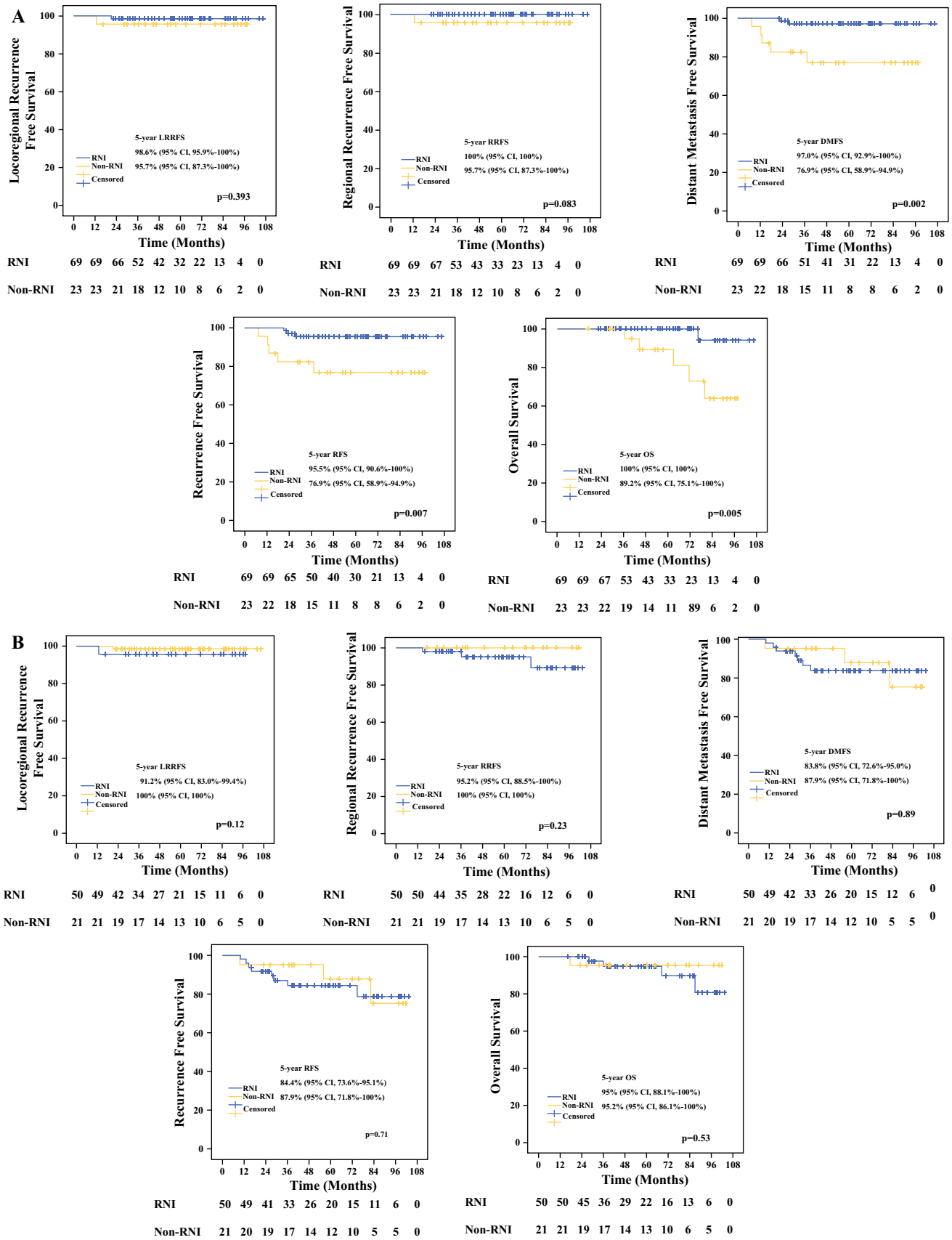
A
Locoregional Recurrence Free Survival
5-year LRRFS
98.6% (95% CI, 95.9%-100%)
95.7% (95% CI, 87.3%-100%)
p=0.393
RNI 69 69 66 52 42 32 22 13 4 0
Non-RNI 23 23 21 18 12 10 8 6 2 0
Regional Recurrence Free Survival
5-year RRFS
100% (95% CI, 100%)
95.7% (95% CI, 87.3%-100%)
p=0.083
RNI 69 69 67 53 43 33 23 13 4 0
Non-RNI 23 23 21 18 12 10 8 6 2 0
Distant Metastasis Free Survival
5-year DMFS
97.0% (95% CI, 92.9%-100%)
76.9% (95% CI, 58.9%-94.9%)
p=0.002
RNI 69 69 66 51 41 31 22 13 4 0
Non-RNI 23 22 18 15 11 8 8 6 2 0
Recurrence Free Survival
5-year RFS
95.5% (95% CI, 90.6%-100%)
76.9% (95% CI, 58.9%-94.9%)
p=0.007
RNI 69 69 65 50 40 30 21 13 4 0
Non-RNI 23 22 18 15 11 8 8 6 2 0
Overall Survival
5-year OS
100% (95% CI, 100%)
89.2% (95% CI, 75.1%-100%)
p=0.005
RNI 69 69 67 53 43 33 23 13 4 0
Non-RNI 23 23 22 19 14 11 89 6 2 0
