

## ORIGINAL ARTICLE

# Omitting Radiotherapy after Breast-Conserving Surgery in Luminal A Breast Cancer

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## ABSTRACT

**BACKGROUND**

Adjuvant radiotherapy is prescribed after breast-conserving surgery to reduce the risk of local recurrence. However, radiotherapy is inconvenient, costly, and associated with both short-term and long-term side effects. Clinicopathologic factors alone are of limited use in the identification of women at low risk for local recurrence in whom radiotherapy can be omitted. Molecularly defined intrinsic subtypes of breast cancer can provide additional prognostic information.

**METHODS**

We performed a prospective cohort study involving women who were at least 55 years of age, had undergone breast-conserving surgery for T1N0 (tumor size <2 cm and node negative), grade 1 or 2, luminal A–subtype breast cancer (defined as estrogen receptor positivity of  $\geq 1\%$ , progesterone receptor positivity of  $>20\%$ , negative human epidermal growth factor receptor 2, and Ki67 index of  $\leq 13.25\%$ ), and had received adjuvant endocrine therapy. Patients who met the clinical eligibility criteria were registered, and Ki67 immunohistochemical analysis was performed centrally. Patients with a Ki67 index of 13.25% or less were enrolled and did not receive radiotherapy. The primary outcome was local recurrence in the ipsilateral breast. In consultation with radiation oncologists and patients with breast cancer, we determined that if the upper boundary of the two-sided 90% confidence interval for the cumulative incidence at 5 years was less than 5%, this would represent an acceptable risk of local recurrence at 5 years.

**RESULTS**

Of 740 registered patients, 500 eligible patients were enrolled. At 5 years after enrollment, recurrence was reported in 2.3% of the patients (90% confidence interval [CI], 1.3 to 3.8; 95% CI, 1.2 to 4.1), a result that met the prespecified boundary. Breast cancer occurred in the contralateral breast in 1.9% of the patients (90% CI, 1.1 to 3.2), and recurrence of any type was observed in 2.7% (90% CI, 1.6 to 4.1).

**CONCLUSIONS**

Among women who were at least 55 years of age and had T1N0, grade 1 or 2, luminal A breast cancer that were treated with breast-conserving surgery and endocrine therapy alone, the incidence of local recurrence at 5 years was low with the omission of radiotherapy. (Funded by the Canadian Cancer Society and the Canadian Breast Cancer Foundation; LUMINA ClinicalTrials.gov number, NCT01791829.)

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\*A list of the LUMINA Study Investigators is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

Drs. Whelan and Smith and Drs. Nielsen and Levine contributed equally to this article.

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**B**REAST-CONSERVING SURGERY IS PREFERRED by most women with early breast cancer.<sup>1</sup> Radiotherapy of the breast is commonly administered after breast-conserving surgery to reduce the risk of local recurrence and thereby avoid mastectomy. However, radiotherapy is inconvenient for patients, involving 3 to 6 weeks of daily treatments, and is costly. It is also associated with considerable short-term side effects, such as fatigue, skin irritation, and breast swelling, and long-term side effects, such as skin telangiectasia, breast pain, induration, and retraction, that can adversely affect cosmesis and quality of life.<sup>2,3</sup> Rarely, breast radiotherapy can cause second cancers and ischemic cardiac disease.<sup>4</sup>

