

CLINICAL INVESTIGATION

Molecular Risk Stratification for Decision-Making Among Patients With Breast Cancer Eligible to Omit Radiation Therapy



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Purpose: Radiation therapy (RT) following breast-conserving surgery reduces the risk of recurrence for early-stage breast cancer. A subset of patients with favorable clinical and pathologic characteristics can safely omit RT with a modest increase in recurrences, yet without survival implications. We sought to evaluate whether molecular risk profiling among such patients could further stratify them into (1) a higher-risk subgroup that may be inappropriate for RT omission and (2) an exceedingly favorable subgroup that might more strongly consider RT omission.

Methods and Materials: Using a prospectively maintained institutional database, we evaluated patients aged ≥ 65 years who underwent breast-conserving surgery for early-stage, estrogen receptor–positive breast cancer (ie, patients putatively eligible for RT omission). Patients were stratified by clinicopathologic features and Oncotype DX Recurrence Score (RS; ≤ 25 vs > 25) and were evaluated for oncologic outcomes and survival by receipt of RT.

Results: The overall cohort comprised 1587 patients: 92% had RS ≤ 25 ($n = 1455$) and 8% had RS > 25 ($n = 132$). With a median follow-up of 74.4 months, the cumulative incidence of local recurrence was low throughout and did not significantly differ between those with RS ≤ 25 vs > 25 (6-year rate 1.9% vs 0.8%; $P = .5$). Among those who did not undergo RT ($n = 350$), patients with RS > 25 ($n = 19$) did not have a significantly higher incidence of local recurrence than patients with RS ≤ 25 (6-year rate 5.6% vs 4.2%; $P = .5$).

Conclusions: Among patients ≥ 65 years of age who underwent breast-conserving surgery for early-stage estrogen receptor–positive breast cancer, Oncotype DX RS did not further refine recurrence risk estimates for RT decision-making beyond the findings of landmark RT omission trials. Although the number of patients with Oncotype DX RS > 25 who omitted RT was limited in this study, this subgroup did not exhibit a significantly higher risk than their low-molecular-risk counterparts,

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suggesting that risk score need not necessarily disqualify select patients who seek to forgo adjuvant RT. Prospective analyses with larger sample sizes will further elucidate the role of molecular assays in guiding RT decision-making across risk strata. © 2026 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

Introduction

The role of adjuvant radiation therapy (RT) following breast-conserving surgery (BCS) in the treatment of breast cancer has been known to reduce the risk of recurrence for over half a century. More recently, landmark trials such as Cancer and Leukemia Group B (CALGB) 9343 and Postoperative Radiotherapy in Minimum-Risk Elderly (PRIME) II have demonstrated that radiation can be safely omitted among select subgroups of older patients with estrogen-positive breast cancer and favorable tumor characteristics in the context of adjuvant hormone therapy.^{1,2} Adjuvant RT among this subset of patients is now a shared decision between physicians and patients, with the understanding that omission of RT poses a modestly higher yet acceptably low risk of recurrence, and does not compromise overall survival (OS).

Since the publication of these pivotal trials, molecular and genomic profiling scores have achieved broad adoption for systemic therapy decision-making.^{3,4} Many ongoing studies aim to further integrate such molecular profiling into radiation treatment decision-making, such as the PRECISION, EXPERT, IDEA, LUMINA, DEBRA, and DCI-SionRT trials.⁵⁻¹⁰ These efforts focus on younger patients with low-risk molecular scores who are assigned to forgo RT. Few efforts are underway to further stratify those patients already eligible for RT omission into lower- or higher-risk groups based on molecular profiles. Thus, despite the routine omission of RT in such select populations, further research is needed to understand the implications of molecular scores in the context of RT omission and to determine whether even lower-risk cohorts exist or whether elevated molecular risk scores should strengthen the recommendation for RT.

To address this, we evaluated a cohort of women ≥ 65 years of age with early-stage, estrogen receptor-positive, progesterone receptor-positive, and HER2neu-negative (ER+/PR+/HER2-) breast cancer treated with BCS. We evaluated the Oncotype DX Recurrence Scores to examine associations between the RSs, with or without receipt of adjuvant RT, and subsequent oncologic outcomes. Namely, we sought to elucidate whether patients with a low Oncotype DX RS had particularly low recurrence risk and whether those with an elevated Oncotype DX RS exhibited increased recurrence risk in the absence of RT.

