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ORIGINAL ARTICLE – BREAST ONCOLOGY

Prognostic Significance of Residual Axillary Nodal Micrometastases and Isolated Tumor Cells After Neoadjuvant Chemotherapy for Breast Cancer

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ABSTRACT

Background. The prognostic significance of low-volume residual nodal disease following neoadjuvant chemotherapy (NAC) is unknown.

Methods. Women with cT1–4N0–1 breast cancer treated with NAC were identified from Dana-Farber/Brigham and Women's Cancer Center (DFBWCC) and the National Cancer Database (NCDB). Disease-free survival (DFS) and overall survival (OS) estimates according to pathologic nodal status were calculated using the Kaplan–Meier method, with Cox proportional hazards regression used to assess the effect of clinical variables on survival outcomes.

Results. Among 967 DFBWCC patients, 27 (2.8%) had residual isolated tumor cells (ITCs) and 61 (6.3%) had micrometastases. Five-year DFS was significantly worse in those with residual ITCs (73.5%) and micrometastases (74.7%) relative to those who were ypN0 following NAC (88.4%, $p < 0.001$). On adjusted analysis, those with residual ITCs (hazard ratio [HR] 2.4, 95% confidence interval [CI] 1.20–3.81) and micrometastases (HR 2.14, 95% CI 1.20–3.81) had increased risk of recurrence relative to ypN0 patients. Among 35,536 NCDB patients, 543 (1.5%) had ITCs and 1132 (3.2%) had micrometastases. Five-year OS estimates were significantly worse with increasing residual nodal burden: ypN0, 88.9%; ypN0[i+], 82.8%; ypN1mi, 79.5%; ypN1, 77.6% ($p < 0.001$). Compared with patients with ypN0 disease, NCDB patients with ITCs and micrometastases had 1.9- and 2.2-fold risk of death ($p < 0.001$). On subgroup analysis, the effect of low-volume residual disease on mortality was most pronounced in patients with triple-negative and human epidermal growth factor receptor 2 (HER2)-positive disease.

Conclusions. Low-volume residual nodal disease following NAC is associated with poorer DFS and OS relative to those who are node negative.

The clinical significance of low-volume residual nodal disease following neoadjuvant chemotherapy (NAC) has not been established. Unlike the upfront surgical setting, where patients with isolated tumor cells (ITCs, < 0.2 mm) and micrometastases (0.2–2.0 mm) demonstrate oncologic outcomes similar to those who are pathologically node negative,[1,2] there is uncertainty regarding whether patients with low-volume nodal metastases following NAC represent a select group of patients with treatment-resistant disease who may have inferior outcomes.[3–5] In an early report from the NSABP B-18 trial, both disease-free survival (DFS) and overall survival (OS) were shown to be significantly worse in patients who had residual micrometastases following NAC, relative to those with

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node-negative disease.[3] In contrast, recent population-based studies contend that patients with ITCs and micrometastases following NAC may carry a similar prognosis to node-negative patients.[6]

Here we report a joint analysis of our single-institution experience of women with residual low-volume nodal metastases following NAC, combined with results from a large population-based cohort of women with ITCs and micrometastases derived from the National Cancer Database (NCDB). The objective of this study is to determine the impact of residual ITCs and micrometastases on recurrence and survival outcomes in patients receiving NAC in the modern era. As clinical nodal status at presentation suggests different degrees of baseline nodal involvement, subgroup analyses were performed in patients who were clinically node negative (cN0) and clinically node positive (cN1). Further analyses were also undertaken to establish the prognostic significance of residual nodal metastases across the various breast cancer biologic subtypes.

PATIENTS AND METHODS

Following Institutional Review Board approval, we retrospectively reviewed the medical records of female patients with cT1–4N0–1 breast cancer treated with NAC followed by surgery at Dana Farber/Brigham and Women's Cancer Center (DFBWCC) from 2002 to 2014. Patients with inflammatory breast cancer (T4d) or those who had nodal surgery prior to NAC were excluded from the analysis. Clinical N1 (cN1) disease was defined as biopsy-proven nodal metastases, either by fine-needle aspiration or core biopsy performed prior to initiation of NAC. A second cohort was then identified from the NCDB, including women with a first diagnosis of histologically proven cT1–3cN0–1 breast cancer treated with NAC from 2005 to 2015. Patients who lacked complete information related to primary surgery, final axillary pathology, and hormone receptor (HR) status were excluded. Patients with significant medical comorbidities were also excluded; only those with Charlson comorbidity index of 0 were retained for analysis.[7,8] In the NCDB cohort, cN1 disease was defined as presence of one or more movable ipsilateral level I–II axillary nodes with characteristics highly suspicious for malignancy on imaging or clinical examination, or presence of fine-needle aspiration or core-needle biopsy-proven metastases. Because the NCDB utilizes anonymized data with no personal identifiers, the population-based cohort was considered exempt from the DFBWCC Institutional Review Board.

