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Scientific Article

Breast Cancer Presenting With Intravascular Tumor Emboli in Axillary Soft Tissue: Recurrence Risk and Radiation Therapy Outcomes

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Purpose: Intravascular tumor emboli in axillary soft tissue (ITE) is a rare pathologic finding in breast cancer and is associated with higher axillary nodal disease burden. The independent prognostic and predictive value of this entity is unknown, as is the role of radiation therapy for ITE.

Methods and Materials: We analyzed a prospectively maintained database of breast cancer patients treated from 1992 to 2020. Patients with ITE were matched to those without (1:2) based on propensity scores to control for potential confounding factors. Locoregional (LRR) and distant recurrence (DR) were evaluated using competing risks methods accounting for death as a competing event. Overall survival (OS) and disease-free survival (DFS) were evaluated by Cox regression models. Among patients with ITE, we also evaluated whether RT improved outcomes.

Results: Among 2377 total patients, 129 had ITE, of whom 126 were propensity score matched to 252 without ITE. Median follow-up from time of surgery was 5.5 years (IQR 2.3, 9.7). There were no statistically significant differences in the 5-year incidence of LRR between groups (5.4% [95% CI, 1.6%-13%] with ITE vs 10% [95% CI, 6.7%-15%] without, $P = .53$) or DR (24% [95% CI, 15% 35%] with ITE vs 21% [95% CI, 16%-27%] without, $P = .51$). Five-year OS and DFS did not differ between groups ($P > .9$ for both comparisons, patients with ITE vs without ITE). In analyzing the effect of RT among patients with ITE, receipt of RT was associated with significantly improved DFS (HR, 0.34, 95% CI, 0.12-0.93, $P = .04$).

Conclusions: Patients with ITE do not exhibit significantly worse LRR, DR, DFS, or OS compared with a propensity-score-matched cohort without ITE. However, among patients with ITE, those who received RT demonstrated significantly improved DFS. Larger studies with longer follow-up are needed to evaluate the prognostic and predictive implications of ITE.

Introduction

Breast cancer is the most common noncutaneous malignancy among women worldwide.[1] In recent years, a series of landmark clinical trials has revealed that regional

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nodal irradiation (RNI) carries significant disease-control and survival benefits even among patients who have a limited axillary disease burden.[2−4] In addition to anatomic nodal burden, other locoregional tumor characteristics are known to yield prognostic and predictive information to help inform shared decision-making regarding treatment optimization.

Intravascular tumor emboli in axillary soft tissue (ITE) is a rare pathologic finding in the axillary evaluation of breast cancer via sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALN).[5] This entity is characterized by the finding of tumor emboli in the axillary vasculature, distinct from disease in nodal tissue or lymphatics. The prognostic and predictive implications of this finding remain unclear as the existing literature on outcomes for patients with ITE remains sparse.

Although ITE may intuitively seem to be an adverse pathologic finding, its independent effect on disease control or treatment response is unknown; therefore, it remains unclear how to incorporate ITE into adjuvant treatment decision-making. Here, we characterized the local-regional (LRR) and distant recurrence (DR) risk associated with ITE, in addition to disease-free (DFS) and overall survival (OS) outcomes among matched breast cancer patients presenting with ITE compared with those without.

Methods

Study population

Patients with invasive breast cancer treated at our center from 1992 to 2020 were identified from a prospectively maintained institutional database for this institutional review board approved study. All patients for whom clinicopathologic and treatment data were available were included. The following parameters were collected: presence of ITE, age, pathologic T stage, number of positive nodes, ER status, HER2 status, lymphovascular invasion (LVI), tumor grade, receipt of radiation therapy, receipt of chemotherapy, surgery type, and type of axillary nodal evaluation. Patients with the following features were excluded to facilitate appropriate matching as described below: primary tumors >5 cm in size, receipt of neoadjuvant chemotherapy, and synchronous bilateral breast cancers.

Statistical analysis

Patients with ITE were matched to 2 controls without ITE based on nearest neighbor propensity score matching. Propensity scores were derived based on the number of positive nodes removed, pathologic T stage, age at diagnosis, ER status, HER2 status, presence of LVI, tumor grade, receipt of radiation therapy or chemotherapy, surgery type, and axillary node sampling type.

