The contribution of axillary lymph node volume to recurrence-free survival status in breast cancer patients with sub-stratification by molecular subtypes and pathological complete response

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Abstract

Purpose This study sought to examine the contribution of axillary lymph node (LN) volume to recurrence-free survival (RFS) in breast cancer patients with sub-stratification by molecular subtypes, and full or nodal PCR.

Methods The largest LN volumes per patient at pre-neoadjuvant chemotherapy on standard clinical breast 1.5-Tesla MRI, 3 molecular subtypes, full, breast, and nodal PCR, and 10-year RFS were tabulated (N = 110 patients from MRIs of I-SPY-1 TRIAL). A volume threshold of two standard deviations was used to categorize large versus small LNs for sub stratification. In addition, “normal” node volumes were determined from a different cohort of 218 axillary LNs.

Results LN volume (4.07 ± 5.45 cm^3) were significantly larger than normal axillary LN volumes (0.646 ± 0.657 cm^3, $P = 10^{-16}$). Full and nodal pathologic complete response (PCR) was not dependent on pre-neoadjuvant chemotherapy nodal volume ($P > .05$). The HR+/HER2− group had smaller axillary LN volumes than the HER2 + and triple-negative groups ($P < .05$). Survival was not dependent on pre-treatment axillary LN volumes alone ($P = .29$). However, when substratified by PCR, the large LN group with full ($P = .011$) or nodal PCR ($P = .0026$) both showed better recurrence-free survival than the small LN group. There was significant difference in RFS when the small node group was separated by the 3 molecular subtypes ($P = .036$) but not the large node group ($P = .97$).

Conclusions This study found an interaction of axillary lymph node volume, pathological complete responses, and molecular subtypes that inform recurrence-free survival status. Improved characterization of the axillary lymph nodes has the potential to improve the management of breast cancer patients.

Introduction

Recurrence-free survival (RFS) is a common measure of treatment outcome in breast cancer patients. Pathologic complete response (PCR) is pathologic determination of breast tumor and axillary lymph nodes (LNs) response to neoadjuvant chemotherapy (NAC) and is possibly a surrogate marker for RFS. However, the ability of PCR to predict RFS in breast cancer is controversial.[1–6] A few studies have shown that breast MRI tumor volume is a moderate predictor of PCR with an area under the receiver-operative curve (AUC) of 0.7–0.8 and RFS AUC of 0.6–0.8.[6, 7] Moreover, patients with different molecular subtypes also respond differently to NAC, affecting PCR profiles and RFS.[8] For example, patients with hormonal receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2−) molecular subtypes are known to be less responsive to NAC compared to patients with a triple-negative (TN) or HER2 + molecular subtype.[8] PCR, tumor volume, and molecular subtype seem to have a complex relationship with RFS with no single parameter able to accurately predict RFS.

Locally advanced breast cancer, defined as breast cancer that has spread beyond the breast to the skin, chest wall, or axillary LNs but not to other organs, is now considered a manageable disease. However,

breast cancer is more concerning when metastasizes.[9] Most of the lymphatic fluid in the breasts passes through the axillary LNs which are the major conduits by which breast cancer cells metastasize. Axillary LN status may thus have prognostic value in determining RFS. Indeed, axillary LN involvement is known to increase the risk of recurrence in breast cancer.[10, 11] Compared to a LN biopsy which is limited to a small region of a node and/or a few nodes, MRI has the potential to visualize most axillary LNs non-invasively in 3-dimensions and *in situ*. With current standards, MRI of axillary LNs is challenging because axillary LNs are small and often not in the field of view. When visualized, most have low sensitivity as current detectors and standard breast MRI protocols are not currently optimized for axillary LN imaging. Although LN involvement by pathology has been associated with poor RFS in breast and other cancers, the contribution of axillary LN volume alone as well as its association with PCR, and receptor status in determining RFS in breast cancer has not been adequately investigated.[12, 13]

This study sought to examine the contribution of axillary LN volume on RFS in breast cancer patients with sub-stratification by molecular subtypes, and full or nodal PCR. We tested the hypothesis that large pre-treatment axillary LN volume is associated with poor RFS in breast cancer patients. We also sought to investigate the interaction amongst axillary LN volume, PCR, and molecular subtypes that inform RFS.

Materials And Methods

Data Sources and Study Definitions

The data used in this study was obtained from the American College of Radiology Imaging Network (ACRIN) 6657 study with Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and molecular Analysis (I-SPY 1 TRIAL).[6, 14, 15] 221 out of 221 patients in this study have been previously reported. Prior literature has shown how breast tumor volumes, molecular subtypes, and PCR relates to patient RFS whereas our study shows how axillary LN volumes relate to RFS independently and in relation to molecular subtypes and PCR. The I-SPY 1 TRIAL took place between 2002–2006 and included women with stage 2 or 3 breast cancer who received neoadjuvant chemotherapy (NAC) with anthracycline-cyclophosphamide regimen with or without taxane. I-SPY 1 TRIAL MR data was acquired across multiple sites on 1.5-T MRI scanners.

