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Article

Omission of postoperative radiotherapy after breast-conserving surgery in low-risk breast cancer

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Abstract

Background: This prospective cohort study aimed to assess whether postoperative radiotherapy could safely be omitted in women aged 65 years and older with low-risk, estrogen receptor–positive T1N0 breast cancer treated with breast-conserving surgery and adjuvant endocrine therapy.

Methods: Eligible patients were women aged 65 years and older with unifocal, nonlobular, grade 1 or 2, estrogen receptor–positive, pT1N0 breast cancer treated with breast-conserving surgery and endocrine therapy for 5 years. Patients were followed up with mammography at least annually for 10 years. The primary endpoint was local recurrence. Secondary endpoints were contralateral breast cancer, recurrence-free survival, and overall survival.

Results: The final study cohort included 601 patients with a median age of 71 years (range = 65-90 years) and a median tumor size of 11 mm (range = 3-20 mm). Median follow-up time was 119 months (interquartile range = 103-121 months). The cumulative incidence of local recurrence was 1.5% (95% confidence interval [CI] = 0.8% to 2.8%) and 5.5% (95% CI = 3.8% to 7.6%) at 5 and 10 years, respectively. The cumulative incidence of contralateral breast cancer was 1.7% (95% CI = 0.9% to 3.0%) at 5 years and 4.5% (95% CI = 3.0% to 6.6%) at 10 years. The overall survival rate at 10 years was 83.1% (95% CI = 80.8% to 85.4%). In total, 3 (0.5%) patients died because of breast cancer.

Conclusion: Our results support the possibility to omit radiotherapy after breast-conserving surgery in a well-defined subgroup of women aged 65 years and older with low-risk, estrogen receptor–positive, pT1N0 breast cancer receiving adjuvant endocrine therapy.

Introduction

Postoperative radiotherapy (RT) after breast-conserving surgery in node-negative early breast cancer reduces the risk of local recurrence substantially with a modest improvement in breast cancer–specific and overall survival.[1] Although the relative benefit of RT in this treatment setting remains similar across different patient subgroups, the absolute benefit varies depending on the baseline risk of recurrence, which depends on patient- and tumor-related characteristics.[1] Based on this observation, it might be feasible to identify patients with a low risk of local recurrence at baseline, where omission of postoperative RT after breast-conserving surgery could be safe in terms of oncological outcome.

Older patients with small tumors and less aggressive biology (estrogen receptor–positive and HER2-negative disease without adverse prognostic factors) might serve as a suitable patient group for this strategy.[2-4] In fact, 2 randomized trials dedicated to older patients with low-risk estrogen receptor–positive breast cancer found that omission of RT results in a higher risk of local recurrence without any difference in distant recurrence or survival after approximately 10 years of follow-up.[5,6] However, some criticism on the implementation of these results in clinical

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practice has been raised. Some of it is based on the lack of information on histopathological prognostic biomarkers (HER2 status, Ki-67) that have been associated with increased risk of local recurrence.[7,8] Also, the recent advances in radiation delivery approaches (ultra-hypofractionated dose schedules,[9] partial breast irradiation[10-12]) diminish several disadvantages related to breast RT. Endorsing these new techniques in clinical practice reduces health-care expenditure and increases patient comfort compared with conventional RT techniques,[9,13-15] but there is still a need for identifying patient groups that lack benefit from RT, where this treatment is unnecessary and might even be harmful.

This Swedish multicenter prospective cohort study was designed to assess whether RT could safely be omitted in women aged 65 years and older with low-risk, estrogen receptor–positive, T1N0 breast cancer treated with breast-conserving surgery and adjuvant endocrine therapy for 5 years. The 5-year results of the trial showed a cumulative incidence of 1.2% for local recurrence that was comparable with the risk of contralateral breast cancer.[16] In this report, we present the final study results in terms of cumulative incidence of local recurrence, regional recurrence, and contralateral breast cancer, as well as survival after a follow-up period of 10 years for all eligible patients.