Survival outcomes were compared between patients with versus without ITE among patients in the propensity matched cohort. The primary outcome was OS from the date of last excision for the primary tumor. For patients with multiple re-excisions, the time from the final excision was used. Secondary endpoints included DFS, LRR, and DR. DFS was defined from final excision; events included local or distant recurrence or death. Patients alive without an event for all endpoints were censored at the study cutoff date (11/2021) for all survival endpoints. OS and DFS were evaluated using Cox regression models. Hazard ratios and 95% confidence intervals (CI) are presented. LRR and distant recurrence were evaluated using competing risks methods accounting for death as a competing event. The cumulative incidence of LRR and DR at 5 and 10 years is presented along with 95% confidence intervals. In this analysis, a diagnosis of contralateral primary breast cancer was not counted as a recurrent event. All survival analyses are based on stratified models to account for the matched pairs.

To assess the robustness of the results based on propensity score matching, we also performed secondary analyses of OS, DFS, and LRR using multivariable adjusted regression models for our primary and secondary endpoints. Covariates included in this model were the same as those used in propensity matching (listed above). Radiation therapy was included as a covariate in these analyses; since radiation was given after surgery but radiation therapy dates were not available, we imposed a 6-month landmark to reflect the clinical expectation that patients complete their course of radiation therapy within 6 months of surgery.

Effect of radiation therapy

Although receipt of radiation therapy was a factor considered for the propensity score matching, it is possible that there is residual confounding due to this feature in the analysis of DFS. We performed an additional analysis of DFS using a multivariable Cox model with covariates indicating the presence of ITE and receipt of radiation therapy with a 6-month landmark to account for the completion of radiation therapy. To avoid only keeping a subset of matched pairs, if the patient with ITE or either matched control was excluded for having an event or being lost to follow-up before the landmark time of 6 months, the entire matched pair (the ITE patient and the controls) was excluded from the analysis.

Lastly, to evaluate if radiation therapy alters the clinical course among patients with ITE, we compared OS, DFS, LRR, and DR in a subanalysis of patients with ITE that were and were not treated with RT. A 6-month landmark was again used for these analyses.

Analyses were performed using R v4.1.2.

Table 1 Patient and disease characteristics of all patients

Characteristic	No ITE, N = 2248*	ITE, N = 129*	*P* value
Age at diagnosis (years)			.12†
Median (IQR)	55 (46, 64)	52 (42, 64)	
Range	20, 85	23, 84	
Pathologic T stage			<.001‡
T0	21 (0.9%)	0 (0%)	
T1	1661 (74%)	58 (45%)	
T2	566 (25%)	71 (55%)	
Positive nodes removed			<.001§
0	1458 (65%)	0 (0%)	
1-3	613 (27%)	72 (56%)	
4+	177 (7.9%)	57 (44%)	
ER status			.6‡
Negative	333 (15%)	16 (12%)	
Positive	1894 (84%)	113 (88%)	
Unknown/Not Done	21 (0.9%)	0 (0%)	
HER2 status			.2‡
Equivocal	22 (1.0%)	1 (0.8%)	
Negative	1842 (82%)	104 (81%)	
Not Done/Unknown	50 (2.2%)	0 (0%)	
Positive	334 (15%)	24 (19%)	
Lymphovascular invasion	722 (32%)	104 (81%)	<.001§
Grade			.017§
I	276 (14%)	9 (7.0%)	
II	939 (47%)	55 (43%)	
III	781 (39%)	64 (50%)	
Unknown	252	1	
Surgery type			.002‡
Breast conservation	1527 (68%)	69 (53%)	
Mastectomy	719 (32%)	60 (47%)	
None	1 (<0.1%)	0 (0%)	
Unknown	1	0	
Axillary surgery			<.001‡
ALN	661 (29%)	83 (64%)	
None	1 (<0.1%)	0 (0%)	
SLN	1586 (71%)	46 (36%)	
Radiation therapy	1,589 (71%)	99 (77%)	.14§
Chemotherapy	1,208 (54%)	105 (81%)	<.00§

Abbreviation: ITE = intravascular tumor emboli in axillary soft tissue.
*n (%).
†Wilcoxon rank sum test.
‡Fisher's exact test.
§Pearson's χ^2 test.

