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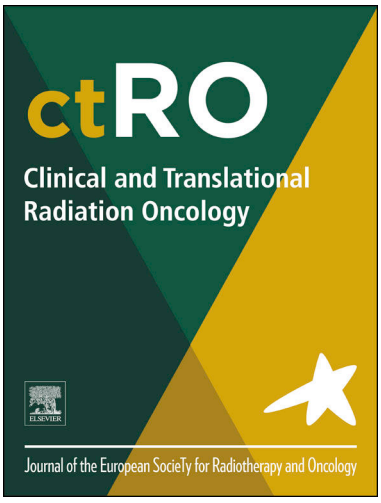

Regional nodal irradiation (RNI) in breast cancer patients with residual isolated tumor cells or micrometastatic nodal disease after neoadjuvant chemotherapy

Joseph K. Kim, Jerome M. Karp, Naamit K. Gerber

PII: S2405-6308(22)00113-6
DOI: https://doi.org/10.1016/j.ctro.2022.11.014
Reference: CTRO 555

To appear in: *Clinical & Translational Radiation Oncology*

Received Date: 10 October 2022
Revised Date: 17 November 2022
Accepted Date: 20 November 2022

Please cite this article as: J.K. Kim, J.M. Karp, N.K. Gerber, Regional nodal irradiation (RNI) in breast cancer patients with residual isolated tumor cells or micrometastatic nodal disease after neoadjuvant chemotherapy, *Clinical & Translational Radiation Oncology* (2022), doi: https://doi.org/10.1016/j.ctro.2022.11.014

Title: Regional nodal irradiation (RNI) in breast cancer patients with residual isolated tumor cells or micrometastatic nodal disease after neoadjuvant chemotherapy

Author Names and Affiliations:

Joseph K. Kim, MD[1], Jerome M. Karp, MD, PhD[1], Naamit K. Gerber MD[1]

[1]Department of Radiation Oncology, NYU Langone Medical Center and School of Medicine, New York, New York

Corresponding Author:

Naamit K. Gerber

Email: Naamit.Gerber@nyulangone.org

Permanent Address:

NYU Perlmutter Cancer Center

Department of Radiation Oncology

160 E. 34th Street

New York, NY 10016

Declaration of Interests: None

Funding Statement: No funding source

ABSTRACT

BACKGROUND/PURPOSE: The optimal management of residual micrometastases and isolated tumor cells (ITC) in patients with invasive breast cancer who undergo neoadjuvant chemotherapy (NAC) followed by definitive surgery is not well-studied. We evaluated the role of regional nodal irradiation (RNI) in clinically node-positive (cN1) breast cancer patients with residual low-volume nodal disease following NAC.

METHODS/MATERIALS: We queried the National Cancer Database (NCDB) and included patients with cN1 invasive breast cancer diagnosed from 2004-2016 who were treated with NAC and definitive surgery and had residual micrometastases (ypN1mi) or ITC (ypN0i+). We used univariable (UVA) and multivariable (MVA) Cox regression analyses to determine prognostic factors and Kaplan-Meier (KM) methods to evaluate overall survival (OS). We used inverse probability treatment weighting (IPTW) to reweight data to account for confounding factors.

RESULTS: Our final cohort included 1980 patients, including 527 patients with ypN0i+ disease and 1453 patients with ypN1mi disease. 1101 patients (45.0%) received RNI in the overall cohort with a higher proportion of ypN1mi patients receiving RNI (56.5%) compared to 53.1% of ypN0i+ patients. There was no significant difference in OS between ypN0i+ and ypN1mi patients. RNI had no significant effect on OS in the overall cohort using Cox MVA and KM methods. With separate subset analysis of ypN0i+ and ypN1mi patients, there was no significant effect of RNI on OS. This was confirmed with IPTW.

CONCLUSIONS: In a national hospital-based study of cN1 invasive breast cancer patients with residual ITC or micrometastases after NAC, RNI did not have a significant effect on OS.