Methods

Study design

This prospective, national, multicenter cohort study was planned and conducted by the Swedish Breast Cancer Group. The study protocol was approved by the regional ethical review board at Uppsala University (reference number 2005:321), and all patients provided written informed consent. The study design has previously been described in detail.[16]

Patients

Study participants were recruited at 14 centers in Sweden between August 2006 and October 2012. Eligible for participation were women aged 65 years and older at diagnosis with newly diagnosed primary invasive breast cancer who had undergone breast-conserving surgery with clear surgical margins (no tumor on ink) and no evidence of lymph node metastasis (according to sentinel node biopsy or axillary dissection) and were scheduled to receive adjuvant endocrine treatment. The primary tumor had to be unifocal, no more than 2 cm in diameter, positive (≥10%, in accordance with current Swedish recommendations) for estrogen receptor and/or progesterone receptor with Elston–Ellis histological grade 1 or 2, and of nonlobular histology.

Patients were excluded if they had a previous diagnosis of in situ or invasive breast cancer, if breast surgery was nonradical or less extensive than sector resection, if an extensive intraductal component was detected (>25% of the tumor), if they had axillary or other metastases, or if adjuvant chemotherapy was planned. HER2 status was not considered as a criterion for inclusion or exclusion.

Enrollment, follow-up, and outcomes

After informed consent, all patients in the cohort were prescribed 5 years of endocrine therapy, either tamoxifen or an aromatase inhibitor (choice at the discretion of the treating physician). Information on tumor characteristics and primary treatment was collected for each patient.

All patients were reassessed with mammography performed annually, or more often if clinically indicated, for 10 years, and they were instructed to contact the treating institution in case of symptoms suggesting recurrence. Regular physical examinations were not mandatory during follow-up, but the participants were contacted at least once a year by a physician or a study nurse.

Each year, every participating center reported any confirmed recurrences, newly diagnosed cancer of other origin, changes in or discontinuation of endocrine therapy, or withdrawal from the study to the Clinical Research Support at Örebro University Hospital, which coordinated the study.

All cases of local recurrence were confirmed by histopathology. An independent safety committee consisting of 2 clinical oncologists and a statistician, none of whom were involved in the study design or execution, reviewed outcome data in 2010, 2012, and 2014.

The study protocol recommended premature termination of the study if the rate of local recurrence exceeded 2% per year. The study database was closed in October 2022, when follow-up time reached 10 years for the last included participant.

The primary endpoint was local recurrence of breast cancer, defined as histologically confirmed in situ or invasive cancer in the ipsilateral breast. Secondary endpoints were contralateral breast cancer, defined as histologically confirmed in situ or invasive cancer in the contralateral breast; recurrence-free survival (RFS), defined as the time between enrollment and any breast cancer recurrence (locoregional or distant) or death; and overall survival, defined as the time between enrollment and death from any cause. Regional recurrence, defined as recurrence in the ipsilateral regional lymph nodes including ipsilateral axillary, supraclavicular, infraclavicular, and/or internal mammary regions, and distant recurrence, defined as any recurrence in distant organs, were also analyzed as exploratory endpoints. The endpoints were assessed by the local investigator and not centrally reviewed.

Adherence to endocrine therapy was assessed annually by asking the patient whether she had taken the medication as prescribed over the past year. This information was not collected for the year in which an event (recurrence or death) occurred. A patient was considered adherent to endocrine therapy if she reported taking the medication as prescribed throughout the entire treatment period—from initiation to either the end of treatment or the year preceding any event of interest.

Statistical analysis

During study design, a cumulative incidence of local recurrence of up to 5% at 5 years and approximately 8% at 10 years was assumed to be acceptable for a low-risk subgroup of breast cancer in women aged 65 years and older. Three previously published studies with 10-year follow-up providing incidence rates for local recurrence in breast cancer patients treated with breast-conserving surgery without adjuvant RT[17-19] supported the notion that a local recurrence frequency of approximately 1% per year was an acceptable limit for a low-risk group of breast cancer patients aged 65 years or older.