Table 2 Patient and disease characteristics after propensity-score matching

Characteristic	No ITE, N = 252*	ITE, N = 126*	*P* value
Age at diagnosis (years)			>.9†
Median (IQR)	52 (44, 63)	52 (42, 64)	
Range	20, 80	23, 84	
Pathologic T stage			.7‡
T1	108 (43%)	57 (45%)	
T2	144 (57%)	69 (55%)	
Positive nodes removed			.7§
0	0 (0%)	0 (0%)	
1-3	136 (54%)	71 (56%)	
4+	116 (46%)	55 (44%)	
ER status			.7‡
Negative	29 (12%)	16 (13%)	
Positive	223 (88%)	110 (87%)	
HER2 status			>.9§
Equivocal	1 (0.4%)	1 (0.8%)	
Negative	200 (79%)	101 (80%)	
Positive	51 (20%)	24 (19%)	
Lymphovascular invasion	199 (79%)	101 (80%)	.8‡
Grade			>.9‡
I	15 (6.0%)	9 (7.1%)	
II	110 (44%)	54 (43%)	
III	127 (50%)	63 (50%)	
Surgery type			.3‡
Breast conservation	121 (48%)	68 (54%)	
Mastectomy	131 (52%)	58 (46%)	
Axillary surgery			.7‡
ALN	171 (68%)	83 (66%)	
SLN	81 (32%)	43 (34%)	
Radiation therapy	202 (80%)	98 (78%)	.6‡
Chemotherapy	213 (85%)	105 (83%)	.8‡

Abbreviation: ITE = intravascular tumor emboli in axillary soft tissue.
*n (%).
†Wilcoxon rank sum test.
‡Pearson's χ^2 test.
§Fisher's exact test.

Results

Patient characteristics

We identified 2377 women with invasive breast cancer treated between 1992 and 2020 for whom complete information regarding clinicopathologic features and treatment were available. Among these, 129 (5.4%) exhibited ITE at the time of surgical axillary evaluation. Compared with those without ITE, patients with ITE were significantly more likely to have pathologic T2 disease (55% vs 25%), ≥4 positive nodes (44% vs 7.9%), high-grade tumors (50% vs 39%), LVI (81% vs 32%), and to be treated with mastectomy (47% vs 32%), ALN (64% vs 29%), and chemotherapy (81% vs 54%). Between those with ITE and those without, age at diagnosis was similar (median (interquartile range): 52 (42, 64) vs 55 (46, 64) years), as was ER positivity (88% vs 84%), HER2 positivity (19% vs 15%), and receipt of radiation therapy (77% vs 71%) (Table 1).

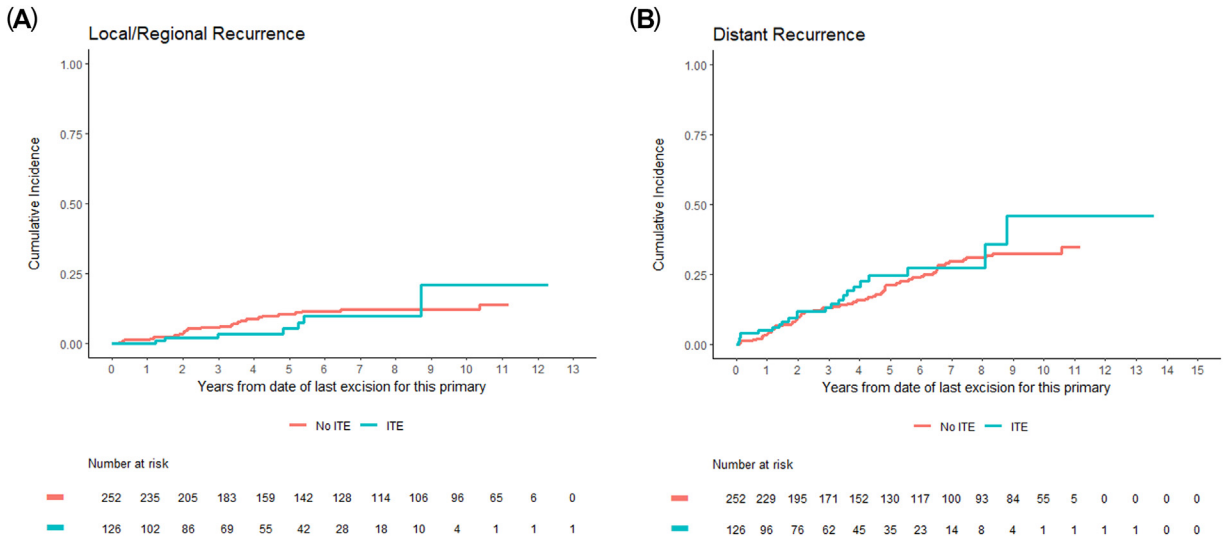

Figure 1 Locoregional and distant recurrence risk. (A) Cumulative incidence of locoregional recurrence (LRR) among patients with intravascular tumor emboli in axillary soft tissue (ITE) versus LRR among those without ITE. (B) Cumulative incidence of distant recurrence (DR) among patients with intravascular tumor emboli in axillary soft tissue (ITE) versus DR among those without ITE.

