Original Study

Risk Factors for Local Relapse and Inferior Disease-free Survival After Breast-conserving Management of Breast Cancer: Recursive Partitioning Analysis of 2161 Patients

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Abstract

Recursive partitioning analysis was found to be a suitable method to assign patients with early stage breast cancer to different risk groups who had considerable variation in local relapse rates and disease-free survival. Lymph node ratio was associated with both endpoints.

Background: The purpose of this study was to analyze risk factors for ipsilateral in-breast relapse and inferior disease-free survival (DFS) after standard adjuvant whole-breast radiotherapy (± boost and systemic treatment) as part of a multimodal breast-conserving approach. **Patients and Methods:** Decision trees were built through recursive partitioning analysis (RPA). The median follow-up for all 2161 patients was 114 months (9.5 years). **Results:** Local relapse in the treated breast was uncommon (actuarial rates after 5 and 10 years were 2.7% and 5.8%, respectively). In RPA, the first split was related to age (52 years), with younger patients having a significantly higher risk of local relapse. The younger patients were stratified further by lymph node ratio (LNR). In patients older than 52 years, lack of endocrine treatment was associated with significantly higher risk. DFS was 80.7% at 10 years. The first split was caused by LNR, and the group with unfavorable LNR (> 0.20) could not be stratified further. Ten-year DFS in this group was as low as 50.6%. Patients with favorable LNR (0-0.20) could be stratified by additional risk factors, in particular primary tumor size. **Conclusion:** RPA is a suitable method to assign patients with early stage breast cancer to different risk groups, both regarding local relapse and DFS. Although age was a major risk factor for local relapse after breast-conserving management, LNR was associated with both endpoints. The systemic treatment approaches used in this study failed to provide satisfactory DFS in patients with LNR > 0.20 and 2 other subgroups.

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Introduction

Breast-conserving surgery has a longstanding and successful track record as a state-of-the-art management approach in early stage invasive breast cancer, a disease that currently is often screening-detected in middle-aged and elderly, often post-menopausal, women.[1] The impact of postoperative radiotherapy on local control is well-established.[2] Besides the historical standard of whole-breast radiotherapy, which intuitively can be considered the safest approach to avoid ipsilateral in-breast recurrence, prospective trials have established eligibility criteria for partial-breast irradiation.[3-6]

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Different techniques of additional tumor bed irradiation (boost) after treatment of the entire breast have also been studied.[7-9] A seminal randomized trial has shown that young age and high-grade invasive carcinoma were the most important risk factors for ipsilateral in-breast recurrence.[10] The 20-year cumulative incidence of this type of relapse in 1616 patients with 160 events was 15% (34% in the age group 40 years or younger, 14% in 41-50-year-old women). The incidence was 18% and 9% in tumors with and without ductal carcinoma in situ (DCIS). High-grade tumors relapsed more frequently early during follow-up, but the relative effect of age and presence of DCIS seemed stable over time. The boost (16 Gy after 50 Gy to the whole breast) reduced the 20-year incidence from 31% to 15% (hazard ratio, 0.37; 95% confidence interval, 0.22-0.62; $P < .001$) in high-risk patients ($\leq$ 50 years with DCIS present).

In the modern era, reduced 5-year locoregional recurrence risks have been reported, as recently reviewed by Horton et al.[11] The luminal tumor types were less likely to recur locoregionally than human epidermal growth factor receptor 2-positive ($HER2^+$) or triple-negative tumors. Still many of the reviewed studies reported rates below 10% even for the $HER2^+$ or triple-negative subsets. Different groups have pursued strategies of de-escalation, such as omission of radiotherapy in low-risk women aged 65 years or older who received adjuvant endocrine treatment.[12] After a median follow-up of 5 years, ipsilateral breast tumor recurrence was seen in 1.3% after whole-breast radiotherapy and 4.1% in patients assigned no radiotherapy ($P = .0002$). Survival rates and other efficacy endpoints were similar. Selection criteria are needed to define the optimal treatment intensity, also taking into account competing risks from life-shortening comorbidity. The purpose of the present study was to analyze risk factors for local relapse and inferior disease-free survival (DFS) after standard adjuvant whole-breast radiotherapy as part of a multimodal breast-conserving approach and to provide additional insight on the basis of recursive partitioning analysis (RPA), a technique of building decision trees that also has been used by other groups.[13,14]