In both cohorts, patients were divided into five groups based on final pathologic nodal status following NAC: node negative (ypN0), ITCs (ypN0[i+]), micrometastases (ypN1mi), macrometastases to 1–3 lymph nodes (ypN1), and macrometastases to 4 or more lymph nodes (ypN2–3). The DFBWCC cohort was used to examine locoregional recurrence-free survival (LRRFS), disease-free survival (DFS), and overall survival (OS) across pathologic nodal groups. LRRFS was defined as the number of months from date of diagnosis to date of ipsilateral breast and/or regional nodal recurrence or death due to any cause. DFS was defined as the number of months from date of diagnosis to date of locoregional or distant recurrence, new primary breast cancer, or death due to any cause, whichever occurred first. In both cohorts, OS was determined by the number of months from date of cancer diagnosis to date of death from any cause, with the population-based NCDB cohort used to refine OS estimates and provide a large enough sample to permit subgroup analysis. Patients without an event were censored at date of last contact. Five-year unadjusted survival rates were estimated using the Kaplan–Meier method. Cox regression models were then fit to model DFS and OS based on pathologic nodal groups, with adjustment for biologic subtype, in-breast pathologic complete response (pCR), and adjuvant radiation therapy. We then performed subgroup analyses by clinical node status at presentation and biologic subtype; for the latter, adjuvant endocrine therapy was also incorporated into the multivariable model for HR-positive subtypes. All statistical analyses were performed using SAS version 9.4 (Cary, NC) with all statistical tests two-sided and a p value of 0.05 used to indicate statistical significance.

RESULTS

Data were obtained for 967 women in the DFBWCC cohort and 35,536 women in the NCDB diagnosed with stage I–III breast cancer and treated with NAC followed by surgery. Clinicopathologic characteristics of all patients are presented in eTable 1. The axillary pCR rate for patients with cN1 disease was 35.8% in both cohorts. In the DFBWCC cohort, pathologic nodal evaluation demonstrated residual ITCs in 27 (2.8%) patients and residual micrometastases in 61 (6.3%) patients. In the NCDB cohort, residual ITCs were reported in 543 (1.5%) and micrometastases in 1132 (3.2%) patients. Median follow-up was 5.3 years (range 0.3–13.8 years) in the DFBWCC cohort, and 3.7 years (range 0.3–10.9 years) in the NCDB cohort.

Dana-Farber/Brigham and Women's Cancer Center Cohort

Surgical Management Among 475 cN0 patients in the DFBWCC cohort, 313 (65.9%) underwent sentinel lymph node biopsy (SLNB) while 162 (34.1%) underwent axillary lymph node dissection (ALND). Among 492 cN1 patients in the DFBWCC cohort, 47 (9.6%) underwent SLNB and 445 (90.4%) underwent ALND. Definitive axillary management according to final nodal pathology is detailed in eTable 2. Among 524 patients who were ypN0, 197 (37.6%) underwent definitive ALND, compared with 19 (70.4%) of 27 patients with ypN0[i+] disease, 49 (80.3%) of 61 ypN1mi patients, and 208 (94.1%) of 221 ypN1 patients. All ypN2–3 patients underwent ALND.