Of the 129 patients with ITE, 126 were matched in 1:2 fashion to 252 patients without ITE. Three patients with ITE could not be matched to non-ITE patients and were excluded from the matched analyses. After matching, the 2 cohorts had similar age, pathologic T stage, number of positive nodes removed, ER/HER2 status, LVI status, grade, radiation therapy and chemotherapy status, surgery type, and axillary nodal sampling type (Table 2).

Characteristics of the 3 patients with ITE that could not be matched are summarized in Supplementary Table E1.

Recurrence

After a median follow-up of 5.5 years (interquartile range, 2.3, 9.7), we observed 33 locoregional recurrence events in the propensity matched cohort (7 among those with ITE, 26 among those without ITE). At 5 years, the cumulative incidence of LRR was 5.4% (95% CI, 1.6%-13%) for patients with ITE vs 10% (95% CI, 6.7%, 15%) for those without ITE (P = .53; Fig. 1A). There were 86 DR events (23 among ITE, 63 among those without ITE), yielding a 5-year DR rate of 24% (95% CI, 15%, 35%) vs 21% (95% CI, 16%, 27%; P = .51; Fig. 1B).

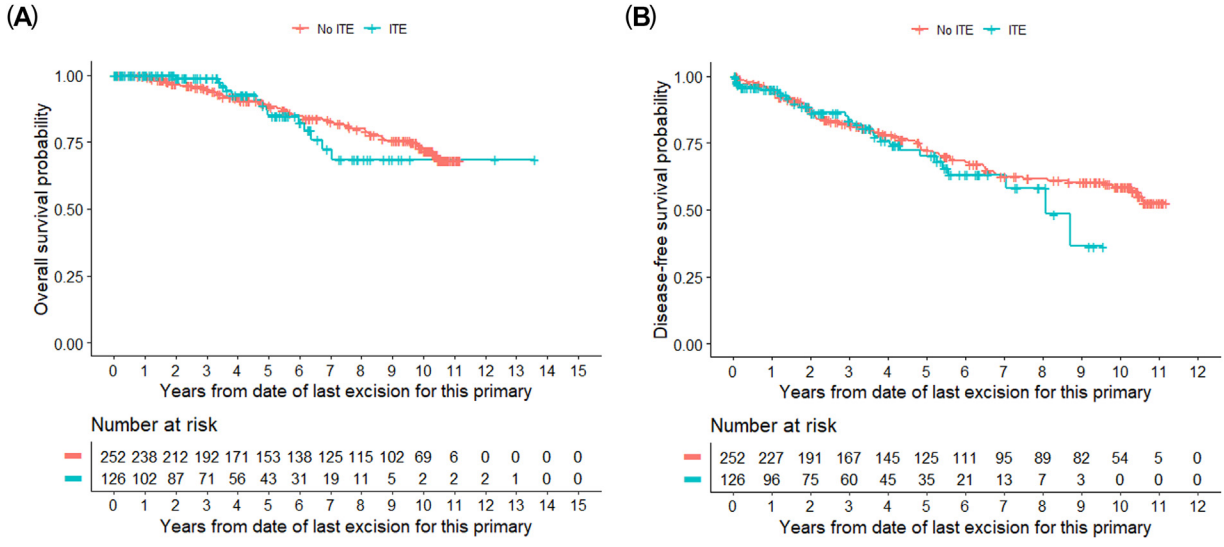

Figure 2 Overall and disease-free survival. (A) Overall survival (OS) among patients with intravascular tumor emboli in axillary soft tissue (ITE) versus OS among those without ITE. (B) Disease-free survival (DFS) among patients with intravascular tumor emboli in axillary soft tissue (ITE) versus DFS among those without ITE.

