

Brief Communication



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Impact of Oncotype DX Recurrence Score on the Patterns of Locoregional Recurrence in Breast Cancer (Korean Radiation Oncology Group 19-06)

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ABSTRACT

The current study evaluated the impact of the Oncotype DX recurrence score (RS) on the patterns of locoregional recurrence (LRR) in node-negative, hormone receptor-positive/human epidermal growth factor receptor 2-negative breast cancer. Totally, 339 patients from 4 institutions were enrolled and analyzed retrospectively. All patients underwent breast-conserving surgery followed by whole-breast irradiation; only 2 patients received regional nodal irradiation (RNI). The RS was < 11 in 55 patients, 11–25 in 241, and > 25 in 43. Sixty-two patients received adjuvant chemotherapy. All patients except 4 received hormonal therapy. During a 62-month median follow-up, local recurrence was observed in 1 patient; regional recurrence, 3; and distant metastasis, 7. All LRRs were observed among patients with a RS > 25, resulting in a 5-year LRR rate of 7.3% in this subgroup. Regional recurrences developed in patients did not receive RNI initially. Thus, RNI might be effective for patients with a high RS.

Keywords: Breast neoplasm; Local neoplasm recurrence; Radiotherapy

As two randomized trials showed the benefit of regional nodal irradiation for early breast cancer [1,2], comprehensive regional radiotherapy (RT) has been recommended for patients with node-positive breast cancer. In contrast, 15% of the study population was node-negative in the Canadian randomized trial [1] and 44% in the European randomized trial [2]. In particular, in the latter study, the disease-free survival rate improved after regional RT, regardless of nodal involvement [2]. On the basis of these findings, the National Comprehensive Cancer Network guidelines recommend that regional RT should be considered even for node-negative patients with central/medial tumors or for patients with tumors > 2 cm with risk factors such as young age or extensive lymphovascular invasion [3].

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Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

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On evaluating the impact of breast RT after breast-conserving surgery (BCS) for node-negative disease, the Early Breast Cancer Trialists' Collaborative Group observed that the reduction of first recurrence after breast RT was consistent in most subgroups classified by age, grade, tumor size, and hormonal receptor status [4]. More recently, however, genomic biomarkers are increasingly being investigated to select patients who will most benefit from breast RT [5,6]. Among the various genomic biomarkers, the Oncotype DX recurrence score (RS) is the most popular biomarker for patients with node-negative, hormone receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer. While the RS was initially known to be associated with distant metastasis [7], subsequent studies showed that it also predicts locoregional recurrence (LRR) [8-10]. However, only a few studies have investigated whether the RS is associated with regional recurrence alone and whether it can be used for selecting a subgroup of patients who will benefit from regional RT.

Therefore, the current study aimed to evaluate the impact of the Oncotype DX RS on the patterns of LRR in patients who underwent BCS and postoperative RT for node-negative, hormone receptor-positive/HER2-negative breast cancer.

The medical records of 401 patients who underwent RT after BCS for node-negative, hormone receptor-positive/HER2-negative breast cancer between January 2010 and December 2015 and whose Oncotype DX RS was available were retrospectively reviewed. After excluding 62 patients whose RT field data were unavailable, a total of 339 patients from 4 institutions were included in this study. The institutional review board approved this study (H-1909-024-1060) and waived the requirement for informed consent.

All the patients underwent BCS and sentinel lymph node (LN) biopsy, or BCS and axillary LN dissection. None of them received neoadjuvant systemic therapy. After Oncotype DX testing, systemic therapy was performed at the treating physician's discretion. If a chemotherapy regimen—apart from the cyclophosphamide, methotrexate, and 5-fluorouracil regimen (which was administered concomitantly with RT)—was offered, postoperative RT was administered after the completion of chemotherapy. All the patients received whole-breast RT, and only 2 patients received regional RT to the supraclavicular fossa. A total of 302 patients received conventional fractionated RT (50–50.4 Gy in 25–28 fractions) and 37 received hypofractionated RT (39–43.2 Gy in 13–16 fractions). Tumor bed boost was performed for all patients, except 1.

We evaluated local, regional, and distant recurrences. Recurrences in the ipsilateral breast were defined as local recurrences, and those in the ipsilateral axillary, supraclavicular, and/or internal mammary LNs as regional recurrences. Distant recurrences indicated tumor recurrences outside the regions identified as locoregional sites. The SPSS software (release 18.0.1. SPSS Inc., Chicago, USA) was used for statistical analysis.

The median age of all the patients was 47 years (range, 29–77 years). A total of 164 patients had right breast cancer and 175 had left breast cancer. Regarding the tumor location, 119 patients had inner tumors, 170 had outer tumors, and 49 had central tumors. One patient had multicentric tumors. Two hundred ninety-nine patients had invasive ductal carcinomas (88.2%). The pathologic tumor size ranged from 0.4 cm to 5.5 cm (median, 1.6 cm). Totally, 233 patients (68.7%) had T1 tumors while 105 (31.0%) had T2 tumors. Only 1 patient had a T3 tumor. The histologic grade was 3 in 57 patients (16.8%), and lymphovascular invasion was observed in 74 patients (21.8%). The patient and tumor characteristics are summarized in **Table 1**.