In recent years, the incidence of local recurrence after breast-conserving surgery has been steadily decreasing, a change attributed to smaller screening-detected cancers, improved surgical techniques, and effective adjuvant systemic therapy.<sup>5</sup> The question, “Can radiotherapy be omitted in very-low-risk patients?” has arisen. Clinicopathologic factors alone (e.g., patient age, tumor size, and tumor grade) are of limited use in the identification of patients at low risk.<sup>6-8</sup> Genetically characterized intrinsic subtypes of breast cancer have been shown to predict cancer outcomes.<sup>9,10</sup> Nielsen and colleagues developed an approach to classify intrinsic subtypes using immunohistochemical analysis of a limited panel of overexpressed protein markers<sup>11</sup> that was able to predict the risk of local recurrence after breast-conserving therapy independent of clinicopathologic factors.<sup>12</sup> Of the four main intrinsic subtypes, luminal A, which overexpresses estrogen pathway genes and is the least proliferative, was associated with the best prognosis. The luminal A subtype was best classified as estrogen-receptor (ER) positivity of at least 1%, progesterone-receptor (PR) positivity of more than 20%, negative human epidermal growth factor receptor 2 (HER2), and a Ki67 index of 13.25% or less when this classification approach was compared with multigene-expression profiling.<sup>11,13</sup> The Ki67 index (the percentage of cells that are positive for Ki67 as determined by immunostaining of the primary tumor) is a marker of cellular proliferation that distinguishes luminal A from higher-risk ER-positive luminal B breast cancer.<sup>14</sup>

In a previous retrospective study, we used archival samples to show that combining the luminal A subtype defined with the use of immuno-

histochemical analysis and clinicopathologic factors identified patients at very low risk for local recurrence after breast-conserving surgery.<sup>15</sup> The objective of the current study was to prospectively evaluate the usefulness of this approach in the identification of patients at very low risk for local recurrence after breast-conserving surgery when they were treated with endocrine therapy without radiotherapy.

## METHODS

### STUDY DESIGN

This single-group, prospective, multicenter cohort study involved women with early-stage breast cancer who had undergone breast-conserving surgery. Patients who were considered a priori to be at low risk for local recurrence on the basis of traditional clinicopathologic factors and the presence of a luminal A subtype and who planned to receive endocrine therapy did not receive breast radiotherapy. These patients were followed prospectively for recurrent invasive or in situ cancer of the ipsilateral breast (the primary outcome). The observance of an event rate that was below a pre-specified boundary would support the hypothesis and influence clinical decision making with regard to radiotherapy.

### PATIENTS

Eligible patients were women who were at least 55 years of age and who had received a new diagnosis of invasive breast cancer (ductal, tubular, or mucinous), had a primary tumor 2 cm or less in diameter, had undergone breast-conserving surgery with margins of at least 1 mm, and had negative axillary nodes as determined by sentinel-lymph-node biopsy or axillary-node dissection. The tumor had to be ER-positive ( $\geq 1\%$ ), PR-positive ( $>20\%$ ), and HER2-negative as determined by immunohistochemical analysis or in situ hybridization. Patients were excluded if they had a lobular carcinoma (including mixed ductal-lobular carcinoma), clinical or pathological evidence of direct extension to the chest wall or skin, multifocal or multicentric disease, grade 3 histologic features, extensive intraductal component, or evidence of lymphovascular invasion. Other exclusion criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

Patients were recruited at 26 centers across

Canada. The protocol (available at NEJM.org) was approved by local research ethics boards, and written informed consent was obtained from all the patients. The study was designed by five of the authors. Data were collected and analyzed by the Ontario Clinical Oncology Group, which coordinated the study. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol. The first draft of the manuscript was written by the first author, with input from all the authors. The sponsors had no role in the collection, analysis, or interpretation of the data or the decision to submit the manuscript for publication.

#### ENROLLMENT

Patients were registered if they met clinical eligibility criteria, including having tumors that met the criteria for being ER- and PR-positive and HER2-negative, and if their treatment plan included endocrine therapy. Tumor samples were sent for Ki67 testing, which was performed centrally at three laboratories in Hamilton, Toronto, and Vancouver with the use of the methods of the International Ki67 Working Group.<sup>14,16</sup> A 4- $\mu$ m slide was stained for the Ki67 MIB1 antibody, and the slide was imaged with the use of the Aperio Scanscope; a minimum of 500 tumor nuclei from five randomly selected sites were counted with the use of keystroke data capture.<sup>17</sup>

Patients with Ki67 positivity of 13.25% or less, consistent with the luminal A subtype, were enrolled in the study and received endocrine therapy in the form of an aromatase inhibitor (i.e., anastrozole, letrozole, or exemestane) or tamoxifen for at least 5 years, but did not receive radiotherapy. Patients who had a Ki67 index that was greater than 13.25%, consistent with the luminal B subtype, received treatment off-study at the discretion of the local investigator. Reliability testing for Ki67 was performed yearly among the laboratories and was shown to be high (interclass coefficient,  $\geq 0.90$ ).