Survival

There were 14 deaths among patients with ITE and 49 deaths among patients without ITE. The 5-year survival estimates were OS 85% (95% CI, 76%-95%) vs 89% (95% CI, 84%-93%), respectively. There was not a statistically significant difference in OS for patients with ITE compared with patients without ITE (HR, 0.98, 95% CI, 0.46-2.08; $P > .9$; Fig. 2A). DFS also did not vary statistically significantly between groups: 5-year DFS for patients with ITE was 70% (95% CI, 60%-82%) compared with 72% (95% CI, 67%-79%) for patients without ITE (HR, 1.01, 95% CI, 0.60-1.71, $P > .9$) (Fig. 2B). These results were consistent with the sensitivity analysis of the unmatched cohort (115 patients with ITE, 2134 patients without ITE alive at 6-month landmark with complete covariate information), using a multivariable competing risk regression model (for LRR) and multivariable Cox regression models (for OS and DFS) (Supplemental Table E2).

Impact of radiation therapy

After implementation of a 6-month landmark on the matched cohort, 97 patients with ITE and 194 non-ITE patients were available for analysis. Most patients received RT: 86 (89%) patients with ITE and 160 (82%) patients without ITE. When stratified by presence of ITE and receipt of RT, patients with ITE and no radiation therapy had the worst 5-year DFS (39%; 95% CI, 14%-100%) (Fig. 3A). Patients who had ITE and received RT had a 5-year DFS of 75% (95% CI, 64%-88%), whereas those without ITE and not receiving RT had a 5-year DFS of 66% (95% CI, 51%-86%), and those without ITE who received RT had a 5-year DFS of 75% (95% CI, 68%-83%).

In a subanalysis among patients with ITE (excluding 21 with events or who were censored within 6 months after surgery via landmark analysis), receipt of radiation therapy was associated with significantly improved DFS (HR, 0.34, 95% CI, 0.12-0.93, $P = .04$) (Fig. 3B). After excluding 14 patients who died or were censored before the 6-month landmark time, OS was not statistically significantly different among patients with ITE, with versus without RT (HR, 0.46, 95% CI, 0.14-1.45, $P = .2$) (Fig. 3C). The 5-year cumulative incidence of LRR among patients with ITE who received RT was 8.3% (95% CI, 2.5%, 19%) compared with 18% (2.1%, 45%) for ITE patients who did not receive RT ($P = .31$) (Fig. 3D). Cumulative incidence of DR at 5 years was 19% (95% CI, 9.9%-29%) versus 44% (5.9%-79%) for patients with ITE, with versus without RT, respectively ($P = .3$) (Fig. 3E).