Patients and Methods

We performed a large retrospective single institution cohort study with long-term follow-up, which was based on a previously established database, after obtaining approval from the institution's ethics and research committee.[15,16] All 2207 patients in the database were treated with breast-conserving surgery, typically lumpectomy, axillary dissection, whole-breast irradiation and, if indicated, adjuvant systemic therapy, in the first author's institution in Linz, Austria. Whole-breast irradiation was followed by a boost to the tumor bed in 1880 (85%) patients, either by external beam or high−dose-rate interstitial brachytherapy techniques. The inclusion period was 1984 to 1999, because we aimed at long-term results. Of 2207 patients, 56 (2.5%) were lost to follow-up and therefore excluded. The median follow-up of the remaining 2161 patients was 114 months (SD, 9.5 years), and 1750 (79%) patients were alive at the time of analysis. Date and patterns of relapse were abstracted from the hospital's patient records, with local control and DFS as co-primary endpoints. If no event of interest had occurred, patients were censored at the time of last documented contact with the hospital. We employed STATA software (STATA Corp, College Station, TX) for the statistical analyses. Actuarial endpoints were evaluated with Kaplan-Meier analyses and log-rank tests. The RPA methodology has been described previously.[14] The relative hazard ratio was estimated for the different prognostic groups. For local control, a minimum group size of 50 patients was required (100 for DFS). To be considered statistically significant, P-values $< .05$ had to be obtained. Potential predictors of relapse that were included in the analyses were age, menopausal status, tumor location, T stage, N stage, number of metastatic axillary lymph nodes, number of metastatic axillary nodes divided by number of removed nodes (node ratio), histopathologic grade, estrogen and progesterone receptors, type of systemic therapy, and utilization of surgical marker clips in the breast.

Results

Age ranged between 25 and 85 years (mean, 57 years; median, 58 years) in the study cohort. Regarding menopausal status, 1450 (66%) patients were post-menopausal and 199 (9%) peri-menopausal. The primary tumor was located in the lateral quadrants in 1431 (65%) patients, medial quadrants in 553 (25%) patients, and centrally in the remaining 223 (10%) patients. Most (68%) patients had T1 disease, as displayed in Table 1. In addition, most (74%) patients were lymph node-negative (N0). For lymph node-positive patients, the node ratio is shown in Table 1 (median, 0.27, corresponding, for example, to 3 positive nodes out of 12 pathologically examined nodes).

Table 2 shows the relapse rates stratified by resection margin. Local relapse in the treated breast was more common than regional relapse. The lowest relapse rates were found in patients who had

Table 1 Baseline Characteristics (2207 Patients)

Variable	No. Patients	%
T stage		
Tis	48	2
T1	1502	68
T2	657	30
N stage		
N0	1590	74
N1	617	29
Adjuvant systemic therapy		
None	614	28
Chemotherapy	484	22
Endocrine therapy	997	46
Chemo- and endocrine therapy	112	5
Node ratio in 617N + patients		
Median	0.27	
0-0.09	221	36
0.1-0.19	187	30
0.2-0.29	78	13
0.3-0.39	47	8
0.4-0.49	25	4
0.5-0.59	18	3
$\geq$ 0.6	41	7

Table 2 Margin Status and Relapse (Crude Rate)

Margin Status, n	Local Relapse	Regional Relapse	Distant Relapse
Clear, 2162[a]	125 (5.8)	30 (1.4)	310 (14.3)
Involved, 31[b]	3 (9.7)	0 (0)	7 (22.6)
Unknown, 14[c]	1 (7.1)	2 (14.3)	7 (50)

All data are presented as n (%).
[a]At least 1 mm margin; patients with smaller margin were offered re-resection.
[b]These patients refused further surgical resection.
[c]Lack of documentation in the hospital files.