KEYWORDS: breast cancer; regional nodal irradiation; radiation therapy; micrometastases; isolated tumor cells; neoadjuvant chemotherapy

1. Introduction

The role of axillary radiation therapy (RT) following neoadjuvant chemotherapy (NAC) varies depending on the response and extent of residual nodal disease [1, 2]. Regional nodal irradiation (RNI) is commonly used in the adjuvant setting for patients with residual macro-metastatic nodal disease following NAC due to the higher rates of locoregional failure [3]. In patients with clinically node-positive breast cancer who achieve a pathologic complete response (pCR) following NAC, the role of RNI is unclear and ongoing clinical trials are evaluating whether RNI is beneficial [1, 4]. The ongoing clinical trial NSABP B-51/RTOG 1304 (B51) aims to address the role of RNI in these patients with nodal pCR following NAC and potentially identify patients in whom we may safely omit RNI. Patients with residual isolated tumor cells (ITC/ypN0i+) are included in B51, but patients with residual micrometastases are not eligible and RNI is considered standard of care in these patients [5]. At the present time, there is no randomized clinical evidence to guide axillary radiation for patients with residual low volume nodal disease in the axilla.

In the upfront surgical setting, RNI is not routinely recommended for patients with ITCs or micrometastatic nodal disease, particularly in the absence of other high-risk features such as young age, lymphovascular invasion (LVI), medial tumor location, and aggressive biology such as triple negative subtype [6, 7]. However, the presence of ITCs and micrometastases after NAC is an entirely different entity as it represents disease that did not respond to chemotherapy. Several retrospective and national cancer registry studies have conflicting findings regarding the prognostic impact of ITC and micrometastases following NAC. In a Netherlands Cancer Registry study, patients with residual ITC or micrometastatic nodal disease had a similar prognosis for disease free survival (DFS) and overall survival (OS) compared to patients with a

nodal pCR [8]. Of note, it is unknown which patients received RNI in this study. In contrast, Wong et al. reported a greater risk for breast cancer recurrence associated with increasing residual nodal burden as well as a two-fold increased risk of death associated with residual ITC or micrometastatic nodal disease as compared to nodal pCR [9]

In the present study, we evaluated RNI and OS in patients with clinically node positive (cN1) invasive breast cancer who underwent NAC and definitive surgery with residual ITC or micrometastatic nodal disease using the National Cancer Database (NCDB).

2. Methods and Materials

2.1 Patient Selection

We used the NCDB, a national registry maintained as a joint project of the American Cancer Society and the American College of Surgeons, which captures 70% of all malignancies diagnosed annually in the United States. We queried the database for adult patients (age ≥18) with cT0-3N1M0 breast cancer diagnosed between 2004 and 2016 who received NAC followed by breast conserving surgery (BCS) or mastectomy and whose post-neoadjuvant therapy (yp) stage at time of surgery was recorded as ypN0i+, ypN0m+ (categorized with ypN0i+) or ypN1mi. Patients were divided into 2 groups: those who did not receive RNI (BCS followed by whole breast irradiation (WBI) or mastectomy followed by no radiation or chest wall (CW) only radiation) and those who received RNI (BCS followed by WBI+RNI or mastectomy followed by RT to the CW+RNI). Patients who underwent BCS without any RT were excluded. We also excluded patients with unknown values of crucial treatment variables, including breast cancer subtype (i.e., estrogen receptor (ER), progesterone receptor [10], and HER2 status were all unknown, or both ER and PR status were unknown), type of surgery, whether lymph nodes were

examined during surgery, margin status at surgery, ypT stage, receipt of RT, and receipt of endocrine therapy (ET). Patients were also excluded if they received RT as neoadjuvant therapy, or if they received RT to a site other than the breast, CW, or regional lymph nodes.

Patients were stratified by year of diagnosis; age; race; Charlson-Deyo comorbidity index score (CCI score); insurance status; median ZIP code income; education level; facility type and distance to healthcare facility (miles, from patient's residence); breast cancer histology, grade, and subtype; clinical T stage; ypT stage; type of surgery; presence of LVI; receipt of RT and ET.

2.2 Statistical Analysis

Chi square testing was used to compare frequency distributions between categorical variables. Overall survival (OS) was calculated using Kaplan-Meier (KM) statistics. Hazard ratios (HR) were computed using a Cox proportional hazards univariable model (UVA), as well as with a Cox multivariable model (MVA) using year of diagnosis, age, CCI score, insurance and income status, tumor histology and grade, tumor subtype, clinical T stage, ypT and ypN stages, LVI, receipt of RT and ET as covariates. To account for imbalance between treatment cohorts, the analysis was repeated using a patient cohort reweighted using the inverse probability of treatment weighting (IPTW) method, adjusting for age, tumor subtype, clinical T stage, ypT stage, type of surgery, surgical margins, LVI, and receipt of ET. All analyses were performed using R statistical software and associated packages. All tests were two-sided with a threshold of $p<0.05$ for significance.