Assuming an acceptable cumulative incidence of local recurrence of up to 5% at 5 years (95% confidence interval [CI] = 3.2% to 6.8%, mean error = 0.9%) and approximately 8% at 10 years (95% CI = 5.7% to 10.3%), enrollment of 600 patients was planned to estimate local recurrences with an accuracy of 5% at 10 years.

Descriptive statistics were applied to present patient-, tumor-, and treatment-related characteristics, with numbers and percentages for categorical variables and median with interquartile range for continuous variables. The cumulative incidence of local and regional recurrence was estimated using the cumulative

Table 1. Patient-, tumor-, and treatment-related characteristics in the study cohort (n = 601)

Characteristic	No. (%)
Age, median (range), y	71 (65-90)
Age distribution, y	
65-70	298 (50)
71-80	247 (41)
Older than 80	56 (9)
Diagnostic route	
Screening	439 (73)
Clinical	162 (27)
Tumor size, mm (range)	11 (3-20)
Tumor grade	
I	342 (57)
II	258 (43)
Not performed or unknown	1 (0.2)
Histological cancer type	
Ductal	534 (89)
Other	67 (11)
Estrogen receptor status	
Positive	600 (99.8)
Negative	0 (0)
Not performed or unknown	1 (0.2)
Progesterone receptor status	
Positive	536 (89)
Negative	63 (10.5)
Not performed or unknown	2 (0.3)
HER2 status	
Positive	11 (2)
Negative	531 (88)
Not performed or unknown	59 (10)
Axillary surgery	
Sentinel lymph node dissection	586 (98)
Axillary lymph node dissection	15 (2)
Type of adjuvant endocrine therapy	
Tamoxifen	534 (89)
Aromatase inhibitors	66 (11)
Unknown	1 (0.2)

incidence function where death was considered a competing risk event. The cumulative incidence of contralateral breast cancer was estimated with a similar procedure. The Kaplan–Meier method was used to estimate RFS and overall survival. For all estimates, 95% confidence intervals were constructed.

Results

Patients

From August 2006 to October 2012, a total of 603 patients were enrolled. Two patients were excluded from the final analysis because of not fulfilling inclusion criteria (aged younger than 65 years at diagnosis), leaving 601 patients in the final study cohort.

Baseline characteristics of the study participants are described in Table 1. The median age was 71 years (range = 65-90 years). The median tumor size was 11 mm (range = 3-20 mm). All tumors were estrogen receptor–positive, and 89% were also positive for progesterone receptor. HER2 status was negative in the majority of tumors (88%), positive in 2%, and unknown in 10% of tumors. Most (98%) patients underwent sentinel node biopsy. Most (89%) patients initially received tamoxifen as endocrine therapy, and the remaining 11% received an aromatase inhibitor.

The median follow-up time was 119 months (interquartile range = 103-121 months). Each patient was followed up until death, patient's choice to discontinue, loss to follow-up, or up to 120 months, whichever occurred first (Figure 1).