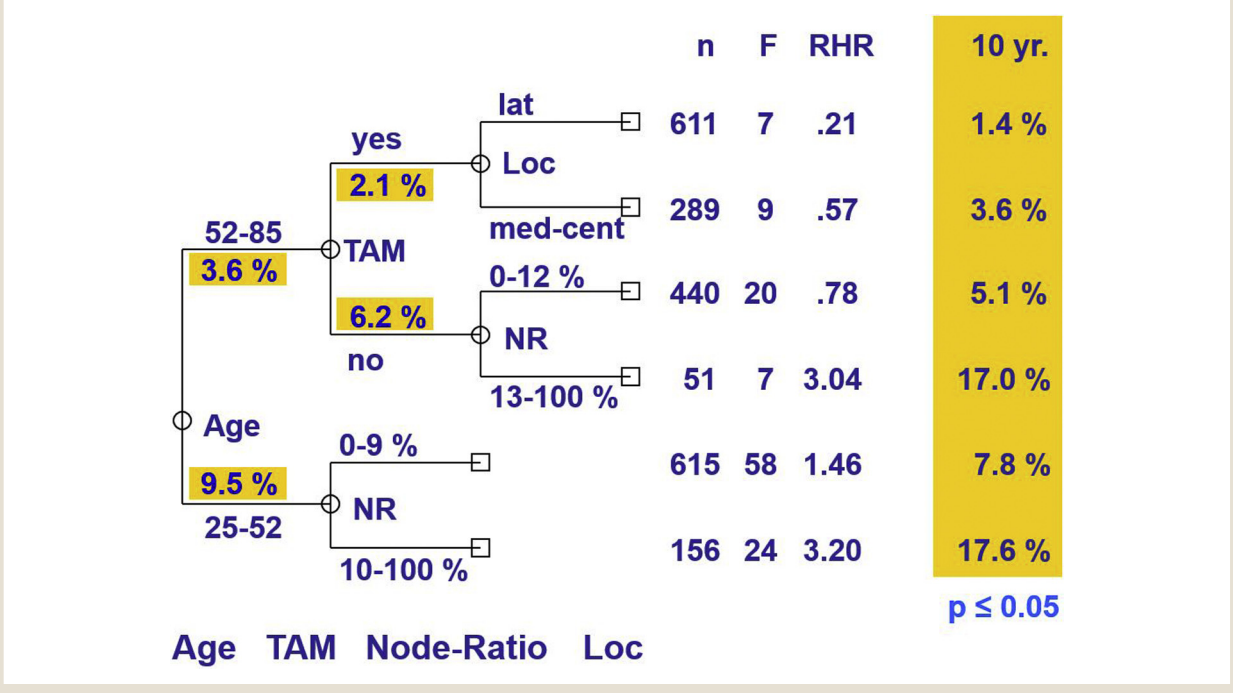
uninvolved surgical margins. The actuarial rates of local relapse after 5 and 10 years were 2.7% and 5.8%, respectively. Figure 1 shows the results of the RPA for this endpoint. The first stratification node in this model was related to age, with younger patients (≤ 52 years) having a significantly higher risk. The younger patients were stratified further by node ratio and had 10-year local relapse rates of 7.8% and 17.6%, respectively. In patients older than 52 years, lack of endocrine treatment was associated with significantly higher risk. Despite further stratification, the 10-year rate of local relapse did not exceed 5.1%, except for 1 subgroup, older patients without endocrine therapy and higher node ratio (10-year rate, 17.0%).

The results of the RPA for disease-free survival (80.7% at 10 years) are shown in Figure 2. The first split was caused by node ratio, and the group with unfavorable node ratio (> 0.20) could not be stratified in different subgroups. Ten-year disease-free survival in this group was as low as 50.6%. Patients with favorable node ratio (range, 0-0.20) could be stratified by additional risk factors, in particular, the maximum size of the primary tumor. If one defines poor DFS as < 80% at 10 years, 2 additional groups were identified; patients with primary tumors ≥ 18 mm and node ratio 0.09 to 0.20 (10-year rate, 63.7%), and those with the same primary tumor size, lower node ratio, younger age, and medial or central tumor location (10-year rate, 71.3%).