3. Results

3.1 Patient characteristics

We included adult patients at least 18 years of age with cT0-3N1M0 breast cancer who underwent NAC followed by BCS or mastectomy and had residual ITC or micrometastases. After applying our selection criteria, our final cohort consisted of 1980 patients (Figure 1). The median age in the cohort was 50 years (range 21 to 90 years). 527 (26.6%) patients had ypN0i+ and 1453 (73.4%) patients had ypN1mi disease. 1311 patients (66.2%) were treated with mastectomy and 669 patients (33.8%) were treated with BCS. RNI was utilized in 1101 patients (55.6%) in the overall cohort, including 53.1% of ypN0i+ patients and 56.5% of ypN1mi patients. Of the mastectomy patients who did not receive RNI (N=582), 54.5% received no PMRT and 45.5% received CW only RT. 20.3% of patients had a pCR in the breast, including 21.3% in the RNI group and 19.1% in the no RNI group. There were no significant differences between the no RNI group and RNI group regarding biologic subtype with the overall cohort consisting of 43.9% hormone receptor positive, 34.4% HER2 positive, and 21.7% hormone-receptor negative. Patients who were treated with RNI were more likely to have a higher clinical T stage, higher ypT stage, shorter distance to the healthcare facility, and use of ET. Additional patient characteristics are detailed in Table 1.

3.2 Survival analysis

The median follow-up for the entire cohort was 36.1 months (range 3.4 to 159.9 months). On KM analysis, RNI had no significant effect on OS among patients in the entire cohort as well as in separate subset analyses of ypN0i + patients only and ypN1mi patients only (Figure 2).

There was no significant association between RNI and OS on either Cox UVA or MVA. Additional predictors of worse OS on MVA included higher tumor grade, hormone-receptor negative disease, lack of breast pCR (ypT1-2 and ypT3-4), more recent year of diagnosis, and

LVI. Mastectomy was trending towards significance for worse OS compared to BCS (HR 1.34 [0.99-1.82], p=0.062) on MVA. HER2-positive disease, use of ET, and higher income were associated with improved OS (Table 2).

After reweighting with IPTW, KM analysis (Figure 3) and Cox MVA did not show a significant effect of RNI on OS.

4. Discussion

To our knowledge, our present study using a national hospital-based registry of clinically-node positive (N1) breast cancer patients is the largest study to evaluate the impact of RNI in patients with residual ITC or micrometastases following NAC. In the upfront surgical setting, ITCs and micrometastases have an overall excellent prognosis and RNI is typically not offered in the absence of other high risk features [6, 11, 12]. However, the significance of low volume residual nodal disease when detected after NAC is not as well studied. Our results show that patients who were treated with RNI were more likely to have higher clinical and pathologic T stage, but RNI utilization was similar among ypN0i+ and ypN1mi. We did not observe any detrimental or beneficial effect of RNI on OS using univariate or multivariable Cox analysis and after reweighting data with IPTW. Thus, this study demonstrates no significant effect of RNI on OS in either patients with residual ITCs or in patients with micrometastases.

In our series, residual micrometastases were not associated with worse OS compared to residual ITC on univariable or multivariable Cox proportional hazard analysis. These findings are similar to a large combined institutional and NCDB analysis by Wong et al. who reported similar OS with residual micrometastases and ITCs in cN1 patients (5-year OS 78.3% vs 81.0%, respectively) [9]. Additionally, the authors also reported higher 5-year OS in patients who had a

nodal pCR, but worse OS in those with residual macrometastatic nodal disease (5-year OS: ypN0 86.7%, ypN1 77.3%, ypN2-3 60.6%). In another study by van Nijnatten et al., 5-year DFS and OS were similar among ypN0 and ypN0i+/ypN1mi patients, but was significantly worse in patients with ypN1-3 disease; however, the investigators did not compare the outcomes for patients with ypN0 to ypN1mi [8]. When assessing the effect of RNI based on extent of residual low volume nodal disease, we also found no significant effect on OS in both ypN0i+ and ypN1mi patients. The similarities of outcomes associated with RNI among patients with ITC and micrometastases suggest that these patients may have an overall similar prognosis to patients with a nodal pCR, which can be an important decision-making factor in determining the need for adjuvant therapy.