Survival Outcomes Five-year LRRFS, DFS, and OS for the 967 patients within the DFBWCC cohort are summarized in Table 1. Five-year LRRFS was 95.7% (95% CI 93.2–97.2%) for those with ypN0 disease, with similar rates seen in those with ITCs (95.2%; 95% CI 70.7–99.3%) and micrometastases (96.6%; 95% CI 87.0–99.1%). Increasing residual nodal disease was associated with higher rates of breast cancer recurrence, with 5-year DFS estimates decreasing from 88.4% in ypN0 disease to 73.5% in ypN0[i+], 74.7% in ypN1mi, 69.5% in ypN1, and 57.4% in residual ypN2–3 disease (Table 1). On adjusted analyses controlling for breast pCR, biologic subtype, and adjuvant radiation, patients with ITCs had significantly poorer DFS relative to those with ypN0 disease (hazard ratio 2.36, 95% CI 1.01–5.51) (Table 2). Similar findings were demonstrated in those with residual micrometastases (hazard ratio 2.14, 95% CI 1.20–3.81), whose clinical behavior was more similar to those with ypN1 disease (hazard ratio 3.13, 95% CI 2.15–4.57). This did not translate into significantly worse 5-year OS relative to those with ypN0 or ypN1 disease given the low number of events (Table 2). As expected, patients with ypN2–3 disease had inferior outcomes.

National Cancer Database Cohort

Survival Outcomes In the NCDB cohort of 35,536 women, residual nodal disease was associated with significantly worse 5-year OS, decreasing from 88.9% in ypN0 disease to 82.8% in ypN0[i+], 79.5% in ypN1mi, 77.6% in ypN1, and 61.6% in ypN2–3 disease (Table 3). On multivariable analysis, presence of residual ITCs or micrometastases was associated with 1.9-fold (95% CI 1.39–2.59) and 2.2-fold (95% CI 1.76–2.70) increased risk of death relative to those who were pathologically node negative (Table 2). This effect persisted across both cN0 and cN1 subgroups, with cN1 patients demonstrating slightly worse 5-year overall survival rates relative to cN0 patients (Table 3; Fig. 1). Among cN0 patients, those with ITCs and micrometastases after NAC experienced a 66% and 85% increase in mortality, as compared with patients who were ypN0. Similarly, among cN1 patients, the relative increase in mortality for residual ypN0[i+] and ypN1mi disease was 81% and 97%, respectively (eTable 3).

On subgroup analysis exploring the effect of low-volume residual nodal disease across different biologic subtypes, presence of either ITCs or micrometastases strongly predicted poorer prognosis in triple-negative breast cancer patients (Fig. 2). Micrometastases were also independently associated with worsened overall survival in patients with HR-positive/HER2-negative and HR-negative/HER2-positive disease (eTable 4; Fig. 2).

TABLE 1 Survival outcomes by pathologic nodal group following neoadjuvant chemotherapy, DFBWCC 2004–2012 (n = 967)

Pathologic nodal status	Total no. of patients	5-Year locoregional recurrence-free survival (LRRFS)			5-Year disease-free survival (DFS)			5-Year overall survival (OS)		
		No. events/no. at risk at 5 years	LRRFS	(95% CI)	No. events/no. at risk at 5 years	DFS	(95% CI)	No. events/no. at risk at 5 years	OS	(95% CI)
ypN0	524	19/286	95.7	(93.2–97.2)	55/286	88.4	(85.2–91.0)	31/307	93.3	(90.6–95.3)
ypN0[i+]	27	1/13	95.2	(70.7–99.3)	6/13	73.5	(49.8–87.3)	2/21	91.5	(70.0–97.8)
ypN1mi	61	2/30	96.6	(87.0–99.1)	13/30	74.7	(60.1–84.7)	5/37	90.1	(77.5–95.8)
ypN1	221	16/90	90.8	(85.3–94.3)	60/90	69.5	(62.3–75.5)	41/111	78.7	(72.1–83.9)
ypN2–3	134	17/50	84.3	(75.6–90.0)	52/50	57.4	(47.9–65.8)	36/69	70.0	(60.8–77.4)

CI confidence interval, *DF/BWCC* Dana-Farber/Brigham and Women's Cancer Center

TABLE 2 Cox proportional hazards regression model assessing factors associated with disease-free and overall survival