Discussion

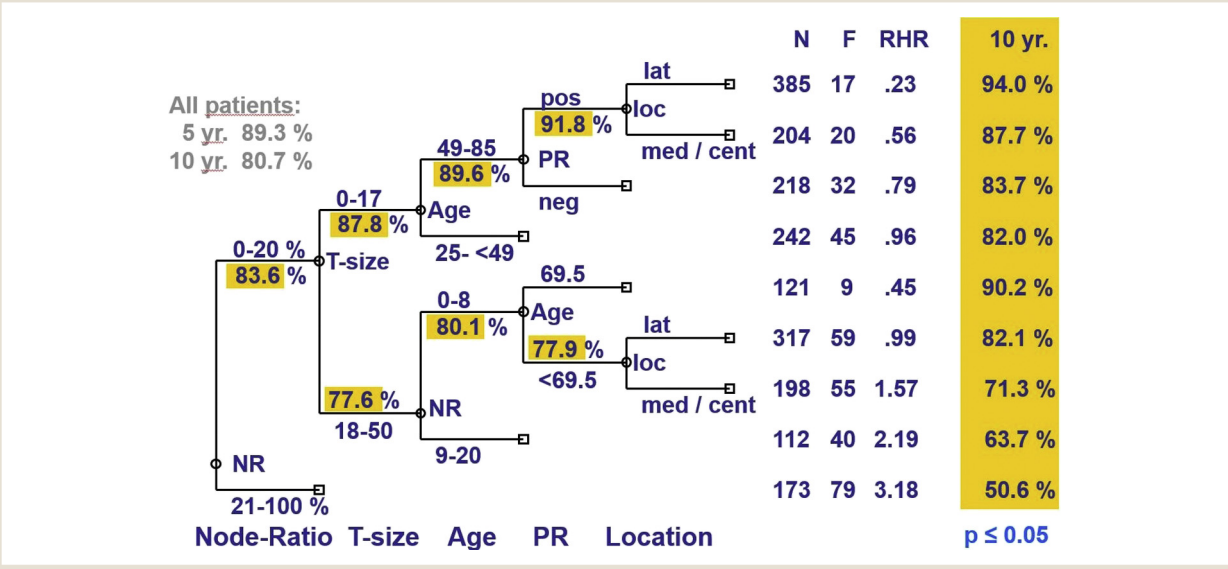
This study employed RPA to analyze risk factors for local relapse and unfavorable DFS after standard adjuvant whole-breast radiotherapy as part of a multimodal breast-conserving approach, mostly in post-menopausal women with stage I or II breast cancer. A previous study included 912 women who underwent breast-conserving surgery, axillary dissection, and adjuvant radiation.[13] Systemic therapy was chemotherapy with or without tamoxifen in 32%, tamoxifen in 27%, or none in 41% (28% without systemic treatment in the present study). The median follow-up was 5.9 years, shorter than in the present analysis. Age was the first split in the partition tree, identical to the present results. Patients more than 55 years old had a 4% 10-year local recurrence rate, the only further division being use of tamoxifen or not (2% vs. 5%; $P = .03$). For patients ≤ 55 years old, extensive intraductal component (EIC) was the next significant split. For EIC-negative tumors, age ≤ 35 years and negative margins were associated with a 10-year rate of 3%; with close (≤ 2 mm) or positive margins, 34%. Node ratio was not evaluated in the previous study, a fact that profoundly influences comparability. The present study's strength lies in the large sample size and long follow-up. The latter, however, is also a disadvantage because of the rapidly changing treatment paradigms (eg, introduction of adjuvant aromatase inhibitors and taxanes, increased

Figure 1 Recursive Partitioning Analysis for the Endpoint of Local In-Breast Recurrence



Abbreviations: F = number of failures; lat = lateral; Loc = location; med-centr = medial-central location; NR = node ratio; RHR = relative hazard ratio; TAM = tamoxifen.

Figure 2 Recursive Partitioning Analysis for the Endpoint of Disease-Free Survival



Abbreviations: F = number of failures; lat = lateral; Loc = location; med-centr = medial-central location; N = number of patients; neg = negative; NR = node ratio; pos = positive; PR = progesterone receptor; RHR = relative hazard ratio.

adoption of neoadjuvant therapy for patients with larger tumors, and the sentinel node concept). In addition, biological classification of subgroups has improved. Some of these baseline data, including EIC status, was not captured in our database. The omission of axillary dissection post-ACOSOG Z0011 (American College of Surgeons Oncology Group) influences clinicians' ability to accurately determine the total lymphatic tumor load.[17] New tools (eg, based on imaging criteria) are currently under investigation and might eventually improve assessment of nodal burden in the absence of complete axillary dissection.[18]