The surgical management of the axilla in patients with breast cancer who received NAC is an important aspect of the care and outcomes of these patients. The false negative rate in detecting positive lymph nodes is higher following NAC [13]. Three prospective trials (ACOSOG-Z1071, SENTINA, and SN FNAC) investigated patients with clinically positive lymph nodes prior to NAC who experienced a clinical CR and underwent sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND). These trials reported an overall false-negative rate of 12.6%, 14.2%, and 13.3%, respectively, which exceed the 10% acceptable rate considered to be safe [14-16]. In ACOSOG-Z1071, the false negative rate was reduced when dual mapping was used (10.8% dual agent vs. 20.3% single agent, p=0.05) and when at least 3 SLN were removed compared to ≤2 SLN (9.1% vs 21.1%, p=0.007) [14]. Similarly, in the SENTINA and SN FNAC trials, the false negative rates were reduced to 7.3% and 4.9%, respectively, when ≥3 SLN were removed [15, 16]. In a meta-analysis of patients with biopsy-proven node positive breast cancer who underwent NAC, the false negative rate following SLNB

was 14%, but was decreased to 11% with the use of dual mapping and 4% when ≥3 SLN were removed [17]. Regarding residual micrometastases, the ALLIANCE A011202 trial will further address if ALND is necessary in cN+ patients who convert to cN0 after NAC but are found to have positive residual nodal disease (including micrometastases) in the sentinel lymph nodes. However, this trial does not include an arm with no radiation and thus this trial will not definitively answer whether all patients with residual micrometastases after NAC benefit from RNI [18]. NEONOD-2 is an Italian prospective non-inferiority trial that includes clinically node positive patients who have a clinical complete nodal response following NAC and undergo SLNB only. The study investigates whether patients with residual micrometastases (ypN1mi) can avoid ALND and achieve similar recurrence and survival rates to ypN0 patients (including ypN0i+). In contrast to ALLIANCE A011202, high tangents and RNI are not permitted including axillary level I/II/III/IV, and the internal mammary chain [19]. The NCDB does not have specific data regarding the type and extent of axillary surgery prior to 2012, so it is difficult to evaluate the type of surgical axillary evaluation in patients included in our study. Nonetheless, at least 70% of all patients in our study had at least 5 lymph nodes surgically evaluated regardless of whether they received RNI (Table 1) and we found no significant difference in number of lymph node examined (1-4 vs. ≥5 lymph nodes) in patients who had RNI vs no RNI. For clinically node positive patients who have a clinical CR after NAC, SLNB may be adequate if ≥3 SLN are identified and/or other surgical techniques such as dual mapping is used. However, for patients who have a positive SLN following NAC (including those with residual nodal micrometastases), completion ALND is still considered the standard of care while we await the results of ALLIANCE A011202 [18].

Currently, there are several active randomized clinical trials that aim to address the uncertainty regarding locoregional management following NAC. The B51 trial includes patients with a nodal pCR following NAC. These patients are randomized following lumpectomy to either WBI alone or WBI with RNI or following mastectomy to PMRT with RNI or no RT. Interestingly, patients with ITCs are included in this trial [5]. If this trial demonstrates a benefit of RNI in this population, then it will provide evidence for the benefit of RNI in patients with residual ITCs after NAC as these patients are included in the trial and presumably represent some of the similar or slightly higher risk patients (vs. those with an axillary pCR) who are also likely to benefit from RNI. By extrapolation, a positive finding in B51 will likely also support the use of RNI in higher risk patients, namely those with micrometastatic or macrometastatic disease in the nodes following NAC. If the trial shows no benefit of RNI in patients with a nodal pCR and ITCs, it is unclear whether this conclusion can be extended definitively to patients with residual micrometastases. If B51 proves to be a negative trial and shows no benefit to RNI in patients with a pCR, then the question asked in our study, do patients with residual micrometastases benefit from RNI, will be crucial to study in a prospective fashion. The ALLIANCE A011202 trial can help determine whether patients with residual micrometastases detected in the sentinel lymph nodes require an ALND with nodal RT or can be treated adequately with nodal RT alone [18]. The NEONOD-2 will address whether similar patients treated with NAC who have a clinical CR and residual micrometastases in the sentinel lymph nodes can avoid both completion ALND and RNI while achieving similar recurrence and survival rates to ypN0 patients (including ypN0i+). This study has the least intensive axillary management (no ALND or RNI) for cN1 patients who convert to ycN0 but have residual ypN1mi or ypN0i+ [19].