Table 1. Patient, tumor, and treatment characteristics (n = 339)

Variables	No. of patients (%)
Age (yr)	
Median (range)	47 (29-77)
Pathology	
Invasive ductal carcinoma	299 (88.2)
Invasive lobular carcinoma	20 (5.9)
Others	20 (5.9)
T stage	
T1a	4 (11.8)
T1b	47 (13.9)
T1c	182 (53.7)
T2	105 (31.0)
T3	1 (0.3)
Histologic grade	
I	52 (15.3)
II	229 (67.6)
III	57 (16.8)
Lymphovascular invasion	
Absent	264 (77.9)
Present	74 (21.8)
Unknown	1 (0.3)
Resection margin	
Negative	321 (94.7)
Positive (invasive carcinoma)	15 (4.4)
Positive (intraductal carcinoma)	3 (0.9)
Recurrence score	
< 11	55 (16.2)
11-25	241 (71.1)
> 25	43 (12.7)
Chemotherapy	
No	277 (81.7)
Yes	62 (18.3)
Hormonal therapy	
No	4 (1.2)
Yes	335 (98.8)
Regional nodal irradiation	
None (breast RT only)	337 (99.4)
Supraclavicular node	2 (0.6)
Internal mammary node	0 (0.0)

RT = radiotherapy.

The Oncotype DX RS ranged from 0 to 71 (median, 17). The RS was < 11 in 55 patients (16.2%), 11-25 in 241 patients (71.1%), and >25 in 43 patients (12.7%). Of the 296 patients, 24 patients (8.1%) with a RS ≤ 25 received chemotherapy. Among the 43 patients with a RS > 25, 5 patients (11.6%) did not receive chemotherapy.

A total of 62 patients received systemic chemotherapy. The chemotherapeutic regimens were doxorubicin and cyclophosphamide in 28 patients; 5-fluorouracil, doxorubicin and cyclophosphamide in 23; docetaxel and cyclophosphamide in 6; cyclophosphamide, methotrexate, and 5-fluorouracil in 4; doxorubicin and cyclophosphamide followed by paclitaxel in 1. All the patients underwent hormonal therapy, except for 4 patients who wanted to get pregnant in future. A total of 265 patients received tamoxifen, 62 received an aromatase inhibitor, and 8 received tamoxifen initially and switched to an aromatase inhibitor.

The median duration of follow-up was 62 months (range, 17-109 months). Local recurrence was observed in 1 patient, regional recurrence in 3 patients, and distant metastasis in 7

Table 2. Summary of recurrences

Recurrence	Age (yr)	Tumor size (cm)	Histologic grade	Lymphovascular invasion	Resection margin	Recurrence score	Chemotherapy	Hormonal therapy	Time to recurrence
Local*	37	1.5	III	No	Negative	49	AC #4	Tamoxifen	37 mon
Regional (axillary LN)	61	1.3	II	No	Negative	30	FAC #6	AI	20 mon
Regional (supraclavicular LN) [†]	56	1.6	II	Yes	Negative	28	AC #4	Tamoxifen	49 mon
Regional (axillary LN)*	37	1.5	III	No	Negative	49	AC #4	Tamoxifen	51 mon
Distant (lung)	40	2	III	Yes	Negative	29	FAC #6	Tamoxifen	19 mon
Distant (mediastinal LN & bone)	49	2	III	No	Negative	24	No	Tamoxifen	21 mon
Distant (liver)	61	2.4	II	No	Negative	12	No	Tamoxifen	7 mon
Distant (bone, lung, liver) [†]	56	1.6	II	Yes	Negative	28	AC #4	Tamoxifen	49 mon
Distant (bone)	32	3.1	III	No	Negative	22	AC #4	Tamoxifen	70 mon
Distant (lung)*	37	1.5	III	No	Negative	49	AC #4	Tamoxifen	51 mon
Distant (bone)	49	2.5	II	Yes	Negative	15	No	Tamoxifen	58 mon

LN = lymph node; AC = doxorubicin and cyclophosphamide; FAC = 5-fluorouracil, doxorubicin and cyclophosphamide; AI = aromatase inhibitor.

*This patient experienced local recurrence first, and subsequently regional and distant recurrences 14 months later; [†]This patient experienced simultaneous regional and distant recurrences.

patients. All the cases of LRR were observed among those patients with a RS >25, resulting in a 5-year LRR rate of 7.3% in this subgroup. The regional recurrence sites were the axillary LNs in 2 patients and the supraclavicular LN in 1 patient, none of whom had received regional RT initially. The detailed summary of recurrences is shown in **Table 2**.