Methods and Materials

Using a prospectively maintained institutional database, we identified all female patients aged ≥ 65 years with early-stage

breast cancer who underwent BCS from 2006 to 2018, yielding tumors ≤ 2 cm in size without lymph node involvement (T1N0). This study was approved by the Memorial Sloan Kettering Cancer Center institutional review board. Patients were included if their cancers were ER+/PR+/HER2- and had evaluable Oncotype DX Recurrence Score (RS). Patients were excluded if they presented with bilateral breast cancer or with nonlocalized disease at the time of diagnosis. Patients were grouped into low-risk Oncotype DX RS (≤ 25) and high-risk Oncotype DX RS (> 25) based on the thresholds for benefit from adjuvant chemotherapy.^{11,12}

Descriptive statistics were used to summarize patient and tumor characteristics stratified by Oncotype DX RS (≤ 25 vs > 25), with variables compared between groups using Wilcoxon rank-sum, Pearson χ^2 , or Fisher exact tests, as appropriate. Local recurrence was analyzed as a time-to-event outcome using cumulative incidence curves, stratified by Oncotype DX RS (≤ 25 vs > 25), with death treated as a competing risk. Comparisons between groups were assessed using Gray test. Kaplan-Meier curves were used to estimate disease-free survival (DFS) stratified by Oncotype DX RS (≤ 25 vs > 25), with comparisons made using the log-rank test.

Univariable (UV) and multivariable (MV) Fine-Gray competing risks regression model analyses were conducted to identify factors associated with local recurrence. UV and MV Cox proportional hazards models were used to estimate hazard ratios (HRs) for DFS. Variables included in all UV analyses were selected a priori based on clinical relevance and included Oncotype DX RS, age at diagnosis, lymphovascular invasion, overall tumor grade, pathologic tumor size, receipt of chemotherapy, use of hormonal therapy, receipt of RT, and RT type (ie, none, outside hospital RT, partial breast irradiation, or whole-breast irradiation). Variables were chosen for MV models based on results from the UV analyses and the number of events that could support reliable HR estimation.

Results

Overall patient population

The overall study cohort included 1587 patients aged ≥ 65 years with ER+/PR+/HER2- early-stage breast cancer who underwent BCS. Of these, 1455 (92%) had an Oncotype DX RS ≤ 25 , and 132 (8%) had an RS > 25 . The median age of the cohort was 69 years, and the median follow-up was 74.4 months. Surgical axillary staging was universal in this cohort (99.9%); 99% of patients underwent sentinel node biopsy, and 0.8% underwent axillary node dissection. Only 2 patients (0.1%) had clinical nodal staging alone.

Higher Oncotype DX RS was significantly associated with adverse pathologic features, including younger age, lymphovascular invasion, and higher grade (all $P \leq .01$; Table 1). Consequently, treatment patterns differed significantly by Oncotype

DX RS. RT receipt varied by Oncotype DX RS (77% received RT among those with RS ≤ 25 vs 86% among those >25 ; $P = .03$), and those with higher RS also had higher rates of whole-breast irradiation in comparison to partial breast techniques

Table 1 Patient characteristics by oncotype (≤ 25 vs >25)

Characteristic	Overall N = 1587*	≤ 25 N = 1455*	>25 N = 132*	P value†
Age at diagnosis (y)	69.0 (64.9, 89.8)	69.1 (64.9, 89.8)	68.0 (65.0, 82.0)	.007
Lymphovascular invasion				.011
No	1381 (87%)	1275 (88%)	106 (80%)	
Unknown	18 (1.1%)	18 (1.2%)	0 (0%)	
Yes	188 (12%)	162 (11%)	26 (20%)	
Overall grade				<.001
I	374 (24%)	357 (25%)	17 (13%)	
II	1002 (63%)	938 (64%)	64 (48%)	
III	167 (11%)	117 (8.0%)	50 (38%)	
Unknown	44 (2.8%)	43 (3.0%)	1 (0.8%)	
Chemotherapy	160 (10%)	63 (4.3%)	97 (73%)	<.001
Hormonal therapy	1499 (94%)	1374 (94%)	125 (95%)	.9
RT	1237 (78%)	1124 (77%)	113 (86%)	.027
RT Type				.028
No RT	350 (22%)	331 (23%)	19 (14%)	
Outside RT	255 (16%)	233 (16%)	22 (17%)	
PBI	267 (17%)	250 (17%)	17 (13%)	
Whole-breast	715 (45%)	641 (44%)	74 (56%)	
Pathologic Size (cm)	1.1 (0.1, 2.0)	1.1 (0.1, 2.0)	1.1 (0.2, 2.0)	.6
Total nodes removed	2.0 (0.0, 24.0)	2.0 (0.0, 24.0)	2.0 (1.0, 16.0)	.8
Margins				.7
<1-mm DCIS	98 (6.2%)	87 (6.0%)	11 (8.3%)	
<1-mm invasive	46 (2.9%)	41 (2.8%)	5 (3.8%)	
≤ 2 -mm	82 (5.2%)	76 (5.2%)	6 (4.5%)	
Negative	1345 (85%)	1235 (85%)	110 (83%)	
Positive	13 (0.8%)	13 (0.9%)	0 (0%)	
Unknown	3 (0.2%)	3 (0.2%)	0 (0%)	
Total nodes removed = 0				>.9
0 nodes removed	2 (0.1%)	2 (0.1%)	0 (0%)	
1 or more nodes removed	1585 (100%)	1453 (100%)	132 (100%)	
Pathologic N stage				
N0	1587 (100%)	1455 (100%)	132 (100%)	
Axillary surgery				.2
ALN	13 (0.8%)	10 (0.7%)	3 (2.3%)	
None	2 (0.1%)	2 (0.1%)	0 (0%)	
SLN	1572 (99%)	1443 (99%)	129 (98%)	