B
Locoregional Recurrence Free Survival
5-year LRRFS
91.2% (95% CI, 83.0%-99.4%)
100% (95% CI, 100%)
p=0.12
RNI 50 49 42 34 27 21 15 11 6 0
Non-RNI 21 21 19 17 14 13 10 6 5 0
Regional Recurrence Free Survival
5-year RRFS
95.2% (95% CI, 88.5%-100%)
100% (95% CI, 100%)
p=0.23
RNI 50 50 44 35 28 22 16 12 6 0
Non-RNI 21 21 19 17 14 13 10 6 5 0
Distant Metastasis Free Survival
5-year DMFS
83.8% (95% CI, 72.6%-95.0%)
87.9% (95% CI, 71.8%-100%)
p=0.89
RNI 50 49 42 33 26 20 15 12 6 0
Non-RNI 21 20 19 17 14 12 10 5 5 0
Recurrence Free Survival
5-year RFS
84.4% (95% CI, 73.6%-95.1%)
87.9% (95% CI, 71.8%-100%)
p=0.71
RNI 50 49 41 33 26 20 15 11 6 0
Non-RNI 21 20 19 17 14 12 10 5 5 0
Overall Survival
5-year OS
95% (95% CI, 88.1%-100%)
95.2% (95% CI, 86.1%-100%)
p=0.53
RNI 50 50 45 36 29 22 16 13 6 0
Non-RNI 21 21 19 17 14 13 10 6 5 0
Time (Months)
RNI
Non-RNI
Censored