Our study has several limitations including its retrospective nature, the heterogeneity of data, and variations in data collection including underreporting or misclassification by different hospital sites. Regarding RNI, the NCDB reports whether regional lymph nodes were irradiated in addition to breast or chest wall, but it does not specify which specific nodal levels were included in the irradiated volume (i.e. axillary level I/II, supraclavicular, internal mammary, etc.). There is also heterogeneity in radiation treatment regarding dose, modality, fractionation, and quality that limits the generalizability of our observed results. For instance, the patients who received WBI without RNI may have received some incidental radiation to the axilla which can affect outcomes and this study is unable to capture that information. There is also a lack of information on the specific chemotherapy agents used as part of NAC which is a relevant variable. We also excluded patients with unknown values for crucial variables which introduces selection bias. Furthermore, we had a relatively short follow-up which limits the conclusions of our trial. One major limitation of our study is that our endpoint of overall survival is perhaps not the best endpoint for this patient population, as early stage invasive breast cancer patients have an excellent prognosis and the vast majority of patients usually die from non-breast cancer related causes. Locoregional control and disease-free survival would be more ideal outcomes to measure for this study as these endpoints are more sensitive than OS in understanding potential benefits of RNI and are clinically meaningful for this patient population; however, data regarding disease recurrence is unavailable in the NCDB.

5. Conclusions

In a large national population-based analysis of breast cancer patients who underwent NAC, we report similar overall survival among patients with residual nodal ITCs or

micrometastases. We found no benefit of RNI in patients with residual ITC or micrometastases in the overall cohort as well in separate subset analyses of ypN0i+ and ypN1mi patients. We eagerly await the results of B51 which will help clarify the role of RNI in patients with a nodal pCR and ITCs. If this trial shows a benefit of RNI in patients with a pCR, then there will likely be a benefit of RNI for patients with higher burden of nodal disease after NAC such as the patients included in this study. If B51 does not support any benefit to RNI, then the need for prospective study on the role of RNI for patients with low volume nodal disease after NAC will be crucial.

Acknowledgements:

Joseph K. Kim, MD – Study design, writing of manuscript, creation of tables and figures.

Jerome K. Karp, MD PhD – Statistical analysis

Tables and Figures Captions

Table 1. Patient characteristics

Table 2. Univariable and Multivariable Cox proportional hazard regression model for overall survival (Without IPTW)

Figure 1. Consort Diagram

Figure 2. Kaplan-Meier curves based on receipt of regional nodal irradiation (RNI): a) Entire cohort; b) ypN0i+ patients only; c) ypN1mi+ patients only

Figure 3. Kaplan-Meier curves based on receipt of regional nodal irradiation (RNI) with IPTW: a) Entire cohort; b) ypN0i+ patients only; c) ypN1mi+ patients only

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Table 1. Patient characteristics