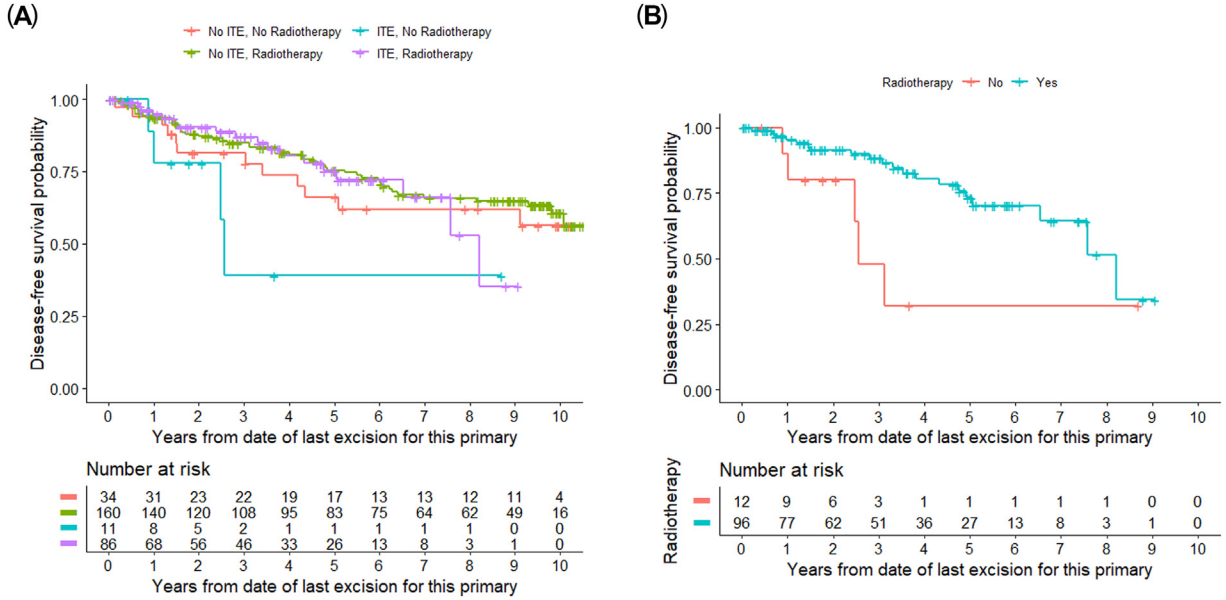

Figure 3 Impact of radiation therapy on outcomes. (A) Disease-free survival, stratified by presence of ITE and whether the patient received radiation therapy. Patients with ITE who did not have radiation therapy exhibited shorter disease-free survival. (B) Kaplan-Meier estimates of disease-free survival among all patients with intravascular tumor emboli in axillary soft tissue, stratified by receipt of radiation therapy. (C) Kaplan-Meier estimates of overall survival among all patients with intravascular tumor emboli in axillary soft tissue did not demonstrate a statistically significant difference when stratified by receipt of radiation therapy. (D) Cumulative incidence of locoregional recurrence among all patients with intravascular tumor emboli in axillary soft tissue stratified by receipt of radiation therapy. (E) Cumulative incidence of distant recurrence among all patients with intravascular tumor emboli in axillary soft tissue stratified by receipt of radiation therapy.