Abbreviations: ALN = axillary lymph node; DCIS = ductal carcinoma in situ; PBI = partial breast irradiation; RT = radiation therapy; SLN = sentinel lymph node.

* Median (min, max); n (%).

† Wilcoxon rank-sum test; Fisher exact test; Pearson χ^2 test; NA.

Table 2 Event numbers over total follow-up time by onco-type (≤ 25 vs > 25)

Characteristic	Overall N = 1587*	≤ 25 N = 1455*	> 25 N = 132*
Local recurrence	40 (2.5%)	38 (2.6%)	2 (1.5%)
Distant recurrence	19 (1.2%)	17 (1.2%)	2 (1.5%)
Regional recurrence	3 (0.2%)	2 (0.1%)	1 (0.8%)
Locoregional recurrence	43 (2.7%)	40 (2.7%)	3 (2.3%)
* n (%).			

(56% vs 44%, $P = .028$). Patients with RS > 25 were more likely to receive chemotherapy (73% vs 4.3%, $P < .001$).

Cumulative incidence of local recurrence was low across both Oncotype DX RS groups throughout the study period (Table 2). At 6 years, the cumulative rate of local recurrence was 1.9% ($n = 23$) for those with Oncotype DX RS ≤ 25 , versus 0.76% ($n = 1$) for those with Oncotype DX RS > 25 ($P = .5$) (Fig. 1). DFS was also similar between Oncotype DX RS groups. Among those with RS ≤ 25 , DFS at 6 years was 93% versus 95% among those with Oncotype DX RS > 25 ($P = .5$; Fig. 2).

RT and oncologic outcomes by RS

In the overall cohort, 350 patients (22%) did not receive RT and exhibited a higher risk of local recurrence compared with their counterparts who did receive RT: cumulative