In this study, large axillary LNs were defined as any axillary LNs that were two standard deviations larger than the average volume of normal nodes. For volume quantitation, the single largest axillary LN was contoured from each of the 110 patients from the I-SPY 1 TRIAL, as the largest axillary LN was the most suspicious of metastasis in all patients. Refer to Fig. 1 for a flowchart of the study design. Normal node volume was obtained using MRIs of breast cancer patients at Stony Brook University Hospital on a 1.5-T GE scanner from 01/01/2010 to 07/30/2018 (I-SPY 1 TRIAL data had no contralateral breast or axillary LN images). The breast and axillary LNs contralateral to the diseased breast were not diagnosed with cancer and assumed to be normal. 218 normal contralateral axillary LNs were collected from 71 breast cancer patients. 192 of the 218 normal contralateral axillary LNs have been previously reported.[16] The prior article studied whether NAC-induced change of axillary LN size could be used as a predictor of PCR

using AUC analyses while this study considered if pre-NAC axillary LN sizes can differentiate patient RFS with Kaplan–Meier estimates.

Study Design

The following 3 parameters were obtained from the I-SPY 1 TRIAL clinical and outcome dataset: a) 3 different molecular subtype categories, b) full, breast, and nodal PCR status, and c) RFS at 10 years. Due to some missing nodal volume, molecular subtype, PCR, and RFS data, analysis of each variable was done with varying sample sizes as shown in Tables 1 and 2. The study was performed in accordance with the research guidelines approved by the Stony Brook University Institutional Review Board.

Table 1
Characteristics and Data Availability of the I-SPY 1 TRIAL Cohort.

Category	Dataset (n = 221)
Molecular subtype	
HR+/HER2–	96 (43.4)
HER+	67 (30.3)
Triple negative	53 (24.0)
Missing	5 (2.3)
Full PCR	
Complete responder	58 (26.2)
Nonresponder	154 (69.7)
Missing	9 (4.1)
Nodal PCR	
Complete responder	99 (44.8)
Nonresponder	97 (43.9)
Missing	5 (2.3)
RFS	
Event (local or distant progression or death)	63 (28.5)
No event	149 (67.4)
Missing	9 (4.1)
Pre-NAC axillary node volume	
Obtainable[1]	
RFS available	110 (49.8)
RFS missing	9 (4.1)
Not obtainable	102 (46.2)
Unless otherwise noted, data are numerators and data in parentheses are percentages.	
Abbreviations: HR: hormone receptor; HER: human estrogen receptor; PCR: pathologic complete response; RFS: recurrence-free survival; NAC, neoadjuvant chemotherapy	
[1] 119 patients had sufficient MRI quality for contouring nodal volumes.	

Table 2
Characteristics of Small and Large Node Group Patients with Pre-NAC Volume and RFS Data.

Characteristic	Small Node (*n* = 52)	Large Node (*n* = 58)	*P* Value
Age			.74*
Mean[1]	49.2 ± 9.8	49.5 ± 9.0	–
Median[2]	49 (28–68)	51 (33–65)	–
Race			.01
Asian	1 (1.9)	3 (5.2)	–
Black or African American	5 (9.6)	19 (32.8)	–
White	45 (86.5)	36 (62.1)	–
Multiple race	1 (1.9)	0 (0.0)	–
Molecular subtype			< .01
HR+/HER2–	29 (55.8)	16 (27.6)	–
HER2+	14 (26.9)	27 (46.6)	–
Triple negative	7 (13.5)	13 (22.4)	–
Missing	2 (3.8)	2 (3.4)	–
Volume (cm^3)			< .001
Mean[1]	1.07 ± 0.52	6.60 ± 0.72	–
Median[2]	1.09 (0.20–1.94)	4.19 (2.00–31.0)	–

Unless otherwise noted, data are numerators and data in parentheses are percentages.

Abbreviations: HR: hormone receptor; HER: human estrogen receptor; RFS: recurrence-free survival; PCR: pathologic complete response

* Wilcoxon Rank Sum *P* value was used for continuous variable and χ^2 *P* value was used for categorical variables.

[1] Data are mean ± standard deviation.

[2] Data in parenthesis are range.