#### FOLLOW-UP AND OUTCOMES

Patients were followed up every 6 months for 2 years and then yearly. Mammography was also performed yearly. Adherence to endocrine therapy was assessed with the use of patient interviews at each follow-up visit. The primary outcome was local breast cancer recurrence, defined as recurrent invasive or in situ cancer confirmed histo-

logically in the ipsilateral breast and measured from the time of enrollment to the time of documented local recurrence. Local recurrence was described as a true or marginal recurrence if it occurred within 2 cm of the original tumor bed, or as an elsewhere recurrence. Secondary outcomes were contralateral breast cancer, any recurrence (i.e., recurrent disease in the ipsilateral breast, regional lymph nodes, or distant sites), disease-free survival (i.e., the time between enrollment and any disease recurrence, contralateral breast cancer, second primary nonbreast cancer, or death), and overall survival. All recurrences, second primary cancers, and deaths were independently adjudicated with the use of supportive documentation.

#### STATISTICAL ANALYSIS

We conducted the study to provide reliable estimates of the incidence of local recurrence. The primary analysis focused on estimation with the use of a two-sided 90% confidence interval equivalent to an upper boundary of the one-sided 95% confidence interval for the incidence of 5-year local recurrence. In consultation with radiation oncologists and patients with breast cancer, we determined that if the upper boundary of the two-sided 90% confidence interval for the cumulative incidence at 5 years was less than 5%, this would represent an acceptable risk of local recurrence at 5 years.

Assuming a local recurrence of 3.5% with the upper boundary of a two-sided 90% confidence interval to be less than 5% and accounting for potential losses to follow-up, we determined that a sample of 500 patients would need to be enrolled. The size of the sample was approximated with the use of a 90% confidence interval for a binomial proportion. The probability of local recurrence was estimated with the use of the cumulative incidence function, accounting for death as a competing event, and the corresponding 90% and 95% confidence intervals were estimated with the use of delta methods.<sup>18</sup>

The methods used to analyze secondary outcomes of contralateral breast cancer and any recurrence were similar to those used to analyze the primary outcome. Data-censoring details are provided in the Supplementary Appendix. Event rates for disease-free and overall survival were estimated with the use of the Kaplan–Meier method. The primary intention-to-treat analysis was planned

at a median follow-up of 5 years. An independent data and safety monitoring committee reviewed outcome data at 2, 3, and 5 years after the first patient was enrolled.

RESULTS

PATIENTS

From August 2013 through July 2017, a total of 740 patients who met the eligibility criteria were registered, and specimens were obtained and submitted for Ki67 testing. A total of 224 patients had a Ki67 index greater than 13.25%, and specimens obtained from 11 patients were insufficient for testing. Thus, 505 patients with a Ki67 index of 13.25% or less were classified as having luminal A breast cancer and were enrolled. Shortly after enrollment, 4 patients were identified by central monitoring as ineligible, and 1 patient withdrew; those 5 patients were not included in the primary-outcome analysis; the remaining 500 enrolled patients were included in the intention-to-treat analysis.

Although the protocol specified that no radiotherapy would be administered to patients who were enrolled, 4 patients received radiotherapy. A total of 21 patients subsequently withdrew from continued follow-up. The median follow-up was 5 years.