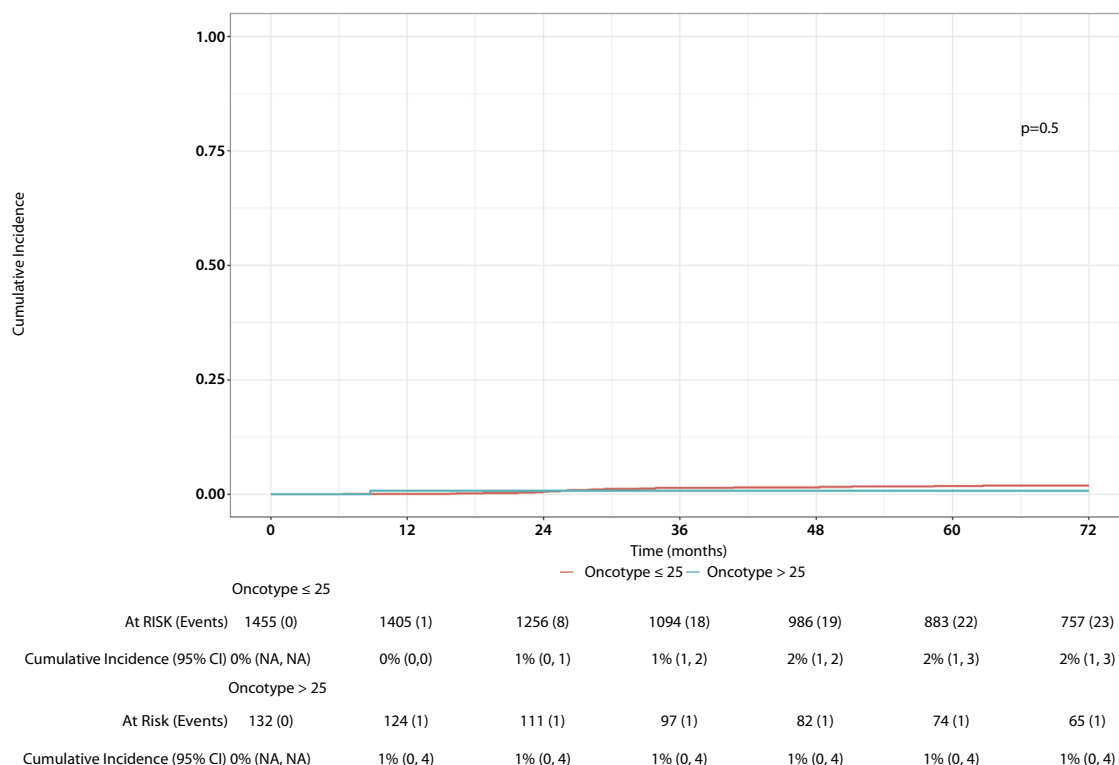
incidence of local recurrence at 6 years was 1.1% ($n = 11$) following RT versus 4.3% ($n = 13$) without RT ($P < .01$; Fig. 3; Table 3).

We then stratified patients who did not undergo RT by Oncotype DX RS > 25 ($n = 19$) versus ≤ 25 ($n = 331$). Among those who did not receive RT and had RS ≤ 25 , the 6-year cumulative incidence of local recurrence was 4.2% ($n = 12$; 95% CI, 2.3-7.0) versus 5.6% ($n = 1$; 95% CI, 0.34-23.0) among those with Oncotype DX RS > 25 ($P = .5$) (Fig. 4).

UV and MV competing risk regression models for local recurrence and DFS

UV and MV Cox proportional hazards analyses were performed to evaluate potential clinicopathologic associations with local recurrence (Table 4). Oncotype DX RS, analyzed as both a continuous and categorical variable (≤ 25 vs > 25), was not significantly associated with local recurrence on either UV (HR, 0.98; 95% CI, 0.93-1.03; $P = .4$) or MV analyses (HR, 0.99; 95% CI, 0.94-1.04; $P = .6$) in this overall low-risk cohort. On sensitivity analysis, no significant differences were observed when assessing the alternative Oncotype DX RS threshold of RS = 18 (≤ 18 vs > 18 ; $P > .9$).

Among treatment-related variables, RT was associated with reduced risk of local recurrence in both UV (HR, 0.20; 95% CI, 0.11-0.38; $P < .001$) and MV analyses (HR, 0.20; 95% CI, 0.09-0.43; $P < .001$). Hormone therapy was also associated with reduced risk of local recurrence on UV analysis (HR, 0.28; 95% CI, 0.11-0.73; $P = .009$), approaching