Characteristic	Small Node ($n = 52$)	Large Node ($n = 58$)	P Value
RFS (years)			.12
Mean[1]	6.21 ± 2.80	5.64 ± 2.96	–
Median[2]	7.27 (0.75–9.77)	6.20 (0.50–10.4)	–
Full PCR			.42
Complete responder	11 (21.2)	17 (29.3)	–
Nonresponder	40 (76.9)	39 (67.2)	–
Missing	1 (1.9)	2 (3.4)	–
Nodal PCR			1
Complete responder	23 (44.2)	27 (46.6)	–
Nonresponder	26 (50.0)	29 (50.0)	–
Missing	3 (5.8)	2 (3.4)	–
Unless otherwise noted, data are numerators and data in parentheses are percentages.			
Abbreviations: HR: hormone receptor; HER: human estrogen receptor; RFS: recurrence-free survival; PCR: pathologic complete response			
* Wilcoxon Rank Sum P value was used for continuous variable and χ^2 P value was used for categorical variables.			
[1] Data are mean ± standard deviation.			
[2] Data in parenthesis are range.			

Hormone receptor positivity and HER2 expression were determined from pre-NAC biopsy of the primary breast tumor by immunohistochemistry, fluorescent in situ hybridization, and Allred score. 3 following molecular subtypes were used for analysis: HR+/HER2−, HER2+, and triple negative (TN). HR+/HER2− are patients that are negative for HER2 and positive for either estrogen and/or progesterone receptor. HER2 + are positive for HER2 regardless of estrogen and/or progesterone positivity status. TN patients are negative for HER2, estrogen and progesterone receptors.

Breast PCR (ypT0/is) was defined by surgical pathology as the absence of invasive cancer in breast, irrespective of remaining *in situ* cancer in the primary tumor. Nodal PCR (ypN0) was defined by surgical pathology as the absence of invasive cancer in the axillary LNs. PCR or full PCR (ypT0/is, ypN0) is a combination of breast and nodal PCR again defined by surgical pathology as no residual invasive

disease in either breast or axillary LNs after NAC. Patients who achieved PCR will be referred to as complete responders and patients who did not achieve PCR will be referred to as non-complete or partial responders.

RFS time was documented in months from the date of chemotherapy initiation and listed as having a recurrence or remaining recurrence-free (or censored) at 10 years.

For axillary LN volumes, all visible axillary LNs on the pre-NAC MRI first post-contrast image (around 2 minutes post-contrast) were manually segmented on ITK-SNAP 3.8.0 (http://itksnap.org) by RC, JK, and VT under the guidance of expert breast radiologists CB, RP, and PF each with more than 20 years of experience. The entire lymph node was contoured to determine the volume, including the fatty hilum. For consistency, only the largest axillary LN prior to NAC in each patient were used for volume analysis. Retrospective review under guidance of breast radiologists confirmed that essentially all (95%) of the largest axillary LNs were the most suspicious of malignancy due to characteristics such as large size, loss of fatty hilum, and clustering.

Statistical Analysis

Kaplan–Meier estimate survival curves and-log rank tests were used to compare the RFS of various subgroups. To compare the characteristics of different subgroups, Wilcoxon Rank Sum *P* value was used for continuous variable and χ^2 *P* value was used for categorical variables.

All statistical analysis were completed on R 3.6.1.[17] *P* values less than .05 was considered statistically significant for a single hypothesis. All values are presented as mean ± standard deviations, unless otherwise indicated.

Data Availability

The ACRIN 6657 breast cancer MRI data that support this study are available from The Cancer Imaging Archive, https://wiki.cancerimagingarchive.net/display/Public/ISPY1.

Results

Patient Characteristics

Table 1 shows the sample sizes of the I-SPY 1 TRIAL cohort for different variables. The distribution of the 3 molecular subtype categories were 43.4%, 30.3% and 24.0% for HR+/HER–, HER2 + and TN, respectively, consistent with literature on prevalence.[18] There were 26.2% of patients with both breast and nodal PCR, henceforth *full PCR*, and 44.8% with nodal PCR, irrespective of breast tumor status. 28.5% of the patients had disease progression or death in this cohort by 10 years post-NAC. Of the 221 patients, only 119 patients had axillary LNs clearly in the field-of-view to contour pre-NAC nodal volumes. Of the 119, only 110 patients had RFS data available.

PCR, Molecular Subtype, and Volume Analysis

Normal axillary LN volume was 0.646 ± 0.657 cm^3 (N = 218 nodes, 71 participants). Abnormal axillary LN volume was 4.07 ± 5.45 cm^3 (N = 119 nodes, 119 participants, $P = 2.2 \times 10^{-16}$).