In the Budapest randomized trial, the 10-year actuarial rate of local relapse was 5.1% in the whole-breast irradiation arm (DFS, 84%).[3] These figures compare well to the present ones (5.8% and 80.7%, respectively). In the seminal European Organisation for Research and Treatment of Cancer (EORTC) trial, the cumulative incidence of local recurrence was 10.2% versus 6.2% for the no boost and the boost group, respectively ($P < .0001$).[19] The 20-year cumulative incidence of ipsilateral breast tumor recurrence was 16% in the no-boost group versus 12% in the boost group, emphasizing the need for long-term follow-up.[20] The impact of age on this endpoint has also been confirmed in the EORTC trial.[10] The feasibility of hypo-fractionated whole-breast irradiation has been confirmed by several groups, allowing patients to spend less time away from home.[21-23]

Attempts have been made to identify groups of women with stage I breast cancer with a 5-year risk of local recurrence $\leq$ 1.5% after breast-conserving therapy plus whole-breast radiation therapy in a Canadian study.[24] These 5974 patients were $\geq$ 50 years of age and diagnosed between 1989 and 2006. RPA was performed in patients treated with and without endocrine therapy to identify combinations of factors associated with a 5-year risk $\leq$ 1.5%. The median follow-up was 8.6 years. Overall 5-year local recurrence rate was 1.5% (10-year rate, 3.4%). Of 2830 patients treated with endocrine therapy, patient subsets identified with 5-year rate $\leq$ 1.5% included patients with grade 1 histology or grade 2 histology plus $\geq$ 60 years of age. Even 10-year rates were not higher than 0.9%. Of 3144 patients treated without endocrine therapy, patients with grade 1 histology plus clear margins had 5-year rate $\leq$ 1.5%, and the 10-year rate was 2.2%. On the other hand, heterogeneous outcomes from prospective studies suggest that omission of radiotherapy should be approached with caution.[25] In general, the risk of distant metastases during follow-up is higher than the risk of ipsilateral recurrence, regional recurrence, and contralateral cancer.[26]

As already mentioned in the Introduction section, several studies suggest that locoregional recurrence risk is lowest in the luminal tumor types.[11] Other studies have shown that biologic subtype and recurrence scores are not necessarily predictive of local recurrence after breast conservation treatment with adjuvant radiation[27,28]; however, some groups reported potentially useful classifications that need further validation.[29,30] In a nomogram validation study (IBTR! 2.0 [Ipsilateral Breast Tumor Recurrence]) with more than 1800 patients, younger age, positive nodal status, and omission of hormonal therapy were associated with ipsilateral recurrence.[31] Furthermore, nonadherence to systemic therapy has been shown to adversely affect DFS.[32] Node ratio has been studied by different groups, including the Netherlands Cancer Registry.[33] Their study of more than 25,000 women with node-positive disease showed that the risk of death increased with increasing node ratio ($\leq$ 0.20, 0.21-0.65, $>$ 0.65). Further supporting evidence has been reported from the Geneva Cancer Registry in a smaller study.[34] In line with these results, the present RPA suggests that node ratio is a statistically significant and clinically meaningful predictor of DFS and that it is

also relevant in explaining the variable risk of local in-breast relapse. Additional studies are needed to determine the relapse rates in the risk groups presented here if improved systemic treatment is given as recommended in today's guidelines, and also to confirm the validity of the prediction model in an independent external dataset. The main limitations of the study include the lack of some baseline data that are routinely evaluated in the modern era (eg, triple-negative and EIC status) and changes in the management of the axilla.

Conclusion

RPA is a suitable method to assign patients with early-stage breast cancer to different risk groups, both regarding local relapse and DFS. Although age was a major risk factor for local relapse after breast-conserving management, node ratio was associated with both endpoints. The systemic treatment approaches used in this study failed to provide satisfactory DFS in patients with LNR > 0.20 and also 2 additional subgroups.

Clinical Practice Points

- Although in-breast recurrence in general is uncommon after breast-conserving management, younger patients with unfavorable node ratio fare less well.
- In older patients, unfavorable node ratio is of concern when endocrine treatment is not given.
- There is also a clear relationship between node ratio and DFS, corroborating other studies that reported that the risk of death increased with increasing node ratio.
- Therefore, node ratio might contribute to improved models for decision-making.

Disclosure

The authors have stated that they have no conflicts of interest.

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