**Fig. 1.** Cumulative incidence of local recurrence by Oncotype DX (≤ 25 vs > 25). Abbreviation: NA = Not Applicable.

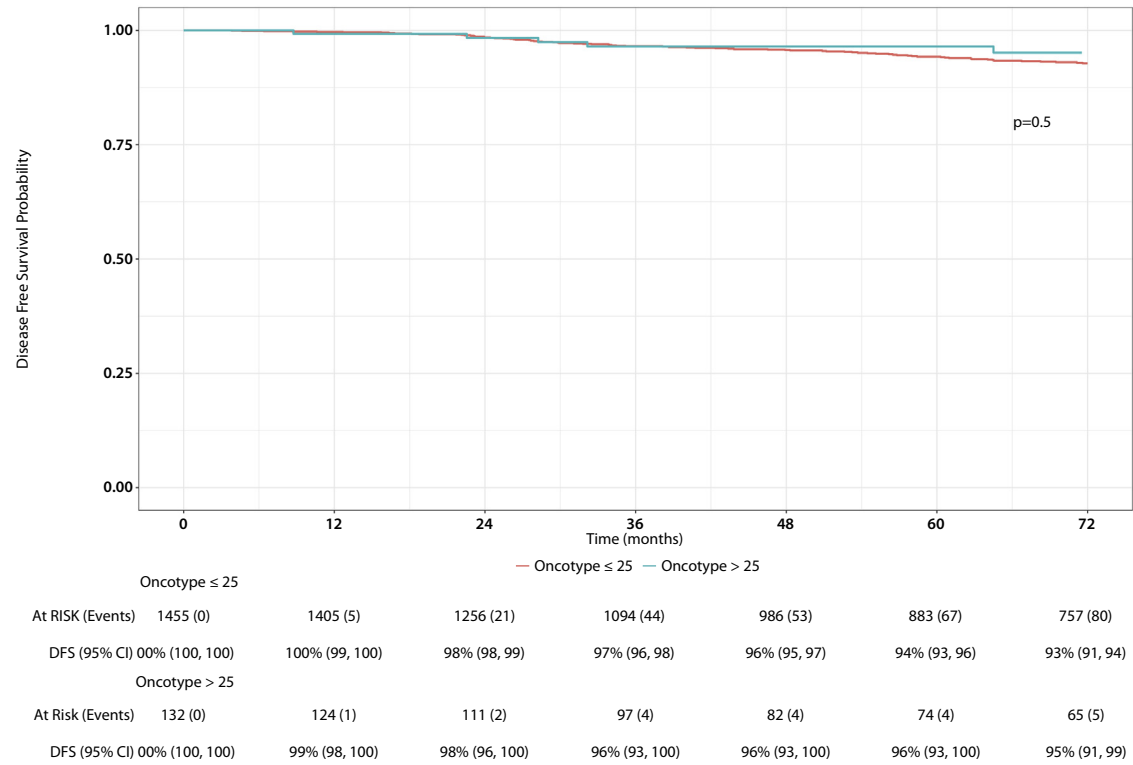


Fig. 2. Kaplan-Meier estimate of disease-free survival by Oncotype DX (≤ 25 vs > 25). *Abbreviation:* DFS = disease-free survival.

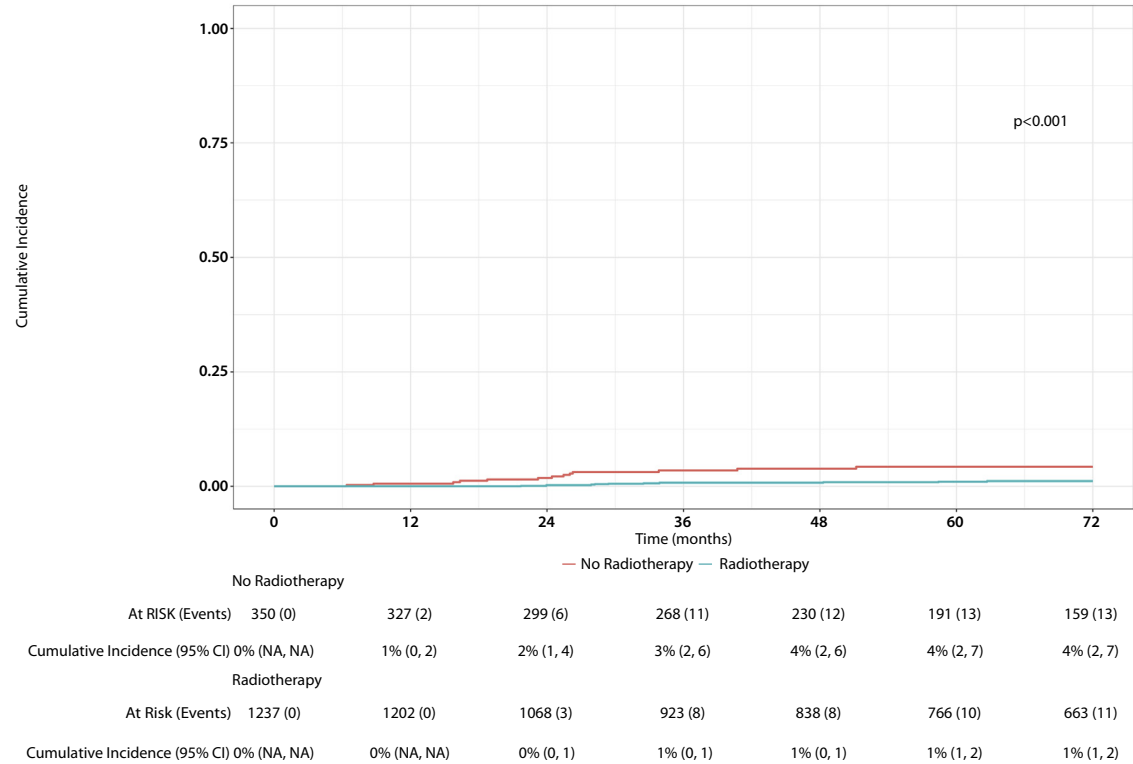


Fig. 3. Cumulative incidence of local recurrence by radiation therapy. *Abbreviation:* NA = Not Applicable.