Abnormal axillary LN volumes were not significantly different between PCR and non-PCR patients (3.48 vs 5.83 cm^3, $P = .14$), nor between nodal PCR and non-nodal PCR patients (3.97 vs 4.46 cm^3, $P = .90$), indicating that full and nodal PCR status did not depend on initial axillary LN size. The average nodal volume of the HR+/HER2− group was significantly smaller (2.40 cm^3 [95% confidence interval: 1.63, 3.16]) compared to the HER2 + group (4.82 cm^3 [3.03, 6.61]; $P < .001$) and the TN group (5.68 cm^3 [3.15, 8.21]; $P = .015$), indicating HR+/HER2−cancers were associated with smaller axillary LN volumes than the other two subtypes.

Survival curves for PCR and nodal PCR are shown in Fig. 1A. Patients with PCR had a more favorable RFS (81.8%) compared to non-PCR patients (58.6%; $P = .031$). Similarly, patients with nodal PCR had more favorable RFS (79.3%) compared to nodal non-PCR patients (50%; $P = .0013$), consistent with the literature.[18] There was no significant difference in survival for patients who achieved PCR and patients who achieved nodal PCR ($P > .05$). There was also no significant difference in survival for patients who did not achieve PCR and patients who did not achieve nodal PCR ($P > 0.05$). Survival was similar across all 3 molecular subtypes ($P = .21$, Fig. 1B).

Patients were divided into two groups using a threshold of two standard deviation from mean of normal nodes (1.96 cm^3). With this threshold, 52.7% of patients were grouped into the *large axillary LN* group and the rest were grouped into the *small axillary LN* group. There was no significant difference in RFS between large and small axillary LNs pre-NAC ($P = .29$, Fig. 1C). The characteristics of the small axillary LN and the large axillary LN group are seen in Table 1. Between the two subgroups, significant differences were seen in the racial composition and molecular subtypes.

Sub-stratification by PCR and Node Size

Subgroup analyses were done with full PCR status, nodal PCR status, and molecular subtypes. In the small axillary LN group, there was no difference whether the patients achieved full PCR ($P = .46$; Fig. 2A) or nodal PCR ($P = .51$; Fig. 2B). However, in the large axillary LN group, patients who achieved PCR had an 88.2% RFS rate compared to a 48.7% RFS rate of patients who did not ($P = .011$; Fig. 3C) and patients who achieved nodal PCR had an 81.5% survival rate compared to 41.4% survival rate of patients who did not have a PCR (p = .0026; Fig. 2D).

Within the nodal non-responder and responder groups, there was no difference in RFS whether there were small or large nodes with P values of .1 and .56, respectively (Fig. 3A **and B**).

Kaplan–Meier curves were analyzed for small and large axillary LNs with stratification into molecular subtypes. For small axillary LNs, log-rank test found that there is significant difference in between the three molecular subtypes ($P = .036$; Fig. 4A), where HR+/HER2− had a significantly better survival outcome than the HER2 + group ($P = .017$) but not the TN group ($P = .70$). There was no difference

between the HER2 + and TN groups (P = .11). For large axillary LNs, similar log-rank test did not find any difference in RFS for the three molecular subtypes (P = .97; Fig. 4B).

Within each molecular subtype, pre-treatment axillary LN size did not have any effect on 10-year RFS with P values of .068, .25, and .34 for the HR+/HER2–, HER2+, and TN subgroups, respectively (Fig. 5A, B, **and C**).

Discussion

Axillary LN volumes (average = 4.07 cm^3) of the I-SPY 1 TRIAL breast cancer patients were significantly larger than our normal axillary LN volumes (average = 0.646 cm^3). There are no similar studies with which to quantitatively compare to our study but our findings are in agreement with the notion that axillary LNs < 1.5 cm diameter are generally considered normal-appearing.[19] A 1.5 cm diameter LN translates to a volume of 1.77 cm^3 assuming a sphere which is comparable to our cutoff of 1.98 cm^3 for the large axillary LN group. Nodal and full PCR did not depend on pre-NAC axillary LN volume, suggesting that NAC is equally effective whether the patients started out with large or small nodes in this cohort. Thus, pre-NAC axillary LN volume alone may not be predictive of full or nodal PCR.

The patients with HR+/HER2– subtype cancers had smaller maximum axillary LN volumes than that of the patients with HER + and TN subtype cancers, consistent with the notion that HR+/HER2– subtype cancers are comparatively less aggressive. On the other hand, HER2 + subtype breast cancers are known to be more aggressive. As chemotherapy is generally more effective with proliferative cancers, the HER2 + subtype breast cancer patients with large maximum LN volumes who achieved great response to chemotherapy may have had the longest RFS since not only did they have a cancer subtype susceptible to chemotherapy, but showed evidence of significant response by achieving PCR in the presence of large axillary LNs.[20]