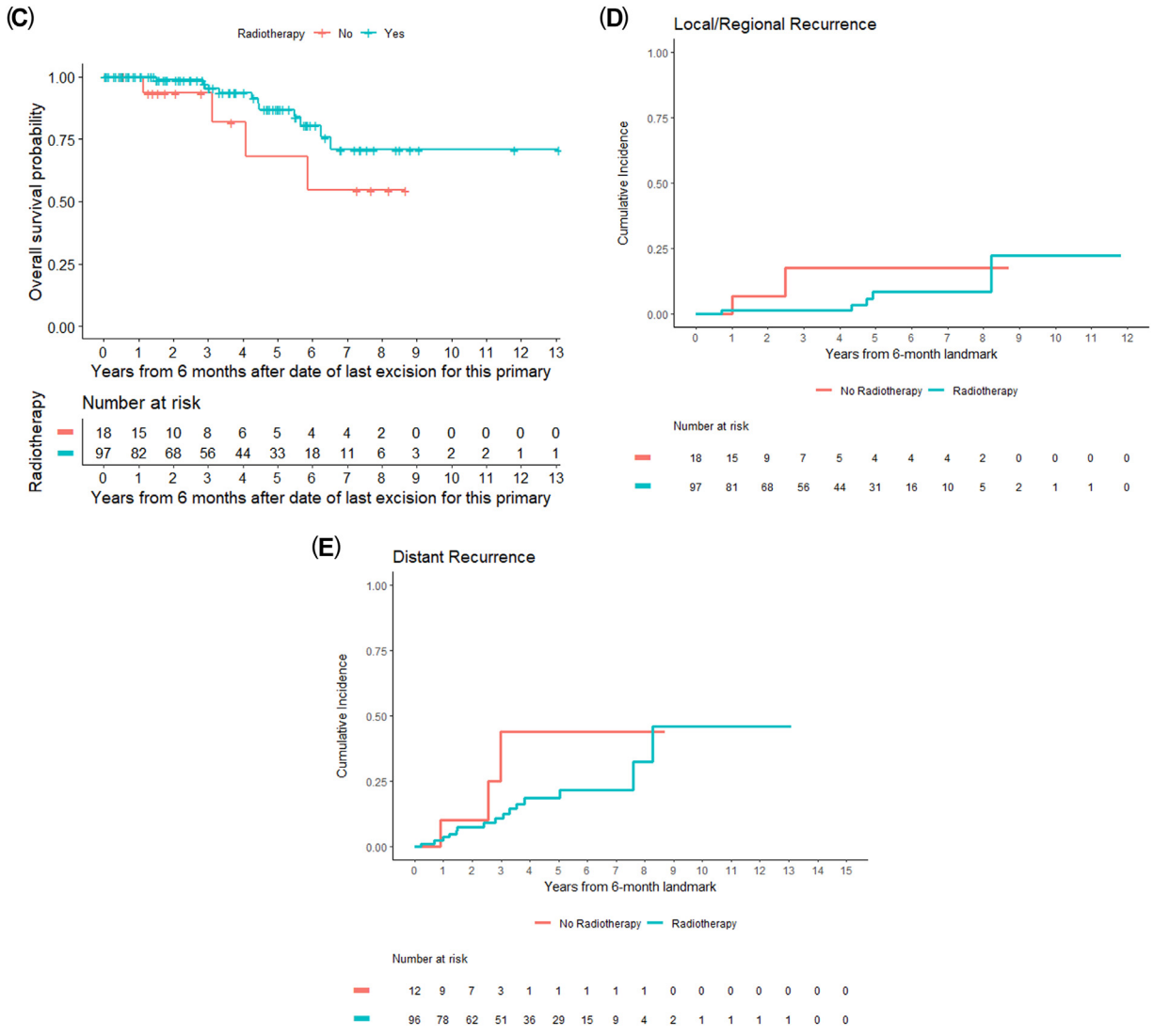

Figure 3 **Continued.**

Discussion

In this large cohort study of patients with intravascular tumor emboli in axillary soft tissue (ITE), we found that ITE was not independently prognostic of adverse outcomes when accounting for salient clinicopathologic risk factors. Neither propensity score matched analyses or multivariable Cox regression demonstrated an association between ITE and adverse LRR or DR outcomes or worse survival. Notably, among those with ITE, RT was associated with an improvement in DFS.

Increasing extent of axillary lymph node involvement has long been associated with adverse disease outcomes in breast cancer and, consequently, with escalation of treatment. The use of regional nodal irradiation is defined by a series of contemporary clinical trials and relies heavily on the constellation of clinicopathologic presenting features. Although generally well-tolerated, the benefit of regional nodal irradiation must be weighed against the increased risks of pneumonitis, dermatitis, and lymphedema.[2] Pooled analyses of ECOG and NSABP trials in which patients received surgery and chemotherapy, but not radiation therapy, have shown that higher number of nodes involved increases locoregional recurrence risk.[6,7] Historical data have further shown that patients with any amount of lymph node involvement experience a locoregional and OS benefit from radiation to the lymph nodes.[8,9] However, these data have been criticized for inadequate axillary surgery and the use of outdated systemic therapies.[10] More recently, MA.20 and EORTC 22922 assessed the utility of RNI in the context of contemporary surgery and systemic therapy, both demonstrating a DFS benefit even among those with limited axillary disease burden.[2,3]

To date, few studies have explored the effect of extranodal axillary disease among breast cancer patients.[5]

Mamtani et al found that the presence of extranodal tumor deposits in axillary fat (including axillary ITE) was predictive of a higher nodal burden of 4 or more positive nonsentinel lymph nodes. They further demonstrated that the presence of extratumoral deposits was associated with larger tumor size and microscopic extracapsular extension. Although the study did not evaluate the oncologic or survival implications of extratumoral deposits, the investigators concluded that patients with extratumoral deposits may benefit from ALN rather than SLNB alone. Our study builds on these findings with a larger cohort of matched patients to demonstrate that ITE specifically (as opposed to disease in axillary fat, generally) is not independently predictive of recurrence or survival.

A potential explanation for similar outcomes with and without ITE in our cohort is that the presence of ITE prompted aggressive therapy in most cases. In our unmatched cohort of patients with ITE, 64% underwent axillary node dissection, 77% received radiation therapy, and 81% received chemotherapy, possibly mitigating the adverse implications of this otherwise adverse risk factor. Of note, upon analyzing RT among those with ITE, DFS was statistically significantly improved among those who received RT compared with those who did not.

These findings must be interpreted in the context of the study design. The retrospective nature of our analyses allows the for the possibility of bias and residual confounding. We attempted to mitigate this risk by controlling for key clinical factors in both (a) propensity-matched cohort analyses whereby the most salient confounders were aligned between those with ITE and those without ITE, and (b) multivariable regression among the larger unmatched cohort, yielding similar results.

Our findings suggest that axillary ITE may not be independently associated with worse LRR, DR, DFS, or OS among appropriately treated patients. However, ITE is significantly associated with other adverse risk factors that must be managed appropriately, such as greater nodal burden, increased tumor size, and higher tumor grade. To that end, our results demonstrate significantly improved DFS among those with ITE in our cohort who received RT. Indeed, regional nodal irradiation in conjunction with contemporary systemic therapy and comprehensive surgical management may have mitigated the underlying risk posed by ITE in our overall cohort. Larger studies inclusive of patients not receiving comprehensive trimodality therapy may further elucidate the underlying risks posed by this uncommon pathologic finding.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2024.101508.

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