TABLE 4 Subgroups analysis of benefit from RNI

Subgroups	No. of patients	LRRFS			RRFS			DMFS			RFS			OS		
		5-year rate (%)		*p* Value	5-year rate (%)		*p* Value	5-year rate (%)		*p*-Value	5-year rate (%)		*p* Value	5-year rate (%)		*p* Value
		RNI	No-RNI		RNI	No-RNI		RNI	No-RNI		RNI	No-RNI		RNI	No-RNI	
All patients	163	95.5	97.7	0.41	98.0	97.7	0.87	91.6	81.8	0.06	90.9	81.8	0.15	98.0	91.9	0.10
Neo-Bioscore																
1–3	92	98.6	95.7	0.39	100	95.7	0.08	97.0	76.9	0.002	95.5	76.9	0.007	100	89.2	0.005
4–6	71	94.0	100	0.12	95.2	100	0.23	83.8	87.9	0.89	84.4	87.9	0.71	95.0	95.2	0.53
Age, years																
≤ 40	31	92.6	100	0.58	96.3	100	0.70	88.0	75.0	0.26	84.5	75.0	0.45	96.0	66.7	0.08
> 40	132	96.3	97.5	0.56	98.5	97.5	0.99	92.8	82.5	0.07	92.8	82.5	0.13	98.5	94.1	0.21
Clinical T category																
T0–2	130	97.5	100	0.37	98.6	100	0.52	92.9	86.0	0.22	91.8	86.0	0.32	97.8	93.9	0.26
T3–4	33	88.5	85.7	0.81	96.2	85.7	0.75	87.2	57.1	0.049	88.5	57.1	0.17	100	50.0	0.03
Clinical TNM stage																
IIA	29	95.2	100	0.54	100	100	1.00	95.2	100	0.54	90.5	100	0.38	100	100	0.41
IIB	101	98.2	100	0.53	98.2	100	0.53	92.2	81.6	0.12	92.2	81.6	0.12	96.8	90.3	0.22
IIIA	17	84.6	100	0.29	92.3	100	0.40	82.1	50.0	0.14	84.6	50.0	0.38	100	75.0	0.02
IIIB	16	92.3	66.7	0.19	100	66.7	0.04	92.3	66.7	0.19	92.3	66.7	0.19	100	100	0.56
Surgery type																
Mastectomy	145	95.0	97.4	0.42	97.8	97.4	0.86	90.7	82.0	0.13	89.9	82.0	0.28	97.7	93.9	0.25
Breast-conserving	18	100	100	1.00	100	100	1.00	100	83.3	0.16	100	83.3	0.16	100	75.0	0.11
Number of positive LNs																
0–2	143	94.7	100	0.15	97.7	100	0.35	90.1	83.0	0.21	89.4	83.0	0.29	97.6	91.4	0.27
3	20	100	66.7	0.14	100	66.7	0.14	100	66.7	0.02	100	66.7	0.14	100	100	0.08
ypT Category																
T0–2	152	97.3	97.6	0.91	99.1	97.6	0.47	93.0	87.4	0.14	92.3	87.4	0.21	97.8	93.9	0.26
T3–4	11	76.2	100	0.55	85.7	100	0.71	76.2	50.0	0.05	76.2	0	0.05	100	50.0	0.03
ypTNM stage																
0–IIA	133	96.9	97.3	0.91	99.0	97.3	0.48	94.3	85.5	0.05	93.5	85.5	0.09	98.6	92.9	0.16
IIB–IIIB	30	89.7	100	0.31	93.8	100	0.39	81.2	68.6	0.62	81.2	68.6	0.83	95.7	85.7	0.34
Tumor pCR																
No	120	95.2	96.6	0.62	97.4	96.6	0.97	90.4	77.2	0.04	90.6	77.2	0.06	98.8	88.4	0.07
Yes	43	96.4	100	0.48	100	100	1.00	95.7	90.0	0.59	92.0	90.0	1.00	95.5	100	0.67
Node pCR																
No	74	96.6	93.8	0.93	100	93.8	0.40	89.1	73.1	0.05	89.1	73.1	0.10	100	90.6	0.09
Yes	89	94.6	100	0.24	96.3	100	0.33	94.2	88.2	0.32	92.9	88.2	0.50	95.8	93.8	0.33