Characteristic	DFBWCC Adjusted HR (95% CI)*		NCDB Adjusted HR (95% CI)*
	DFS	OS	OS
Pathologic nodal status			
ypN0	Ref	Ref	Ref
ypN1[i+]	**2.36 (1.01–5.51)**	1.34 (0.32–5.61)	**1.89 (1.39–2.59)**
ypN1mi	**2.14 (1.20–3.81)**	1.46 (0.61–3.51)	**2.18 (1.76–2.70)**
ypN1	**3.13 (2.15–4.57)**	**4.11 (2.61–6.47)**	**2.58 (2.32–2.86)**
ypN2–3	**4.43 (2.95–6.63)**	**6.38 (3.96–10.3)**	**6.13 (5.48–6.85)**
Breast pCR			
Yes	Ref	Ref	Ref
No	**2.44 (1.55–3.82)**	**2.36 (1.35–4.14)**	**2.35 (2.03–2.72)**
Biologic subtype			
HR+/HER2−	Ref	Ref	Ref
HR+/HER2+	0.97 (0.66–1.43)	0.89 (0.54–1.48)	**0.75 (0.63–0.89)**
HR−/HER2+	1.13 (0.65–1.96)	1.43 (0.76–2.70)	**1.75 (1.51–2.03)**
TNBC	**2.56 (1.83–3.57)**	**3.73 (2.54–5.47)**	**3.33 (3.03–3.65)**
Adjuvant radiation			
No	Ref	Ref	Ref
Yes	0.76 (0.46–1.26)	0.72 (0.39–1.33)	**0.66 (0.60–0.73)**

DF/BWCC Dana-Farber/Brigham and Women's Cancer Center, *DFS* disease-free survival, *HER2+* human epidermal growth factor receptor 2 positive, *HER2−* human epidermal growth factor receptor 2 negative, *HR* hazard ratio, *HR+* hormone receptor positive, *HR−* hormone receptor negative, *NCDB* National Cancer Database, *OS* overall survival, *pCR* pathologic complete response, *TNBC* triple-negative breast cancer

*Bold indicating statistical significance, $p < 0.05$

TABLE 3 Overall survival outcomes by pathologic nodal group, NCDB 2005–2015 (n = 35,536)

Pathologic nodal status	Total no. of patients	5-Year overall survival (all patients)			5-Year overall survival (cN0 patients)			5-Year overall survival (cN1 patients)		
		No. events/no. at risk at 5 years	OS	(95% CI)	No. events/no. at risk at 5 years	OS	(95% CI)	No. events/no. at risk at 5 years	OS	(95% CI)
ypN0	20,657	1246/4817	88.9	(88.3–89.6)	783/3273	89.9	(89.2–90.6)	463/1546	86.7	(85.5–87.9)
ypN0[i+]	543	47/115	82.8	(77.3–87.1)	24/78	84.4	(78.3–90.5)	23/50	81.0	(73.2–88.7)
ypN1mi	1132	122/210	79.5	(75.1–82.4)	54/100	80.8	(75.7–86.0)	68/111	78.3	(73.3–83.2)
ypN1	8776	1277/2456	77.6	(76.4–78.7)	325/658	78.3	(76.1–80.5)	952/1806	77.3	(76.0–78.7)
ypN2–3	4428	1212/1089	61.6	(59.8–63.4)	189/228	65.9	(61.8–70.0)	1023/864	60.6	(58.6–62.6)

CI confidence interval, *cN0* clinically node negative, *cN1* clinically node positive, *NCDB* National Cancer Database, *OS* overall survival

DISCUSSION

In patients undergoing neoadjuvant therapy, lack of axillary pCR has been shown to be independently associated with decreased recurrence-free and overall survival.[9–12] Because patients with residual ITCs and micrometastases constitute a small minority of those treated with neoadjuvant chemotherapy, the impact of this low-volume residual nodal disease on prognosis has remained less well defined. The results of the present study show that patients with low-volume residual nodal disease following NAC have inferior prognosis compared with those with complete eradication of nodal metastases. The effect of residual ITCs and micrometastases on long-term survival persists regardless of clinical nodal status at presentation, and is particularly pronounced in patients with triple-