When patients were subgrouped into patients with large axillary LN and patients without pre-chemotherapy, there was no significant difference in RFS. This is in contrast to head and neck, lung, and esophageal cancers, where large LN volume negatively impact survival.[12, 13, 21] Interestingly, when substratified by pathologic response outcomes, the large axillary LN group with full or nodal PCR showed better RFS. This was not the case for the small axillary LN group. This may be the result of treatment effect heterogeneity as the large node group had more HER2 + subtype cancers. Since there is a higher proportion of HER2 + cancers in black or African Americans and HER2 + subtype cancers are comparatively more aggressive, it is understandable that black or African Americans had larger axillary LNs.[18, 20] In short, pre-NAC axillary LN volume did not inform RFS in any sub-stratification but appeared to inform RFS when it is combined with PCR status. This innovative observation could mean that If the NAC regimen can successfully treat a large node to a complete remission, this probably means the treatment is very effective, which may lead to a better RFS. This finding could have practical clinical utility.

Survival was similar across all 3 molecular subtypes despite HR+/HER2 − patients having the worst full PCR, consistent with literature.[3] This suggests that even though HR+/HER2 − had markedly poorer PCR rates, the post-NAC treatment was equally effective among the 3 molecular subtypes. Interestingly, there was significant difference in Kaplan − Meier estimates among the 3 molecular subtypes for the small but not the large axillary LN group. HER2 + subtype patients fared significantly worse when compared to the HR+/HER2 − subtype patients but not the TN subtype patients. This was unexpected since both HR+/HER2 − and TN subtype patients had around 70% survival at the 10-year mark. This finding suggests that there is a markedly different pattern of survival between HR+/HER2 − and TN subtype patients with TN subtype patients having recurrence or expiring more commonly within the first 5 years. There are likely unaccounted factors of TN cancers that make patients susceptible to recurrence within the first 5 years after NAC, such as Ki-67 status. This observation needs to be interpreted with caution as there is potential of bias due to small sample sizes.

There are several limitations in this study. A limitation is the small sample sizes after sub-stratification into axillary LN volumes, PCR status, and molecular subtypes. These findings need to be replicated on a large sample sizes to be generalizable. Another limitation was that there was no pathological confirmation of the diseased nodes. It is challenging to identify the same nodes on MRI that was biopsied. Nonetheless, the largest axillary LNs in this study were confirmed to be the most suspicious of malignancy due to morphological features, such as loss of fatty hilum, increased size, and/or thickening of cortex by our expert radiologists. Additionally, although radiologists tend to measure long and short diameter, we did not make this measurement because volumetric measurements were more reliable especially for small size objects. Future studies to improving MRI spatial resolution and contrast of axillary LNs and applying texture analysis and artificial intelligence to the axillary LNs, among others, could yield additional clinically useful information. Patients with different molecular biomarker subtypes usually received different adjuvant treatments, e.g. hormonal therapy in HR + patients, and additional HER2 targeting therapy for maintenance in HER2 + patients. These could affect the RFS. However, the sample size was insufficient to further divide based on post NAC treatment.

Conclusions

LN = lymph node, AUC = area under the receiver-operator curve, CI = confidence interval, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, NAC = neoadjuvant chemotherapy, PCR = pathologic complete response, RFS = recurrence-free survival, TN = triple negative

Declarations

Ethical Approval and Consent to participate

Ethical approval is not necessary as this is a publicly available, deidentified dataset.

Consent for publication

All authors agree to publish.

Availability of supporting data

All data will be upload to an acceptable public server (such Github)

Competing interests

All authors declare no conflicts of interests.

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Authors' contributions

James Kang, Haifang Li – collected data, analyzed data and draft paper

Renee Cattell, Varsha Talanki - analyzed data

Jules A Cohen, Clifford S. Bernstein – edited paper, participated in discussion of results

Tim Q Duong – edited paper, analyzed data supervised.