	No RNI N=879 (%)	RNI N=1101 (%)	p-value
Age			
Mean	50.8	50.0	
≤50	447 (50.9)	583 (53.0)	0.377
>50	432 (49.1)	518 (47.0)	
Race			
White	589 (67.0)	731 (66.4)	0.577
Black	152 (17.3)	216 (19.6)	
Hispanic	79 (9.0)	85 (7.7)	
Asian/Southeast Asian/Pacific Islander	38 (4.3)	41 (3.7)	
Other	21 (2.4)	28 (2.5)	
Charlson-Deyo Score			
0	786 (90.6)	984 (89.4)	0.427
1-3	83 (9.4)	117 (10.6)	
Histology			
Invasive ductal carcinoma	763 (86.8)	932 (84.7)	0.393
Invasive lobular carcinoma	43 (4.9)	61 (5.5)	
Mixed ductal/lobular or other	73 (8.3)	108 (9.8)	
Grade			
Low (1-2)	349 (39.7)	439 (39.9)	0.294
High (3 or undifferentiated/anaplastic)	453 (51.5)	586 (53.2)	
Unknown	77 (8.8)	76 (6.9)	
Margins			
Negative	844 (96.0)	1062 (96.5)	0.694
Positive	35 (4.0)	39 (3.5)	
Subtype			
Hormone-receptor positive	372 (42.3)	497 (45.1)	0.157
Hormone-receptor negative	208 (23.7)	222 (20.2)	
HER2 positive	299 (34.0)	382 (34.7)	
Clinical Tumor Stage			
0-1	165 (18.8)	152 (13.8)	<0.001
2	500 (56.9)	568 (51.6)	
3	214 (24.3)	381 (34.6)	
Number of lymph nodes examined			
1-4	240 (27.3)	319 (29.0)	0.441
≥5	639 (72.7)	782 (71.0)	
ypT Stage			
0/is	168 (19.1)	234 (21.3)	0.048
1-2	665 (75.7)	785 (71.3)	
3-4	46 (5.2)	82 (7.4)	
ypN Stage			
0i+/0m+	247 (28.1)	280 (25.4)	0.199
1mi	632 (71.9)	821 (74.6)	
Lymphovascular Invasion			
Absent	435 (49.5)	534 (48.5)	0.746

Present	230 (26.2)	305 (27.7)	
Other/Unknown	214 (24.3)	262 (23.8)	
Hormone Therapy			
No	343 (39.0)	377 (34.2)	0.032
Yes	536 (61.0)	724 (65.8)	
Surgery Type			
Breast Conserving Surgery	297 (33.8)	372 (33.8)	1.000
Mastectomy	582 (66.2)	729 (66.2)	
Facility Type			
Community	51 (5.8)	57 (5.2)	0.346
Comprehensive Community	272 (30.9)	327 (29.7)	
Academic/Research	269 (30.6)	316 (28.7)	
Integrated Network	122 (13.9)	188 (17.1)	
NA	165 (18.8)	213 (19.3)	
Distance to Healthcare Facility (miles)			
<10	414 (47.1)	585 (53.1)	0.009
≥10	463 (52.7)	516 (46.9)	
NA	2 (0.2)	0 (0.0)	
Insurance			
Not insured	17 (1.9)	47 (4.3)	0.005
Private	599 (68.1)	764 (69.4)	
Medicaid	130 (14.8)	123 (11.2)	
Medicare	117 (13.3)	136 (12.4)	
Other government	13 (1.5)	21 (1.9)	
Unknown	3 (0.3)	10 (0.9)	
Income			
≤48,000	317 (36.1)	385 (35.0)	0.130
>48,000	559 (63.6)	716 (65.0)	
NA	3 (0.3)	0 (0.0)	
Education			
<13	536 (61.0)	680 (61.8)	0.147
≥13%	340 (38.7)	421 (38.2)	
NA	3 (0.3)	0 (0.0)	
Year of diagnosis			
2004 to 2011	213 (24.2)	259 (23.5)	0.753
2012 to 2016	666 (75.8)	842 (76.5)	

Table 2. Univariable and Multivariable Cox proportional hazard regression model for overall survival (Without IPTW)