The current study analyzed the outcomes of BCS plus RT for node-negative, hormonal receptor-positive/HER2-negative breast cancer according to the Oncotype DX RS. LRR was observed in only 4 patients, all of whom had a RS > 25. In addition, patients with regional recurrences did not receive regional RT initially.

The Oncotype DX RS is well known to be associated with distant metastasis [7], and the correlation with LRR has been reported in several studies [8,9]. For example, in the combined analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 and B-20 trials, the 10-year LRR rates of the low (< 18), intermediate (18–30), and high RS (> 30) groups were 4.3%, 7.2%, and 15.8%, respectively ($p < 0.0001$), in patients receiving tamoxifen [8]. In those patients receiving chemotherapy and tamoxifen, the corresponding values were 1.6%, 2.7%, and 7.8%, respectively ($p = 0.028$). Moreover, Turashvili et al. [9] from the Memorial Sloan Kettering Cancer Center observed that the 4-year LRR rates of the low, intermediate, and high RS groups were 0.84%, 2.72%, and 2.80%, respectively ($p < 0.01$). Although these studies suggest that the LRR rate was significantly separated by using the RS, the differences in the local and systemic treatments as well as the follow-up duration should be considered in the interpretation. In addition, the risk factors other than RS should be considered. Moreover, age, type of surgery [8], T stage, and lymphovascular invasion [9] were additional prognostic factors for LRR in the multivariate analyses performed in the aforementioned studies. In the current study, we adopted a cutoff value of 25 for the RS from the TAILORx trial [11]. All the patients underwent BCS and RT, and 88% of patients with a RS > 25 received chemotherapy. Although risk factor analysis could not be performed owing to the small number of events, all the 4 cases of LRR were observed in patients with a high RS, consistent with the observations in previous studies.

Considering the correlation between the RS and LRR, many studies are underway to guide the optimal indications of RT. Most of these studies are focusing on the necessity of post-mastectomy RT for patients with pT1-2N1 breast cancer [12,13] or the omission of whole-breast RT after BCS for patients with a low RS [14,15]. Meanwhile, only a few studies are

investigating whether the RS is associated with regional recurrence alone and if it can be used to select the subgroup of patients who will benefit from regional RT. Mamounas et al. [16] analyzed the correlation between the RS and LRR in a subgroup of the NSABP B-28 trial, in which all patients were treated with chemotherapy and hormonal therapy. Among patients with 1–3 positive LNs who underwent BCS + RT, the 10-year regional recurrence rates of the low, intermediate, and high RS groups were 0%, 0%, and 3.5%, respectively. Even in patients with ≥ 4 positive LNs, the corresponding values were as low as 0%, 2%, and 0%, respectively. Regional recurrences were also rare in the aforementioned studies involving node-negative patients. In the NSABP B-14 and B-20 trials, axillary LN recurrence was observed in 1 patient, supraclavicular LN recurrence in 3 patients, and local and regional recurrence (location not specified) in 1 patient in the BCS + RT + tamoxifen group ($n = 390$) [8]. Data from the Memorial Sloan Kettering Cancer Center showed that axillary LN recurrence was observed in 7 patients, supraclavicular LN recurrence in 2 patients, and internal mammary LN recurrence in 1 patient, among a total of 2,326 patients [9]. In the current study, regional recurrence was observed in only 3 patients among 339 patients, but these patients did not receive regional RT initially. As the 5-year LRR rate was 7.3% in patients with a RS > 25 and 88% of these patients received standard chemotherapy, these findings suggest that more comprehensive regional RT might be considered for these patients.

In the current study, the surgical resection margin was involved in 18 patients (15 with invasive carcinoma and 3 with intraductal carcinoma), but all of them were free of LRR. The surgical resection margin is among the most important prognostic factors for LRR. However, 8 of these patients had involvement of the superficial or deep margin, which is known to have a lesser impact on LRR [17]. In addition, 10 of these patients received a higher dose of tumor bed boost (12.5–15 Gy in 3–6 fractions), which might contribute to the increased local control, although such a dose-response relationship was not observed in a previous randomized controlled trial [18].

The present study includes the typical shortcomings associated with a retrospective study design, such as selection bias. In addition, as LRR was observed in only 4 patients, risk factors such as surgical resection margin could not be analyzed further. Moreover, the follow-up period was relatively short considering the indolent course of node-negative, hormone receptor-positive breast cancer. Hence, further studies with a larger population and long-term follow-up are warranted to validate the findings of the current study.

In conclusion, excellent locoregional control was achieved in patients with node-negative, hormone receptor-positive/HER2-negative breast cancer who underwent BCS plus RT—including risk-adapted systemic therapy—according to the Oncotype DX RS. As regional recurrence was observed only in patients with a RS > 25 who were treated with only breast RT, regional RT might be considered for those patients with a high RS.

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