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Figures

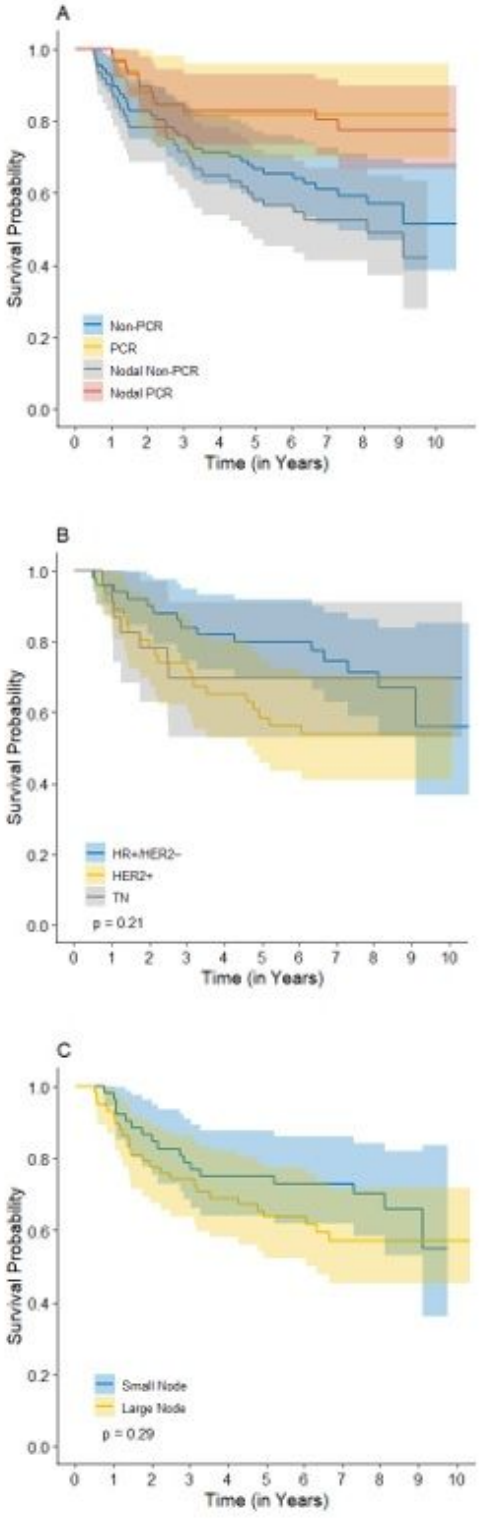

Figure 1

Flowchart of study design and lymph node grouping. Numeric values are shown as mean ± standard deviation. FOV: field-of-view; RFS: recurrence-free survival.