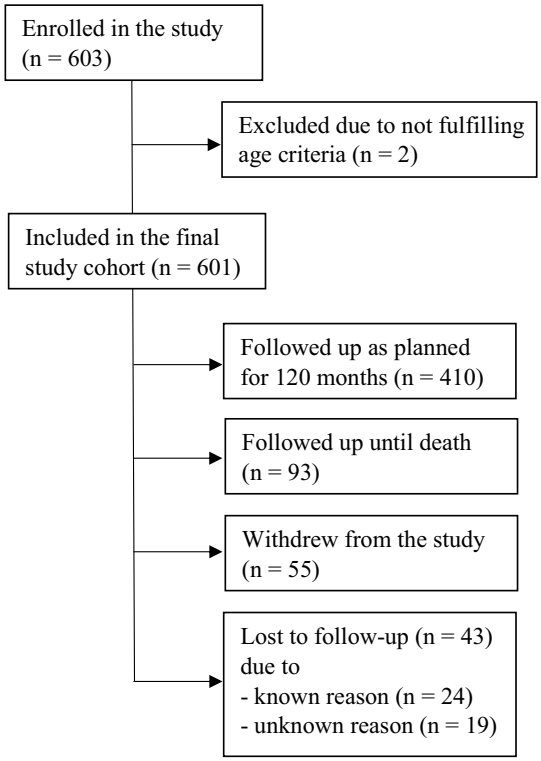

Figure 1. Flowchart showing the process of inclusion and causes for study termination. Patient relocation and clinically significant comorbidity preventing further participation were defined as known reasons for loss to follow-up. Of the 55 patients who withdrew from the study, 4 cited adverse events to endocrine therapy as the cause for withdrawal.

Adherence to endocrine therapy during follow-up was 86.6% (95% CI = 83.9% to 89.4%; 511 of 590 patients).

Event rates at 5 and 10 years

During the follow-up period, 31 of 601 (5.2%) patients had a local recurrence. Of those, 8 underwent breast-conserving surgery, whereas 21 underwent mastectomy (no data for 2 patients). Postoperative RT was given to 13 patients (6 of the patients treated with breast-conserving surgery and 7 treated with mastectomy). The cumulative incidence of local recurrence at 5 years was 1.5% (95% CI = 0.8% to 2.8%) and at 10 years was 5.5% (95% CI = 3.8% to 7.6%) (Figure 2). No difference in cumulative incidence of local recurrence at 10 years was observed in clinically relevant patient subgroups (based on HER2 status, progesterone receptor status, and type of endocrine therapy) (Table S1).

Eight (1.3%) patients had a regional recurrence during follow-up, of which 7 were axillary lymph node metastases and 1 unknown localization. In an exploratory analysis, the cumulative incidence of regional recurrence at 5 years was 0.3% (95% CI = 0.1% to 1.2%) and at 10 years was 1.4% (95% CI = 0.7% to 2.7%) (Figure 3).

Contralateral breast cancer was diagnosed in 25 (4.2%) patients during follow-up. The cumulative incidence of contralateral breast cancer was 1.7% (95% CI = 0.9% to 3.0%) at 5 years and 4.5% (95% CI = 3.0% to 6.6%) at 10 years (Figure 4).

Distant recurrence of breast cancer occurred in 5 (0.8%) patients during the 10-year follow-up period. None of these recurrences was preceded by local or regional recurrence. A total of 54 (9.0%) patients were diagnosed with a second primary