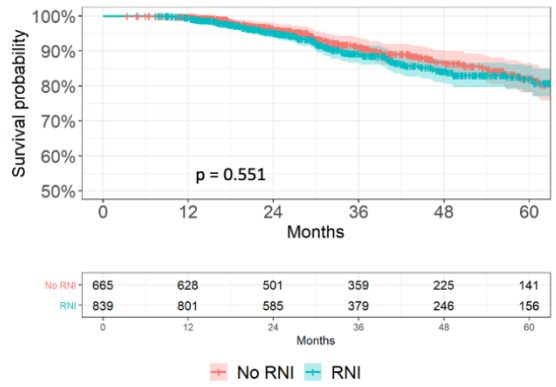
	Univariable			Multivariable		
	HR	95% Confidence Interval	p-value	HR	95% Confidence Interval	p-value
Age						
≤50	Reference			Reference		
>50	1.14	0.88-1.47	0.321	1.01	0.99-1.02	0.520
Race						
White	Reference					
Black	1.11	0.80-1.53	0.540			
Hispanic	0.69	0.40-1.20	0.190			
Asian/Southeast Asian/Pacific Islander	0.98	0.48-2.00	0.964			
Other	0.19	0.03-1.38	0.101			
Charlson-Deyo Score						
0	Reference			Reference		
1-3	1.13	0.75-1.68	0.560	1.26	0.83-1.91	0.288
Histology						
Invasive ductal carcinoma	Reference			Reference		
Invasive lobular carcinoma	0.88	0.48-1.61	0.671	1.08	0.56-2.05	0.824
Mixed ductal/lobular or other	0.75	0.45-1.27	0.286	0.82	0.48-1.39	0.454
Grade						
Low (1-2)	Reference			Reference		
High (3 or undifferentiated/anaplastic)	1.82	1.35-2.45	<0.001	1.51	1.09-2.08	0.012
Unknown	1.90	1.19-3.02	0.007			
Margins						
Negative	Reference					
Positive	0.93	0.49-1.75	0.813			
Subtype						
Hormone-receptor positive	Reference			Reference		
Hormone-receptor negative	2.51	1.89-3.34	<0.001	1.18	0.75-1.84	0.473
HER-2 positive	0.67	0.47-0.97	0.033	0.47	0.31-0.71	<0.001
Clinical Tumor Stage						
0-1	Reference			Reference		
2	1.04	0.71-1.54	0.834	0.96	0.64-1.43	0.841
3	1.39	0.93-2.09	0.109	1.18	0.77-1.81	0.460
Number of lymph nodes examined						
1-4	Reference					
≥5	0.71	0.51-0.97	0.031			
ypT Stage						
0/is	Reference			Reference		
1-2	1.81	1.21-2.70	0.004	2.22	1.46-3.37	<0.001
3-4	2.29	1.29-4.05	0.004	2.66	1.44-4.90	0.002
ypN Stage						
0i+	Reference			Reference		

1mi	1.22	0.90-1.66	0.202	1.26	0.92-1.73	0.146
Lymphovascular Invasion						
Absent	Reference			Reference		
Present	1.65	1.22-2.22	0.001	1.59	1.17-2.15	0.003
Other/Unknown	1.08	0.77-1.50	0.662	1.05	0.74-1.47	0.794
Surgery Type						
Breast Conserving Surgery	Reference			Reference		
Mastectomy	1.44	1.07-1.93	0.016	1.33	0.98-1.81	0.072
Endocrine Therapy						
No	Reference			Reference		
Yes	0.37	0.29-0.48	<0.001	0.41	0.27-0.62	<0.001
Regional Nodal Irradiation						
No	Reference			Reference		
Yes	1.04	0.81-1.35	0.749	1.05	0.80-1.37	0.716
Facility Type						
Community	Reference					
Comprehensive Community	1.38	0.71-2.66	0.341			
Academic/Research	1.19	0.61-2.30	0.613			
Integrated Network	1.16	0.58-2.33	0.681			
Distance to Healthcare Facility (miles)						
<10	Reference					
≥10	0.96	0.74-1.24	0.75			
Insurance						
Not insured	Reference			Reference		
Private	0.50	0.27-0.93	0.027	0.57	0.31-1.08	0.084
Medicaid	0.73	0.37-1.45	0.368	0.71	0.36-1.43	0.341
Medicare	0.87	0.45-1.70	0.690	0.70	0.33-1.47	0.341
Other government	1.02	0.38-2.75	0.975	0.89	0.33-2.45	0.826
Unknown	0.67	0.15-3.05	0.603	0.82	0.18-3.75	0.792
Income						
≤48,000	Reference			Reference		
>48,000	0.74	0.57-0.96	0.026	0.70	0.53-0.91	0.008
Education						
<13%	Reference					
≥13%	1.04	0.80-1.36	0.757			
Year of diagnosis						
2004 to 2011	Reference			Reference		
2012 to 2016	1.60	1.18-2.17	0.002	1.69	1.24-2.29	0.001

- Using the NCDB, we investigated the role of adjuvant regional nodal irradiation (RNI) in clinically node-positive (cN1) invasive breast cancer with residual nodal micrometastases (ypN1mi) or ITC (ypN0i+) following neoadjuvant chemotherapy and definitive surgery.