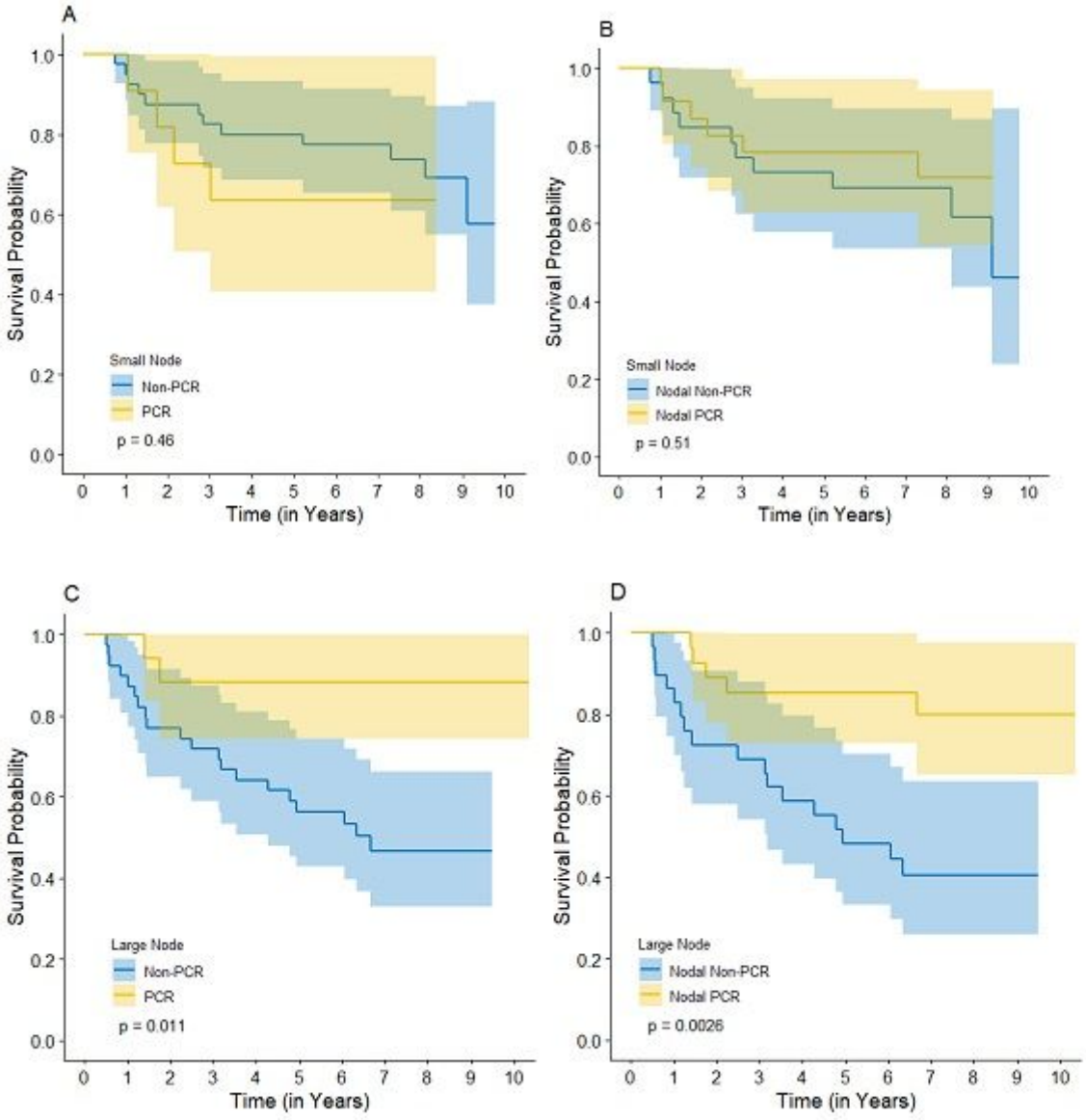

Figure 2

Kaplan–Meier recurrence-free survival estimates for PCR & nodal PCR (A), molecular subtype (B), and volume (C) subgroups. The log-rank test P value is shown for B and C. Shaded areas signify 95% confidence interval thus non-overlapping curves signify P < .05. PCR: pathologic complete response; TN: triple negative.

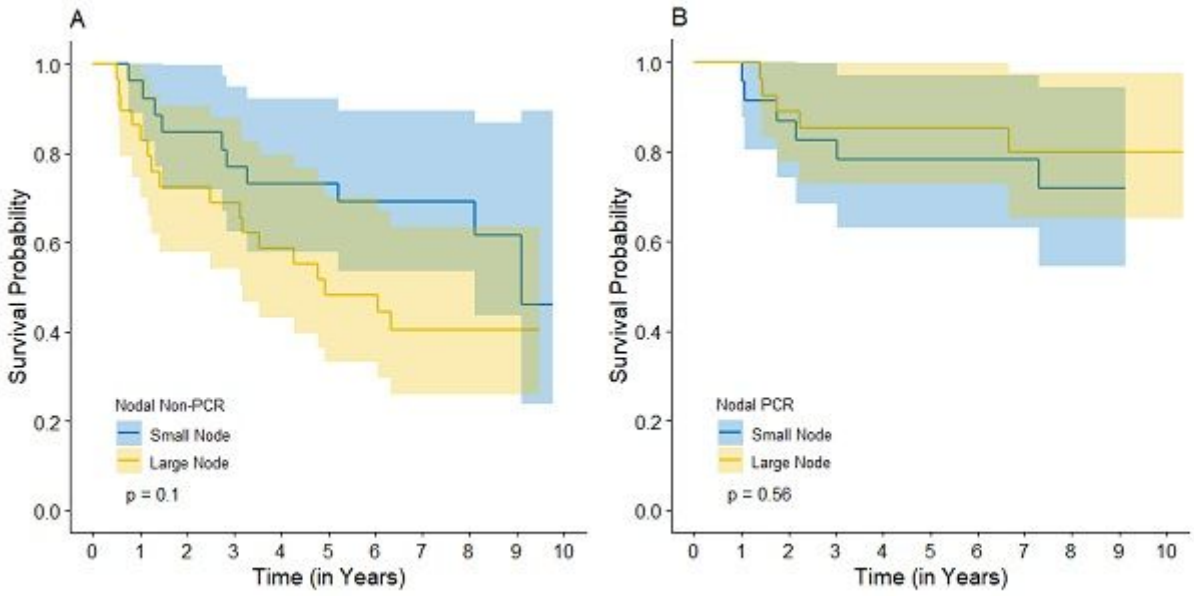

Figure 3

Kaplan–Meier recurrence-free survival estimates of small node (top; A & B) and large node groups (bottom; C & D) with sub-stratification into full PCR non-responder and responder (left; A & C), and nodal PCR non-responder and responder subgroups (right; B & D). The log-rank test P value is shown. A volume threshold of 1.96 cm3 was used. Shaded areas signify 95% confidence interval thus non-overlapping curves signify P < .05. PCR: pathologic complete response.