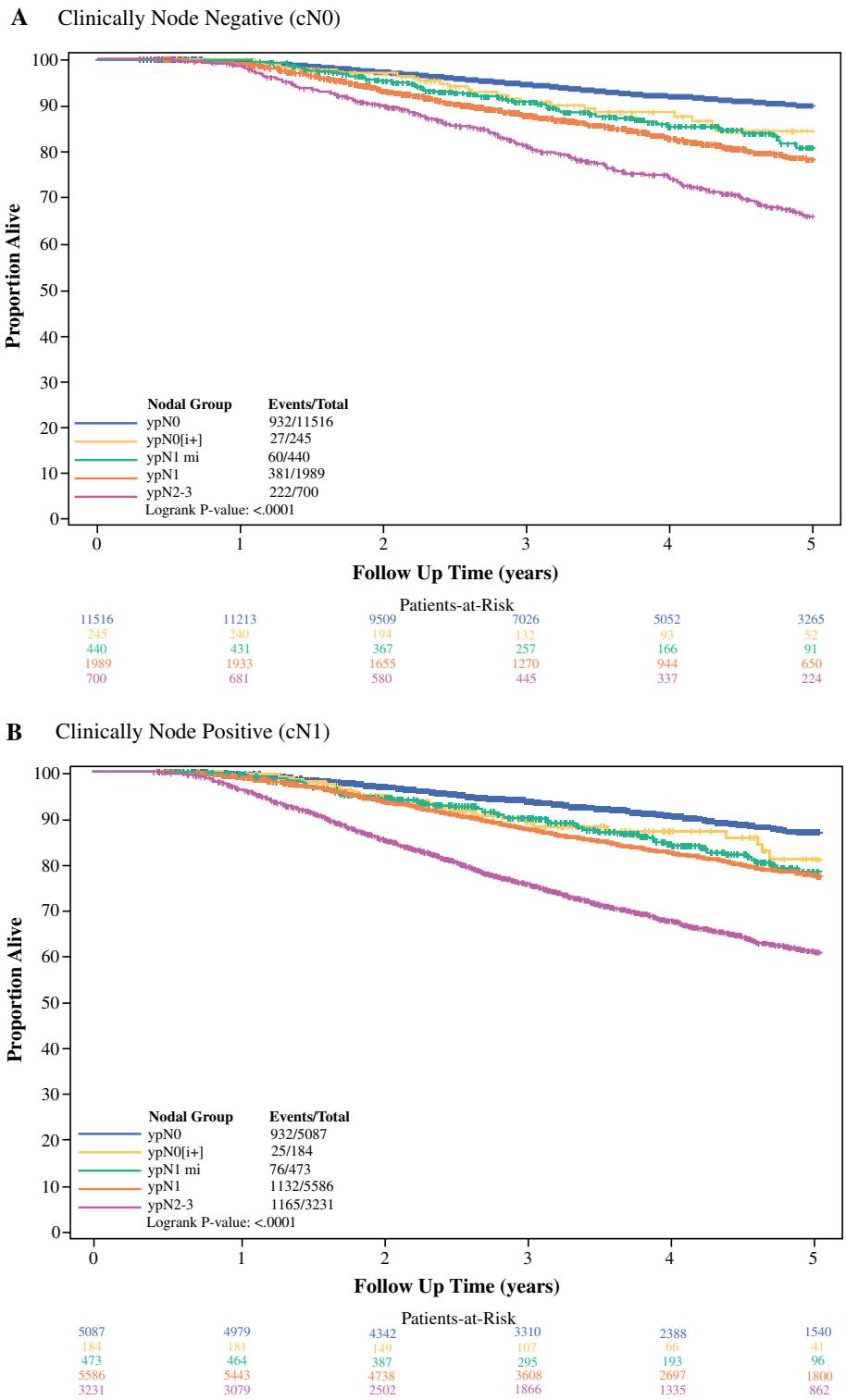

FIG. 1 Five-year overall survival according to pathologic nodal status in stage I–III invasive breast cancer patients who received neoadjuvant chemotherapy in clinically node-negative (cN0) and node-positive (cN1) patients at presentation, National Cancer Database (2005–2015)

negative and HR-negative/HER2-positive breast cancer, for whom axillary pCR rates approach 50–65% in the modern era.[13]

This study extends earlier work by Fisher et al., whose examination of pathologic material from the NSABP B-18 trial found that patients with residual nodal disease < 1.0 mm, termed "mini micrometastases," experienced significantly worse OS compared with those with ypN0 disease. DFS was also decreased for patients with low-volume residual nodal disease compared with those with ypN0 disease, although these patients fared better than those with residual macrometastases.[3] Another single-