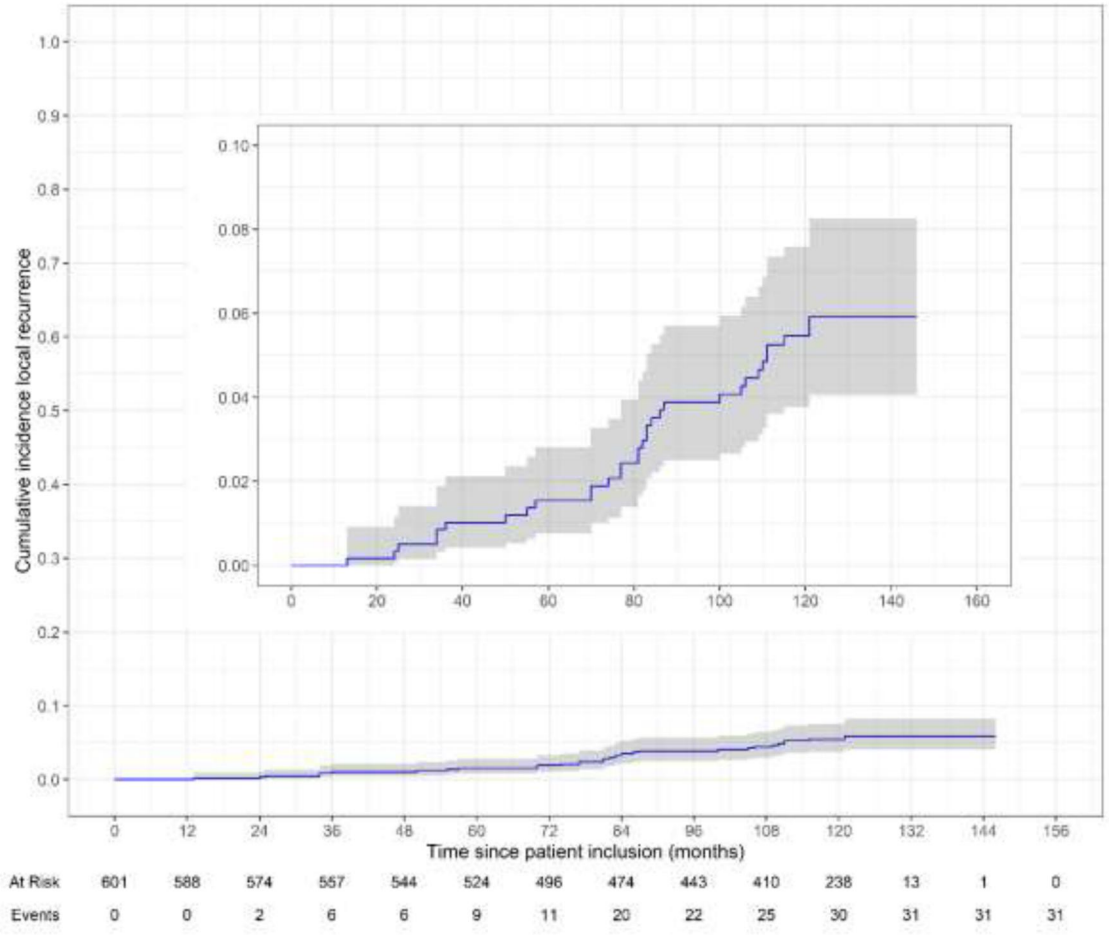

Figure 2. Cumulative incidence of local recurrence. The **shaded area** around the curve indicates the 95% confidence interval. The inset shows the same data on an expanded y axis.

cancer, with gynecological malignancies and colorectal cancer as the most common diagnoses with 15 patients each.

During follow-up, 150 events were captured as first events (33 locoregional recurrences, 25 contralateral cancers, 5 distant recurrences, and 87 deaths). The 5-year RFS was 89.9% (95% CI = 87.1% to 92.7%) and the 10-year RFS was 73.5% (95% CI = 68.9% to 78.1%) (Figure 5, A).

A total of 95 (15.8%) patients died during follow-up. Three (3.2%) of the deaths were due to breast cancer, whereas 88 (92.6%) patients died of causes other than breast cancer. In 4 (4.2%) patients, the cause of death was unknown. None of these patients had a recurrence registered. In total, 0.5% of the study cohort died because of breast cancer during follow-up. At 5 years, overall survival was 92.9% (95% CI = 90.5% to 94.9%) and at 10 years was 83.1% (95% CI = 80.8% to 85.4%) (Figure 5, B).

Discussion

Our long-term results suggest that a well-defined group of women aged 65 years or older with T1N0, estrogen receptor–positive, low-risk breast cancer can safely be treated with breast-conserving surgery and endocrine therapy alone without jeopardizing risk of recurrence or death from breast cancer. The actual cumulative incidence of local recurrence at 10 years was lower than the anticipated upper 95% confidence interval of local recurrence rate used for sample size calculation, thus suggesting that omission of postoperative RT in this selected group of older patients is a feasible alternative.