Table 3 Event numbers over total follow-up time by radiation therapy

Characteristic	Overall N = 1587*	No N = 350*	Yes N = 1237*
Local recurrence	40 (2.5%)	22 (6.3%)	18 (1.5%)
Distant recurrence	19 (1.2%)	3 (0.9%)	16 (1.3%)
Regional recurrence	3 (0.2%)	0 (0%)	3 (0.2%)
Locoregional recurrence	43 (2.7%)	22 (6.3%)	21 (1.7%)
* n (%).			

significance on MV analysis without data on treatment adherence (HR, 0.40; 95% CI, 0.15-1.08; $P = .071$).

Discussion

In this cohort of patients ≥ 65 years of age with ER+/PR+/HER2– breast cancer treated with BCS, Oncotype DX RS identified neither a subgroup at exceedingly low risk of recurrence, nor a subgroup at elevated risk that might preclude the possibility of RT omission. Although RT was associated with a reduced risk of local recurrence across the overall cohort, this benefit was not modulated by RS grouping (≤ 25 vs > 25), nor did this benefit translate to DFS.

Our findings demonstrate that adjuvant RT significantly reduces the risk of local recurrence among older patients with early-stage, hormone receptor–positive breast cancer, but that omission of RT is reasonable in carefully selected patients with favorable clinicopathologic features, consistent with prior landmark trials such as CALGB 9343 and PRIME II.^{1,2} CALGB 9343 demonstrated a difference in local recurrence between those treated with RT compared with RT omission (2% vs 10% at 10 years, respectively).^{1,13} A similar randomized trial, PRIME II, found 10-year local recurrence rates to be 1% among those who received RT compared with 10% for those omitting RT, with neither study showing a difference in distant recurrence or OS.²

Although these studies facilitated the adoption of RT omission among select cohorts, molecular and genomic profiling have subsequently contributed to the identification of additional appropriate cohorts for de-escalation. The IDEA trial included 200 patients aged 50 to 69 years with pT1N0 invasive breast cancer with RS ≤ 18 who omitted RT. The study found that breast cancer–specific survival rates and OS at 5 years were 100%, and 5-year recurrence-free survival was 99%.¹⁰ Other studies have explored additional molecular diagnostic tests. LUMINA is a prospective study including 500 patients with early-stage breast cancer who underwent BCS and had a Ki67 index, which is a marker of cell proliferation, of $\leq 13.25\%$. These patients received adjuvant hormone therapy, and radiation was omitted. At 5 years, the cumulative incidence of recurrence was 2.3%,