TABLE 4 continued

Subgroups	No. of patients	LRRFS			RRFS			DMFS			RFS			OS		
		5-year rate (%)		*p* Value	5-year rate (%)		*p* Value	5-year rate (%)		*p*-Value	5-year rate (%)		*p* Value	5-year rate (%)		*p* Value
		RNI	No-RNI		RNI	No-RNI		RNI	No-RNI		RNI	No-RNI		RNI	No-RNI	
pCR																
No	127	95.5	96.8	0.61	97.6	96.8	0.96	89.8	80.6	0.05	90.0	78.6	0.10	100	100	0.26
Yes	36	95.7	100	0.47	100	100	1.00	100	88.9	0.17	95.7	88.9	0.66	97.5	89.0	0.13
Histological grade																
1–2	52	94.8	100	0.41	100	100	1.00	94.7	83.1	0.26	92.0	83.1	0.46	100	100	0.26
3	111	95.8	96.8	0.65	97.0	96.8	0.84	90.0	81.3	0.12	90.3	81.3	0.21	96.9	88.0	0.24
ER status																
Negative	76	92.0	100	0.21	97.5	100	0.54	87.5	90.5	0.86	85.6	90.5	0.71	95.3	95.2	0.78
Positive	87	98.4	95.7	0.90	98.4	95.7	0.90	95.1	75.8	0.008	95.3	75.8	0.03	100	90.2	0.04
HER2 status																
Negative	107	97.2	100	0.22	100	100	0.41	89.6	92.6	0.92	89.6	92.6	0.71	96.5	96.2	0.66
Positive	56	93.1	92.9	0.86	95.2	92.9	0.61	94.9	53.6	< 0.001	93.1	53.6	0.002	100	81.3	< 0.001
Molecular subtype																
Luminal	87	98.4	95.7	0.90	98.4	95.7	0.90	95.1	75.8	0.008	95.3	75.8	0.03	100	90.2	0.04
Triple-negative	42	93.5	100	0.40	100	100	1.00	82.0	100	0.16	82.0	100	0.16	91.6	100	0.19
HER2 overexpressing	34	90.5	100	0.40	94.7	100	0.57	94.7	80.0	0.11	90.5	80.0	0.27	100	90.0	0.02
Targeted therapy in HER2+																
No	22	92.9	87.5	0.65	92.9	87.5	0.65	92.9	50.0	0.04	92.9	50.0	0.04	100	80.0	0.01
Yes	37	92.7	100	0.61	95.8	100	0.72	95.8	60.0	0.002	92.7	60.0	0.009	100	80.0	< 0.001

LRRFS locoregional recurrence-free survival, *RRFS* regional recurrence-free survival, *RFS* recurrence-free survival, *DMFS* distant metastasis-free survival, *OS* overall survival, *RNI* regional nodal irradiation, *pCR* pathological complete response, *ER* estrogen receptor, *HER2* human epidermal growth factor receptor 2, *LNs* lymph nodes

any first recurrence and improving survival.[26–28] In their recent retrospective study, Stecklein et al.[29] reported a significant reduction of any recurrence associated with RNI following NAT in 1289 patients with cN+ disease.

Similar to the Neo-Bioscore, another score has been developed to incorporate biomarkers with clinical and pathological staging so as to improve the efficacy of predicting LRR following NAT. In an international collaborative meta-analysis, Valachis et al.[30] found that ER negativity with other unfavorable anatomical factors was predictive of LRR after NAT and BCS. The number of total risk factors in each patient can thus help to quantify individual recurrence risk.

Apart from the Neo-Bioscore, biomarkers such as ER positivity, HER2 positivity and luminal subtype also predicted benefit from RNI. Data from the DBCG 82b and 82c trials found that PMRT was most effective in patients with ER/PR-positive, HER2-negative disease prior to anti-HER2 therapy.[31] As Poortmans has proposed, subsequent to effective systemic therapy that has decreased the risk of distant metastasis, optimized locoregional therapy will contribute more to survival.[32] Subgroups who benefited from RNI in our study is in accord with the above hypothesis, which implies that the significance of comprehensive locoregional therapy should not be neglected in these patients.

As a retrospective study, we do have several limitations. An imbalance in sample size existed between the RNI and non-RNI groups, which might reduce our statistical power. Partly due to the incomplete coverage of social security systems, not all patients with HER2-positive tumors received trastuzumab, which might weaken the predictive value of the Neo-Bioscore staging system. Furthermore, the median follow-up in our study was 5 years, which might underestimate the overall recurrence rate and mortality. Further follow-up, as well as prospective and large-sample studies, are necessary to verify the value of the Neo-Bioscore staging system in the therapeutic decision to undergo radiotherapy in these patients.

CONCLUSIONS

RNI was found to significantly improve DMFS following NAT in patients with cN1 and ypN0–1. For the subgroup of patients with a low Neo-Bioscore (1–3), RNI was associated with improved prognosis in terms of DMFS, RFS, and OS.

ACKNOWLEDGMENT This study was supported in part by the National Natural Science Foundation of China (Grants 81172504, 81673102, and 81602791), National Key Research and Development Program of China (Grant 2016YFC0105409), Youth Foundation of Shanghai Health and Family Planning Commission (Grant 20164Y0066), and Clinical Research Plan of Shanghai Hospital Development Center (Grant 16CR1037B).

DISCLOSURE None.

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