In this population of older patients with early breast cancer, the frequency of second primary cancer and death from other causes was considerable and exceeded the incidence of breast cancer recurrence and breast cancer–related deaths, respectively. Although 95 patients in the study cohort died during the follow-up period, only 3 deaths were due to breast cancer, whereas deaths from other causes dominated largely. Previous research has shown that with increasing age and comorbidity, the risk of death from causes other than breast cancer increases, making nonbreast cancer–related death a major contribution to the risk of mortality in older breast cancer patients.[20-22]

In the recent PRIME II trial,[6] patients aged 65 years and older with hormone receptor–positive, node-negative T1 or T2 breast cancer were randomly assigned to either standard postoperative RT or no RT after breast-conserving surgery with the addition of adjuvant endocrine therapy. The cumulative incidence of local recurrence at 10 years was 9.5% in the no-RT group and 0.9% in the RT group, but overall survival was similar in both groups. Our results show a lower rate of local recurrence at 10 years in patients not treated with postoperative RT (5.5% vs 9.5%), which could partly be explained by differences in patient selection. The PRIME II study allowed inclusion of patients with T2 tumors up to 3 cm in diameter (constituting 12.6% of the no-RT group) and cancer with high-risk characteristics such as histological grade 3 (3.5% of the no-RT group) as well as lobular cancer (proportion not