The median age of the patients was 67.1 years (interquartile range, 62.9 to 71.6), and only 11.6% of the patients were 75 years of age or older (Table 1). The median tumor size was 1.1 cm (interquartile range, 0.7 to 1.4) in the longest diameter, with most (92%) measuring 0.5 to 2 cm. The endocrine therapy that was administered was an aromatase inhibitor (in 59% of the patients) or tamoxifen (in 41% of the patients). Eight patients did not receive endocrine therapy. Of the patients who started endocrine therapy, 82.7% were still receiving endocrine therapy at their last follow-up visit if the visit occurred at 5 years or earlier.

EVENT RATES AT 5 YEARS

Local recurrences were observed in 10 patients within 5 years after enrollment. The cumulative incidence at 5 years was 2.3% (90% confidence interval [CI], 1.3 to 3.8; 95% CI, 1.2 to 4.1) with the upper boundary of the confidence interval less than the prespecified boundary of 5% (Fig. 1). Of the 10 local recurrences, all were invasive, 6 were deemed to be true or marginal

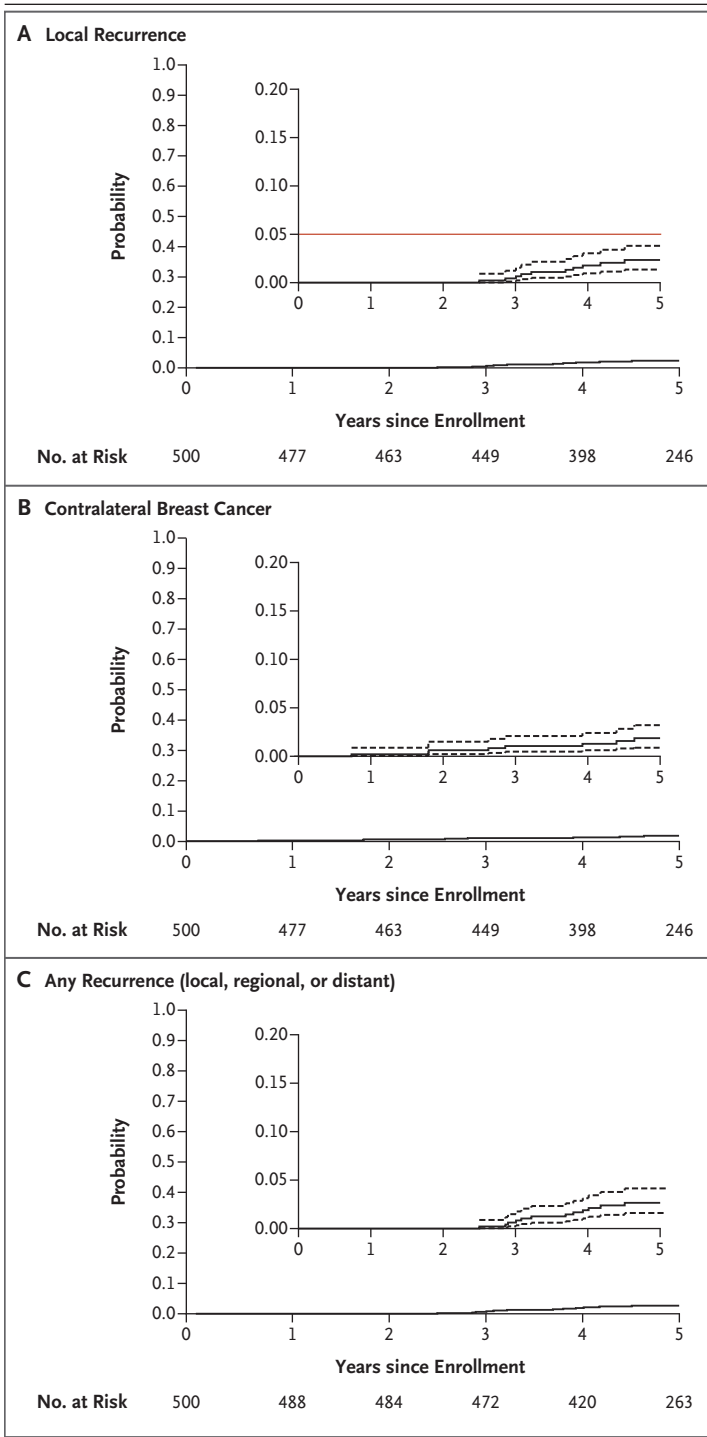
Table 1. Characteristics of the Patients at Baseline.\*