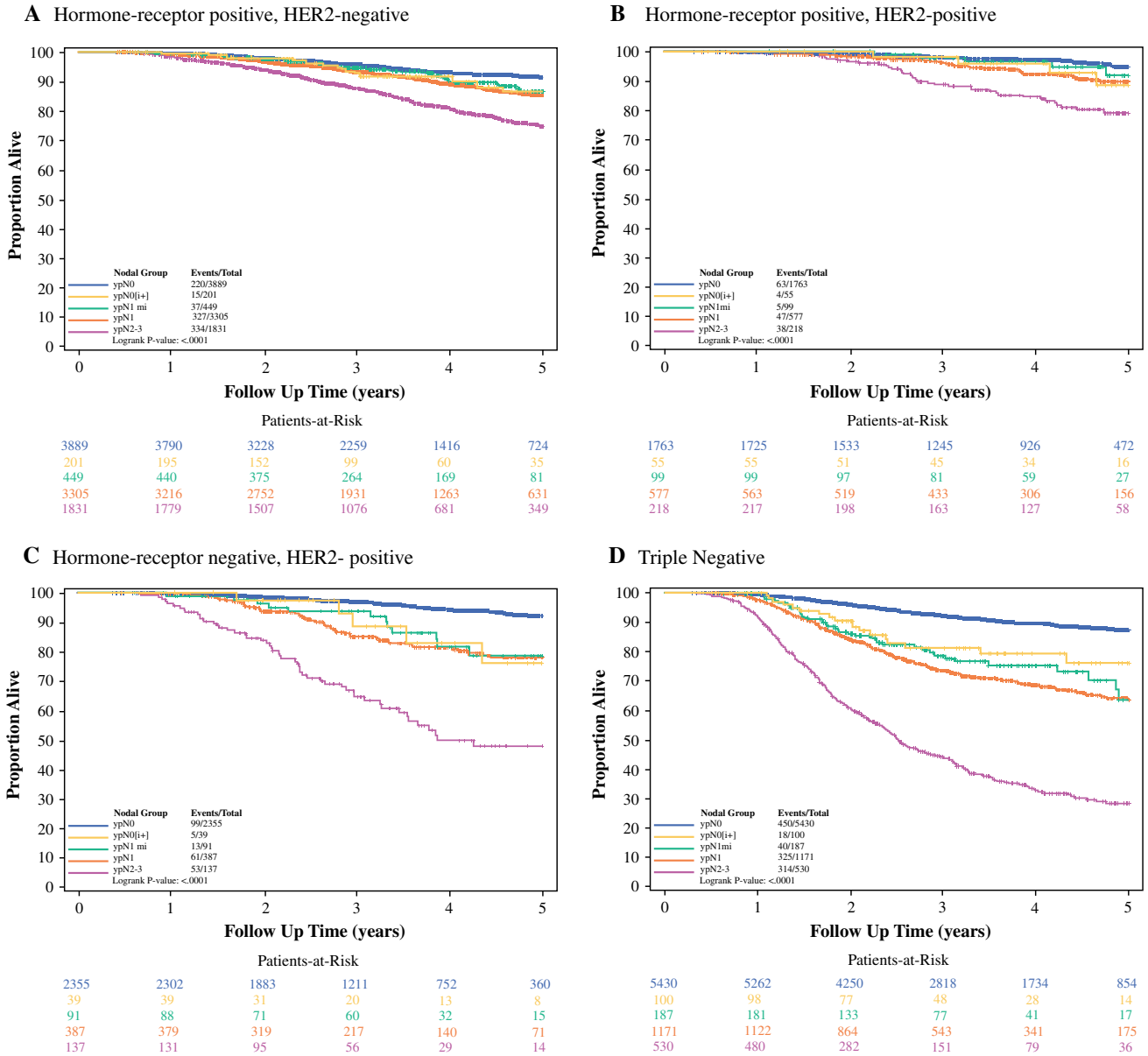

FIG. 2 Five-year overall survival according to pathologic nodal status by biologic subtype, National Cancer Database (2005–2015)

institution cohort of 122 patients treated between 1991 and 2002 at the University of North Carolina Chapel Hill provided further evidence substantiating these results, demonstrating significantly poorer 5-year distant DFS (42% versus 85%, $p = 0.02$) and OS (43% versus 94%, $p = 0.005$) for patients with residual micrometastases compared with those who were node negative following neoadjuvant treatment with traditional cytotoxic regimens.[4]

In contrast, in a recent population-based cohort of 1347 clinically node-positive patients treated with NAC between 2005 and 2008 from The Netherlands, there was no difference in OS and DFS between ypN0 patients and those with low-volume residual nodal disease.[6] Several differences in our methodological approach may explain the discrepancy in results noted between our studies. In addition to being performed in separate populations between Europe and North America, our analyses also uncoupled ypN1 patients from those with ypN2–3 disease, allowing for refined survival comparisons across various node-positive strata. In our study, cN1 patients with residual micrometastases behaved similarly but to a lesser magnitude compared with patients with ypN1 disease following NAC, whereas ypN2–3 patients demonstrated substantially poorer survival outcomes.