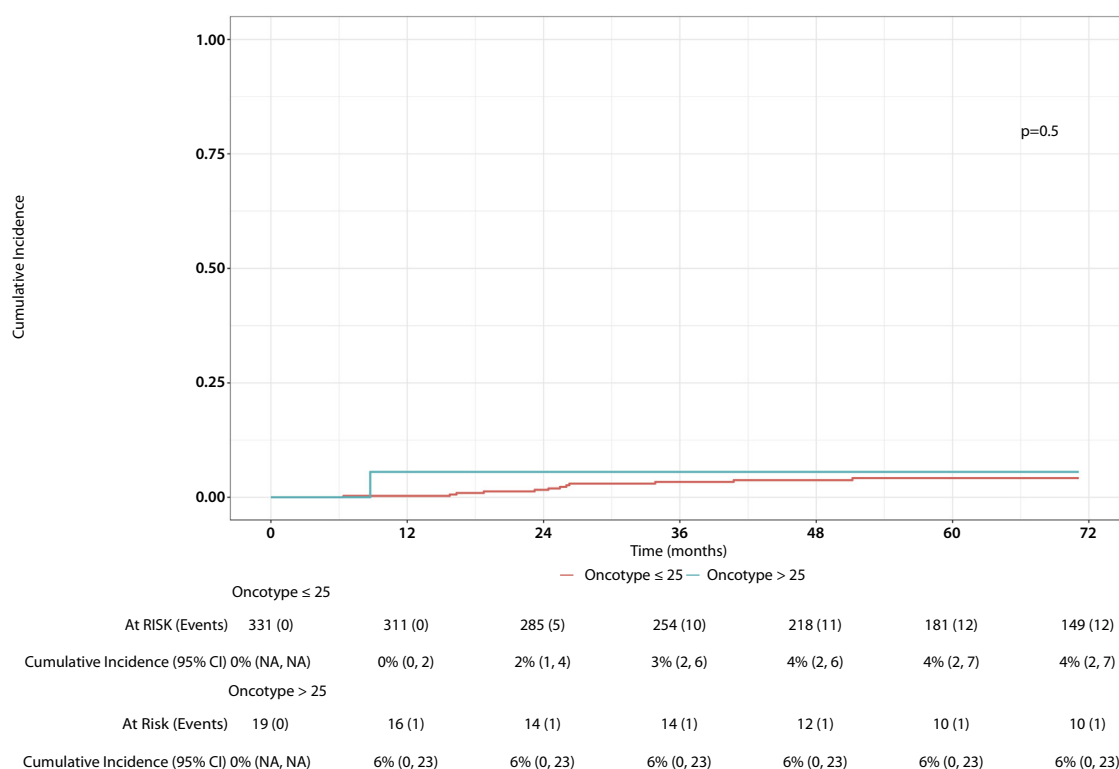


Fig. 4. Cumulative incidence of local recurrence without radiation therapy by Oncotype DX (≤ 25 vs > 25). *Abbreviation:* NA = Not Applicable.

Table 4 Univariable and multivariable competing risk regression models for local recurrence with competing risks of death and other recurrence

Characteristic	Univariable					Multivariable				
	N	Event N	HR	95% CI	P value	N	Event N	HR	95% CI	P value
Oncotype Dx Score	1587	40	0.98	0.93-1.03	.4					
Oncotype category 1										
≤18	1115	28	—	—						
>18	472	12	0.99	0.50-1.94	>.9					
Oncotype category 2										
≤25	1455	38	—	—		1455	38	—	—	
>25	132	2	0.60	0.14-2.48	.5	132	2	0.69	0.17-2.79	.6
Age at diagnosis	1587	40	1.05	1.00-1.11	.055	1587	40	0.98	0.91-1.05	.5
Lymphovascular invasion										
No	1381	33	—	—						
Yes	188	7	1.47	0.65-3.33	.4					
Overall grade										
I	374	4	—	—						
II	1002	28	2.49	0.88-7.09	.087					
III	167	8	3.66	1.09-12.3	.036					
Chemotherapy										
No	1427	37	—	—						
Yes	160	3	0.63	0.19-2.03	.4					
Hormonal therapy										
No	88	5	—	—		88	5	—	—	
Yes	1499	35	0.28	0.11-0.73	.009	1,499	35	0.40	0.15-1.08	.071
RT										
No	350	22	—	—		350	22	—	—	
Yes	1237	18	0.20	0.11-0.38	<.001	1,237	18	0.20	0.09-0.43	<.001
RT Type										
No RT	350	22	—	—						
Outside RT	255	4	0.20	0.07-0.57	.003					
PBI	267	2	0.17	0.04-0.72	.017					
Whole-breast	715	12	0.21	0.10-0.43	<.001					
Pathologic size (cm)	1587	40	1.81	0.93-3.52	.079					
Total nodes removed	1587	40	0.84	0.69-1.02	.072					
Abbreviations: HR = hazard ratio; PBI = partial breast irradiation; RT = radiation therapy.										

with a DFS of 89.9%.⁵ PRECISION, a single-arm cohort study, used the Prosigna PAM50 assay, preliminarily identifying a 2-year cumulative rate of locoregional recurrence of 0.3%.⁹ Additionally, a meta-analysis by Jayasekera et al¹⁴ of 7 trials of stage I, hormone-positive breast cancer with RS ≤18, reported a 10-year recurrence-free interval of 95.3% with RT versus 86.1% without RT, and no difference in distant recurrences or OS.

In our study, on evaluating patients who did not receive adjuvant radiation, the cumulative incidence of local recurrence

was not significantly different by Oncotype DX RS ≤25 versus >25. Additionally, Oncotype DX RS was not significantly associated with an increased risk of local recurrence or DFS on UV and MV modeling, likely as a function of the very low overall risk of this cohort. Despite this lack of statistical significance, it is important to note that the rate of local recurrence among patients with Oncotype DX RS >25 who did not receive RT was higher than historical controls, with a 5-year cumulative incidence of 5.6%. Moreover, this subset of patients was modest in our study (n = 19), suggesting that further study is needed.