Characteristic	All Patients (N = 500)
<b>Age</b>	
Median (IQR) — yr	67.1 (62.9–71.6)
Distribution — no. (%)	
55 to <60 yr	61 (12)
60 to <65 yr	138 (28)
65 to <70 yr	136 (27)
70 to <75 yr	107 (21)
75 to <80 yr	42 (8)
≥80 yr	16 (3)
<b>Tumor size</b>	
Median (IQR) — cm	1.0 (0.7–1.4)
Distribution — no. (%)	
≤0.5 cm	39 (8)
0.5–1.0 cm	217 (43)
1.1–2.0 cm	244 (49)
Tumor grade — no. (%)	
1	330 (66)
2	170 (34)
Histologic cancer type — no. (%)	
Ductal	437 (87)
Tubular	25 (5)
Mucinous	26 (5)
Other	12 (2)

\* Percentages may not total 100 because of rounding. IQR denotes interquartile range.

recurrences, and 4 were elsewhere recurrences in the ipsilateral breast. Of the 10 patients with local recurrence, 4 underwent further breast-conserving surgery and 6 underwent mastectomy. A sensitivity analysis assumed that the 5-year incidence in the 21 patients who withdrew would have been equal to the upper 90% confidence interval in the observed patients, which would have led to 1 additional patient having a local recurrence. This yielded a 5-year incidence of recurrence of 2.5% (90% CI, 1.5 to 4.0) in which the upper boundary of the confidence interval was still less than the prespecified boundary of 5%.

With regard to other cancer events, 8 contralateral breast cancers were observed, all of which were invasive, for a cumulative incidence of 1.9% at 5 years (90% CI, 1.1 to 3.2) (Fig. 1). There were 12 recurrences (10 local, no regional, and 2 dis-



**Figure 1. Cumulative Incidence of Local Recurrence, Cancer in the Contralateral Breast, and Any Recurrence.**

Shown are the probabilities of local recurrence in the ipsilateral breast (Panel A), contralateral breast cancer (Panel B), and any recurrence (Panel C) among the 500 patients with luminal A breast cancer who were enrolled in the study. The red horizontal line at 5% (Panel A) represents the prespecified boundary for an acceptable incidence of local recurrence at 5 years. Dashed lines indicate the 90% confidence interval, and the insets show the same data on an expanded y axis.

47 overall and 5-year disease-free survival of 89.9% (90% CI, 87.5 to 92.2). A total of 13 deaths occurred (of which only 1 was related to breast cancer), for a 5-year overall survival of 97.2% (90% CI, 95.9 to 98.4).

DISCUSSION

Since the era of early trials, conducted 40 years ago, that showed the efficacy of postoperative radiotherapy,<sup>19</sup> a lower incidence of ipsilateral breast cancer recurrence has been observed over time. It is conceivable that many patients at low risk for local recurrence can be cured with surgery and endocrine therapy alone. Consequently, improving care by omitting radiotherapy is a goal in the treatment of patients in whom the risk of local recurrence is minimal, thereby avoiding the short- and long-term side effects of radiotherapy.