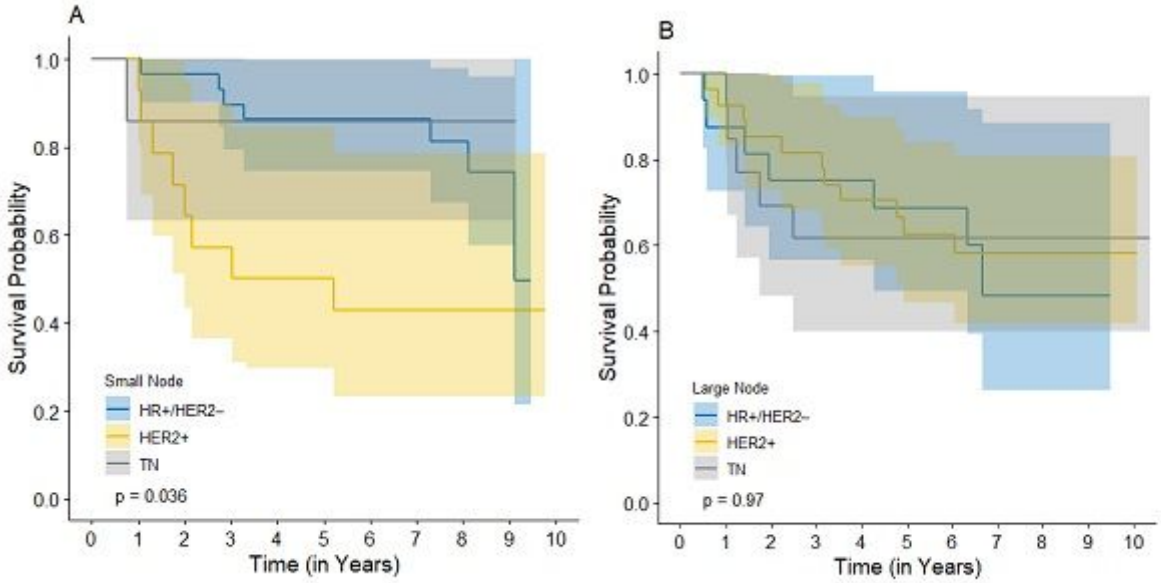

Figure 4

Kaplan–Meier recurrence-free survival estimates for nodal non-PCR (A) and nodal PCR (B) subgroups. The log-rank test P value is shown. Shaded areas signify 95% confidence interval thus non-overlapping curves signify P < .05. PCR: pathologic complete response.

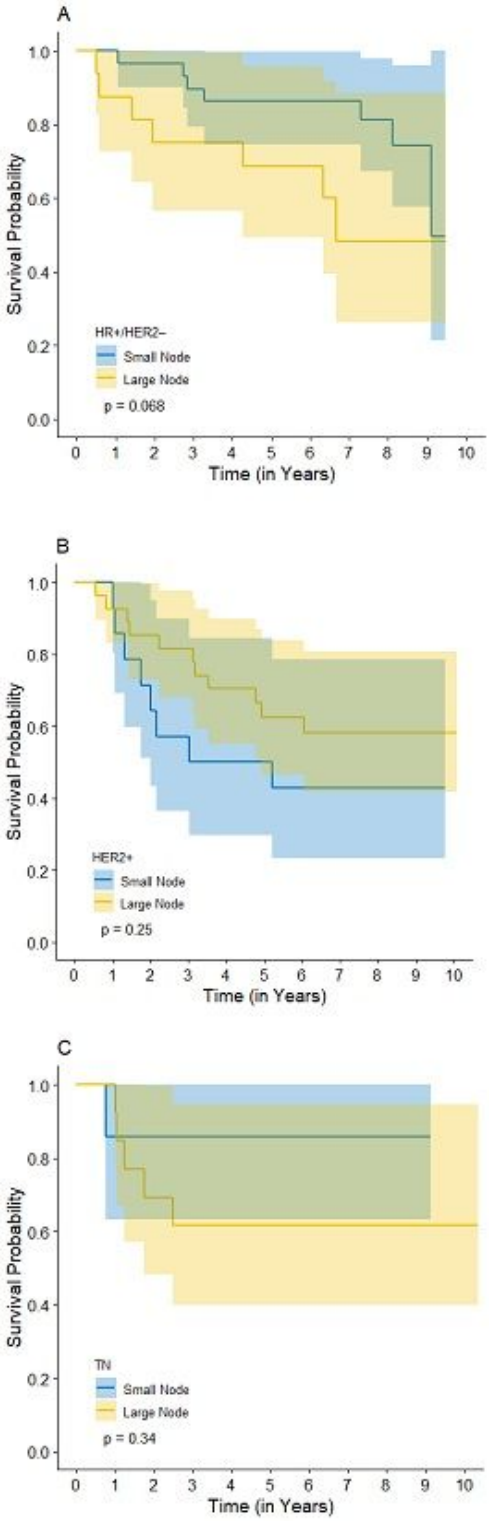

Figure 5

Kaplan–Meier recurrence-free survival estimates of small nodes (A) and large nodes (B) with sub-stratification into molecular subtype subgroups. The log-rank test P value is shown. A volume threshold of 1.96 cm3 was used. Shaded areas signify 95% confidence interval thus non-overlapping curves signify P < .05. TN: triple negative.