Other studies have attempted to evaluate the association of Oncotype DX RS with local recurrence. National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 evaluated the effect of tamoxifen versus placebo,¹⁵ whereas NSABP-20 randomly assigned patients to receive tamoxifen alone, tamoxifen with methotrexate and fluorouracil, or tamoxifen with cyclophosphamide, methotrexate, and fluorouracil.¹⁶ The data from both studies were pooled to analyze the association between Oncotype DX RS and locoregional recurrence rate (LRR), demonstrating that, when stratified by RS, 10-year LRR rate differed significantly between low, intermediate, and high groups (6.8%, 10.8%, and 14.6%, respectively).¹⁷ In our study, distinctions between these groups were less apparent, likely as a function of the overall lower-risk nature of the cohort, compressing the various risk categories, and further highlighting the very limited size of the molecular high-risk group without RT among our otherwise-favorable population.

The Korean Radiation Oncology Group 19-06 study analyzed 339 patients with early-stage, hormone receptor–positive disease who underwent BCS followed by whole-breast RT and found that all LRRs arose among those with RS >25, with a 5-year LRR of 7.3%. Within this group, however, patients were younger with a median age of 47 years, and the rate of positive margins was elevated at 5%, suggestive of a higher-risk cohort beyond merely the RS.¹⁸ Similarly, a Surveillance, Epidemiology, and End Results (SEER) analysis found that when defining Oncotype DX RS 18–30 as intermediate risk and RS >30 as high risk, both categories were significantly associated with worse survival outcomes when compared with a low-risk cohort (RS < 18). Interestingly, in the intermediate-risk group, the use of RT was independently associated with improved survival outcomes. This significant association, however, was not seen in the low- or high-risk cohorts.¹⁹

Of note, Terry et al²⁰ investigated whether partial breast irradiation might be feasible for low-risk, early-stage breast cancer with high Oncotype DX RS, demonstrating no significant difference in local recurrence between partial- versus whole-breast approaches. This study, along with ours, highlights that de-escalation among patients with low-risk, early-stage breast cancer may be safely implemented, possibly even in the context of elevated genomic risk classification.

These findings must be interpreted in the context of the study design. Luminal breast cancers are known to be indolent in contrast to their HER2+ or triple-negative counterparts. As such, the true long-term risk of recurrence may manifest beyond the 6-year results reported here, suggesting that longer studies are needed. Moreover, breast tumors expressing the estrogen receptor are known to benefit from hormone therapy; thus, as borne out by a large and growing literature, any attempts to forgo RT must be counterbalanced by a commitment to adhere to several years of hormone therapy. The converse is also increasingly recognized: among those in low-risk cohorts who receive RT, the benefit of long-term hormone therapy may be somewhat diminished.

Regarding our particular methodology, as a retrospective analysis, there remains potential for residual bias and unmeasured confounding. Treatment decisions regarding RT and systemic therapy were not randomly assigned; as such, patients might have been influenced by factors not captured in the data set, such as comorbidities, health care professional preferences, access to care, or personal preference and risk perception. For example, our finding of an adverse association between age and DFS may be driven partly by nonbreast cancer–related mortality. Increased age may also be associated with additional comorbidities and decreased ability to tolerate adjuvant therapies. Similarly, all included patients were treated at a single institution, which may limit the generalizability of these findings. Additionally, although our cohort was large, the number of patients with high Oncotype DX RS who did not receive RT was relatively small, and the number of recurrences was also modest, thereby limiting statistical power to detect subtle differences in recurrence risk within this subgroup. Importantly, the Oncotype DX RS was not initially developed as a tool to predict local recurrence; however, multiple studies have validated a significant association between locoregional recurrence and RS.^{21–24}

Thus, our findings suggest that among patients aged ≥65 years with early-stage, ER+/PR+/HER2– breast cancer treated with BCS in contemporary practice, Oncotype DX RS need not necessarily drive the considerations surrounding adjuvant RT decision-making. Neither low nor high Oncotype DX RS modified the risk estimates established from the landmark trials of RT omission in these otherwise-favorable populations. Prospective studies among larger cohorts will be needed to validate these findings and establish true risk estimates from randomly assigned populations to establish whether low Oncotype DX RS can refine patients suitable for RT omission, or whether high Oncotype DX RS should uniformly prompt adjuvant RT.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT, OpenEvidence, and VeraHealth in order to identify relevant published manuscripts and edit written manuscript. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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