We previously found that intrinsic subtyping with the use of immunohistochemical analysis can independently predict the risk of local recurrence.<sup>12</sup> We subsequently evaluated whether clinicopathologic factors combined with intrinsic subtyping could identify a group of patients who were at sufficiently low risk that radiotherapy could be omitted from their treatment.<sup>15</sup> We performed a retrospective analysis of the Toronto–British Columbia trial in which patients treated with breast-conserving surgery and tamoxifen were randomly assigned to receive radiotherapy or no radiotherapy. Archival samples obtained from 501 patients were analyzed with the use of the immunohistochemical signature. Clinical-risk group and intrinsic subtype independently predicted the risk of local recurrence; patients who were in the low-clinical-risk group (age >60 years, T1N0, grade 1 or 2) and who had the luminal A subtype were at the lowest risk (1.3%) after breast-

tant), for a cumulative incidence at 5 years of 2.7% (90% CI, 1.6 to 4.1). With regard to disease-free survival, there were 11 recurrences, 7 contralateral cancers, 23 second primary cancers, and 6 deaths that were reported as first events, for a total of

conserving surgery alone. On the basis of this data, we decided to prospectively test this novel combination of old and new markers. Given that the use of intrinsic subtype combined with clinical risk factors to identify patients in whom radiotherapy could be omitted would be a major change in practice, we performed a multicenter prospective study to validate the potential use of such an approach.<sup>20,21</sup>

Our results showed that among women who were at least 55 years of age and had T1N0, grade 1 or 2, luminal A breast cancer that had been treated with breast-conserving surgery and endocrine therapy alone without radiotherapy, the incidence of local recurrence at 5 years was very low. The upper boundary of the 90% confidence interval and the 95% confidence interval for the observed incidence satisfied our prespecified boundary. These observed results were consistent with the prespecified incidence and boundary, thus validating our hypothesis.

The incidence of recurrence in the ipsilateral breast was similar to that of new breast cancers observed in the contralateral breast, findings that confirmed the low risk and suggested that at least some of the ipsilateral breast cancers may have been new breast cancers. Indeed, of the 10 cases of ipsilateral breast cancer observed, 4 occurred away from the site of the original breast cancer, a finding that suggests that they may have been new cancers, which are often associated with a more favorable outcome.<sup>22,23</sup>

The risks of distant recurrence and death due to breast cancer were also very low, probably because of the luminal A subtype and use of adjuvant endocrine therapy. Of note, the incidence of second new primary nonbreast cancers and deaths from any cause in this older population far exceeded the incidence of any recurrences and deaths due to breast cancer.

We chose a prospective cohort design to evaluate the strategy of omitting radiotherapy because the research question was primarily related to prognosis rather than treatment efficacy and was targeted to a very-low-risk group. A randomized trial could address the effectiveness of radiotherapy in such a population but would require a very large sample to rule out a very small difference. A carefully controlled prospective cohort study is more efficient yet can also be very precise. Such a design has been used to identify low-risk breast cancer with the use of a genetic

signature in which adjuvant chemotherapy can be omitted.<sup>24</sup>

Other biomarker assays (21-gene recurrence score<sup>25</sup> and the prediction analysis of microarray [PAM] 50 assay<sup>26</sup>) are being evaluated for their usefulness in identifying patients in whom radiotherapy might be omitted, but follow-up in these trials is short.<sup>27,28</sup> For our study, we chose to use immunohistochemical analysis for intrinsic subtyping to identify low-risk patients for several reasons: our previous data supported this approach, and other genetic-signature testing was costly, logistically difficult to apply in clinical practice, and sometimes required samples to be sent to a single laboratory. Such signature testing was not routinely performed in all patients unless adjuvant chemotherapy was being considered. Testing for ER, PR, and HER2 was routinely performed in hospital laboratories with high quality assurance. In addition, although there had been some concerns regarding the reliability of the Ki67 assay, Nielsen et al., through the International Working Group for Ki67, had developed a systematic approach to staining and scoring Ki67 that showed that it could be reliably performed by multiple pathologists.<sup>16</sup> This approach is significantly less expensive than assays that use genetic signatures. In our study, we chose to use three laboratories to measure Ki67 and to ensure agreement among the three laboratories. This was a practical and efficient approach. Further work is needed to explore whether a central laboratory approach or performance of the assay by a local laboratory can be used.