- We found no significant difference in overall survival with the use of regional nodal irradiation in patients with residual ITC or micrometastases.

- There was no significant difference in overall survival difference between residual micrometastases and isolated tumor cells.



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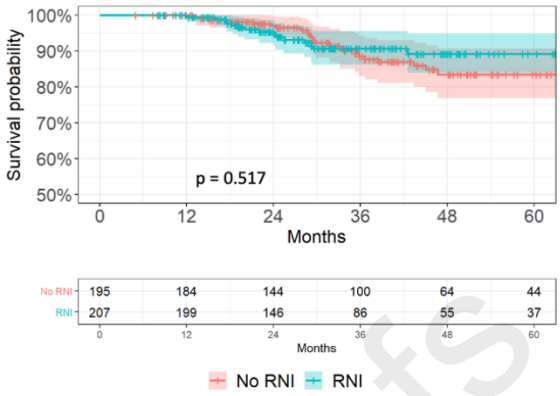

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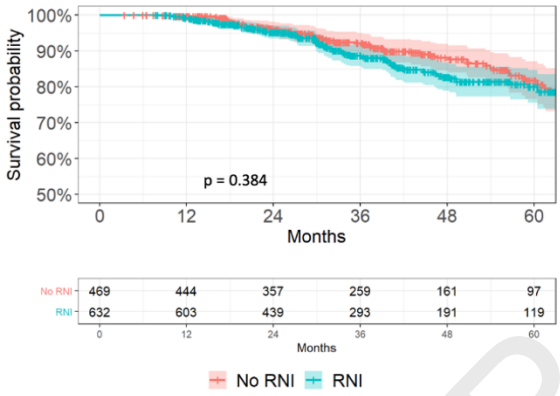

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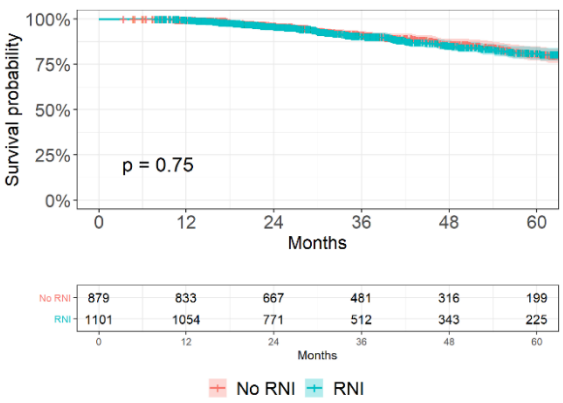

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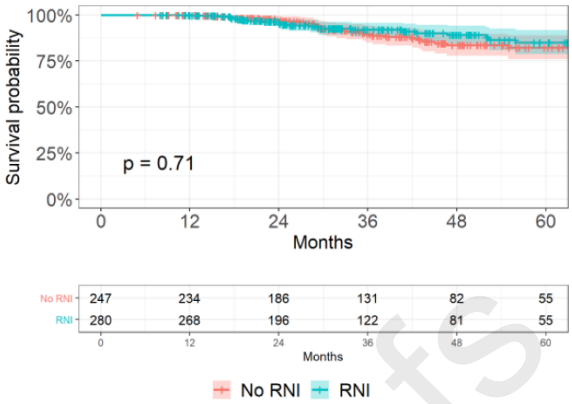

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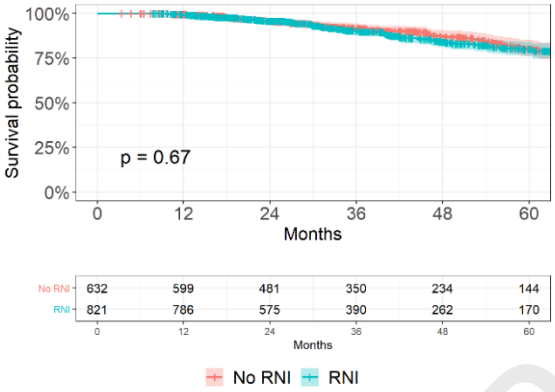

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