Biologic subtype is an important predictor of long-term outcome with or without NAC, with several validated scoring systems incorporating information on volume of residual tumor with HR and HER2 expression to stratify patients with respect to prognosis following preoperative therapy.[12,14,15] In the present study, subgroup analyses performed across biologic subtypes demonstrated vast differences in survival outcomes for patients with ITCs and micrometastases, with triple-negative and HR-negative/HER2-positive patients demonstrating inferior outcomes as compared with HR-positive patients with similar extent of nodal disease. These data support considerations for additional treatment in patients with triple-negative and HR-negative/HER2-positive breast cancer with any degree of residual nodal disease after preoperative therapy, with respect to both further local management and adjuvant systemic therapy decisions. Recent clinical trials demonstrating substantial benefit associated with addition of adjuvant capecitabine in patients with residual triple-negative disease after NAC or trastuzumab emtansine (T-DM1) in HER2-positive patients with residual disease lend further support to this observation.[16,17]

In addition to their prognostic significance, accurate identification of residual disease in sentinel lymph node(s) (SLNs) following NAC has expanded implications with respect to the remaining axillary nodes. In the SN FNAC trial, sentinel lymph node metastases of any size were considered positive on the basis that ITCs and micrometastases were associated with an increased likelihood of additional positive non-SLNs.[18] In that trial, the mean number of positive non-SLNs was 0.5 among those with ITCs, 0.7 among those with micrometastases, and 2.8 among those with macrometastases. A recent retrospective study by Moo et al.[19] supports this finding, reporting a 17% and 64% likelihood of identifying additional positive nonsentinel nodes in patients with ITCs and micrometastases following NAC, respectively. In their subgroup of patients with SLN micrometastases, 34% had two or more positive non-SLNs. Within our institutional cohort, in which nearly all cN1 patients underwent upfront axillary dissection, approximately one-fifth of those with residual ITCs and micrometastases had three or more positive nodes on pathologic examination. Taken together, these studies argue for performance of immunohistochemistry on all SLN in patients receiving NAC, as well as the continued recommendation for ALND of any residual nodal disease until further clinical trial data are available.

The optimal local therapy of the axilla in clinically node-positive women with ITCs and micrometastases on SLNB following NAC remains controversial[20] and is the subject of ongoing research. In the NSABP B-51/RTOG 1304 trial, patients with residual ITCs on either SLNB or ALND are considered to have node-negative disease and are eligible for randomization following lumpectomy to standard whole-breast irradiation with or without regional nodal irradiation, and in those undergoing mastectomy, to postmastectomy radiotherapy with regional nodal irradiation versus omission of radiotherapy.[21] It remains of interest to see if additional radiotherapy in this setting will affect locoregional recurrence and survival. In the Alliance A011202 trial, patients with ITCs are considered node negative, whereas patients with micrometastases in the SLN are eligible for enrollment on the basis that they represent node-positive disease. These patients are to be randomized to axillary radiotherapy versus ALND, whereas those with ITCs, representing node-negative disease, will go on to receive no further therapy. Both trials will help to address important issues related to tailoring local treatment based on extent of nodal disease in response to preoperative systemic therapy.

This study has several limitations. Although our institutional cohort allowed for analysis of recurrence data, the small number of women with ITCs and micrometastases and low number of events precluded subgroup analyses as well as meaningful comparisons of LRRFS and OS across nodal groups. While the use of the large NCDB cohort mitigated many of these issues, the NCDB lacks important outcomes data on cancer recurrence and disease-specific survival. Furthermore, as with any population-level database, the NCDB is subject to possible underreporting or misclassification, particularly from sites where use of immunohistochemistry for pathologic analysis of axillary nodes is not routine.

Despite the stated limitations, these analyses provide the largest body of evidence to date demonstrating the prognostic implications of residual axillary ITCs and micrometastases following receipt of neoadjvuant therapy. At a minimum, the data here argue for performance of immunohistochemistry on sentinel nodes after NAC, both for the purposes of axillary staging and for the potential impact of such information on further local and systemic treatment decisions. Until data from ongoing randomized trials are available, ALND should remain the standard of care for any residual nodal disease after NAC.

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