We chose patient age, tumor size, and tumor grade as clinicopathologic factors. Previous studies had shown these factors to be predictive of local recurrence after breast-conserving surgery, and this finding was confirmed in our retrospective study.<sup>15</sup> We also excluded patients with lobular cancer, tumor multifocality, an extensive intraductal component, or lymphovascular invasion, since these factors are routinely reported by pathologists and also have been associated with an increased risk of local recurrence.<sup>29</sup> Our ultimate goal was to identify a group of patients whose risk of local recurrence was so low that any benefit of radiotherapy would be negligible and outweighed by the risks associated with treatment. Although the risk of recurrence of cancer in the ipsilateral breast among patients in our study will probably increase with further follow-

up, the incidence is not likely to be much higher than 5% at 10 years, when any benefit of radiotherapy is still likely to be small.<sup>30</sup> A recent Scottish trial<sup>31</sup> reported a risk of local recurrence of approximately 10% at 10 years with the omission of radiotherapy, findings that are consistent with the results of the previous Cancer and Leukemia Group B 9343 trial.<sup>30</sup> Despite these results and subsequent guidelines,<sup>32</sup> older women ( $\geq 70$  years of age) with early-stage hormone-receptor–positive breast cancer are still receiving radiotherapy after breast-conserving surgery.<sup>33</sup> Local recurrence is an important concern for patients after breast-conserving surgery for cancer.<sup>34</sup> Often treated by mastectomy, a local recurrence is usually associated with considerable psychological effects. In the current era of shared patient–physician decision making and precision medicine, the notion that a 10% incidence of local recurrence would be acceptable to patients could be invalid. The results of our study suggest that by combining molecular biomarkers with clinicopathologic factors, this risk can be reduced.

We selected a group of women at low risk on the basis of traditional clinicopathologic factors and a molecular biomarker, and we carefully treated and followed patients prospectively. Our results are generalizable to this group and should not be extrapolated to other groups. Other thresholds for ER and Ki67 have been applied for characterizing the luminal A subtype with the use of immunohistochemical analysis.<sup>35</sup> The results of our study reflect the thresholds we used.<sup>11,13</sup>

Our study showed that women 55 years of age or older with T1N0, grade 1 or 2, luminal A breast cancer had a very low risk of local recurrence at 5 years after breast-conserving surgery when treated with endocrine therapy alone. The prospective and controlled nature of this study supports our conclusion that such patients are candidates for omission of radiotherapy.

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Disclosure forms provided by the authors are available with the full text of the article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

#### APPENDIX

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#### REFERENCES

- Breast cancer facts & figures 2022-2024. Atlanta: American Cancer Society, 2022 (<https://www.cancer.org/research/cancer-facts-statistics/breast-cancer-facts-figures.html>).
- Whelan TJ, Julian JA, Berrang TS, et al. External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *Lancet* 2019; 394:2165-72.
- Waljee JF, Hu ES, Ubel PA, Smith DM, Newman LA, Alderman AK. Effect of esthetic outcome after breast-conserving surgery on psychosocial functioning and quality of life. *J Clin Oncol* 2008;26:3331-7.
- Taylor C, Correa C, Duane FK, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* 2017;35:1641-9.
- Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld? *Radiother Oncol* 2009;90:14-22.

6. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. *J Clin Oncol* 2002;20:4141-9.
7. Lim M, Bellon JR, Gelman R, et al. A prospective study of conservative surgery without radiation therapy in select patients with stage I breast cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1149-54.
8. Fyles AW, McCreedy DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. *N Engl J Med* 2004;351:963-70.
9. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature* 2000;406:747-52.
10. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 2001;98:10869-74.
11. Cheang MCU, Chia SK, Voduc D, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst* 2009;101:736-50.
12. Voduc KD, Cheang MCU, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. *J Clin Oncol* 2010;28:1684-91.
13. Prat A, Cheang MCU, Martín M, et al. Prognostic significance of progesterone receptor-positive tumor cells within immunohistochemically defined luminal A breast cancer. *J Clin Oncol* 2013;31:203-9.
14. Dowsett M, Nielsen TO, A'Hern R, et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst* 2011;103:1656-64.
15. Liu F-F, Shi W, Done SJ, et al. Identification of a low-risk luminal A breast cancer cohort that may not benefit from breast radiotherapy. *J Clin Oncol* 2015;33:2035-40.
16. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in breast cancer: updated recommendations from the International Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst* 2021;113:808-19.
17. Nielsen T, Leung S, Riaz N, Kos Z, Bane A, Whelan TJ. Ki67 Assessment Protocol: companion diagnostic biomarker for LUMINA prospective cohort study. Presented at the 45th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 6–10, 2022. poster.
18. Marubini E, Valsecchi MG. Analysing survival data from clinical trials and observational studies. Chichester, United Kingdom: John Wiley, 1995:341.
19. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087-106.
20. Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst* 2009;101:1446-52.
21. Hayes DF. Biomarker validation and testing. *Mol Oncol* 2015;9:960-6.
22. Gage I, Recht A, Gelman R, et al. Long-term outcome following breast-conserving surgery and radiation therapy. *Int J Radiat Oncol Biol Phys* 1995;33:245-51.
23. Haffty BG, Fischer D, Beinfeld M, McKhann C. Prognosis following local recurrence in the conservatively treated breast cancer patient. *Int J Radiat Oncol Biol Phys* 1991;21:293-8.
24. Sparano JA, Gray RJ, Makower DF, et al. Prospective validation of a 21-gene expression assay in breast cancer. *N Engl J Med* 2015;373:2005-14.
25. Paik S, Shak S, Tang G, et al. A multi-gene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;351:2817-26.
26. Parker JS, Mullins M, Cheang MCU, et al. Supervised risk predictor of breast cancer based on intrinsic subtypes. *J Clin Oncol* 2009;27:1160-7.
27. Jagsi R, Griffith K, Harris EE, et al. Planned interim analysis results from a prospective multicenter single-arm cohort study of patients receiving endocrine therapy but not radiotherapy after breast-conserving surgery for early-stage breast cancer with favorable biologic features. *J Radiat Oncol Biol Phys* 2019;105:Suppl:S7-S8. abstract.
28. Braunstein LZ, Wong J, Dillon D, et al. Preliminary report of the PRECISION trial (profiling early breast cancer for radiotherapy omission): a phase II study of breast-conserving surgery without adjuvant radiotherapy for favorable-risk breast cancer. Presented at the 45th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 6–10, 2022.
29. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 2009;74:987-1001.
30. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;31:2382-7.
31. Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM. Breast-conserving surgery with or without irradiation in early breast cancer. *N Engl J Med* 2023;388:585-94.
32. Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN guidelines insights: breast cancer, version 1.2017. *J Natl Compr Canc Netw* 2017;15:433-51.
33. Downs-Canner S, Zabor EC, Wind T, et al. Radiation therapy after breast-conserving surgery in women 70 years of age and older: how wisely do we choose? *Ann Surg Oncol* 2019;26:969-75.
34. Whelan TJ, Levine MN, Gafni A, et al. Breast irradiation postlumpectomy: development and evaluation of a decision instrument. *J Clin Oncol* 1995;13:847-53.
35. Meattini I, Poortmans PMP, Marrazzo L, et al. Exclusive endocrine therapy or partial breast irradiation for women aged ≥70 years with luminal A-like early stage breast cancer (NCT04134598 — EUROPA): proof of concept of a randomized controlled trial comparing health related quality of life by patient reported outcome measures. *J Geriatr Oncol* 2021;12:182-9.

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