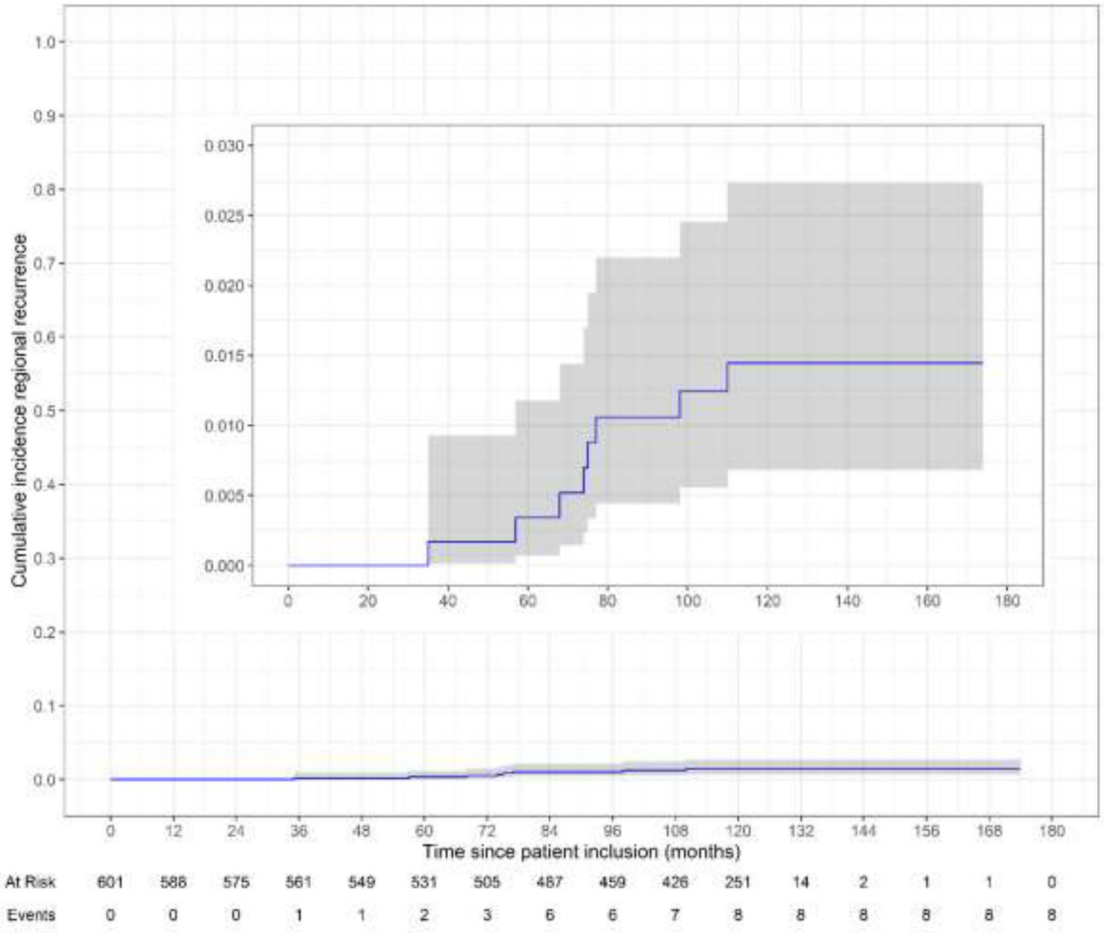

Figure 3. Cumulative incidence of regional recurrence. The **shaded area** around the curve indicates the 95% confidence interval. The inset shows the same data on an expanded y axis.

reported), whereas information on HER2 status and proliferation rate is lacking. In comparison with the PRIME II trial, the inclusion criteria in our study enables a more stringent selection of a low-risk patient cohort where omission of RT might be justified.

Similar to our study, the LUMINA trial[23] was a single-arm prospective cohort study where postoperative RT was omitted in patients aged 55 years and older with T1N0 breast cancer with luminal A characteristics. At 5 years of follow-up, the reported cumulative incidence of local recurrence was 2.3% to be compared with a cumulative incidence at 5 years of 1.5% in our study. Because age is an established risk factor for local recurrence,[18,19,24-26] the difference in age distribution between the study populations may contribute to differences in rates of recurrence. Apart from different age criteria, the study cohort of the LUMINA is similar to the cohort in our study, reflecting a low-risk patient subgroup. The adoption of a prospective single-arm cohort design in our study, as well as in the LUMINA trial, is justified by the primary objective of evaluating the long-term prognosis following the omission of RT in low-risk early breast cancer rather than assessing the efficacy of RT in this group.

The current study suggests that the use of a combination of standard clinicopathological factors such as patient age, tumor size, nodal status, histological grade, and immunohistochemistry-based biomarkers seems to be adequate to define a group of patients with breast cancer whose risk of local recurrence is sufficiently low that omission of postoperative RT can be considered. A major advantage for this strategy is that this information is readily available in standard clinical practice and requires no additional analyses for implementation. In the IDEA trial,[27] gene expression profiling through Oncotype Dx was added to standard clinicopathological factors to define a low-risk subgroup of younger (50-69 years) postmenopausal breast cancer patients in which RT was omitted and 5 years of endocrine therapy was prescribed. After 5 years of follow-up, the crude rates of ipsilateral breast cancer recurrence were 3.3% and 3.6% for patients aged 50-59 years and 60-69 years, respectively. In contrast to our study, the IDEA trial allowed certain high-risk clinicopathological criteria such as lobular histology, high tumor grade, and extensive intraductal component, which as well as younger age have been associated with a higher risk of local recurrence.[18,19,24-26] Our results indicate that the selection of a low-risk subgroup of patients can be based on clinical and pathological factors alone, without the addition of a gene expression analysis. Although analyses of gene expression profiles are becoming more widely used, they are currently not a standard part of the diagnostic workup in patients with clinicopathological low-risk tumors or patients who are not candidates for adjuvant chemotherapy because of comorbidities.[28]

With the implementation of modern RT techniques such as ultra-hypofractionation and partial breast irradiation, many of the burdens related to RT delivery have been reduced.[9-15] Still, the omission of RT in selected patients with a low risk of local recurrence, and therefore a very small anticipated absolute benefit from treatment, could be beneficial for patients and healthcare systems. The patient has the option of choosing to forego RT

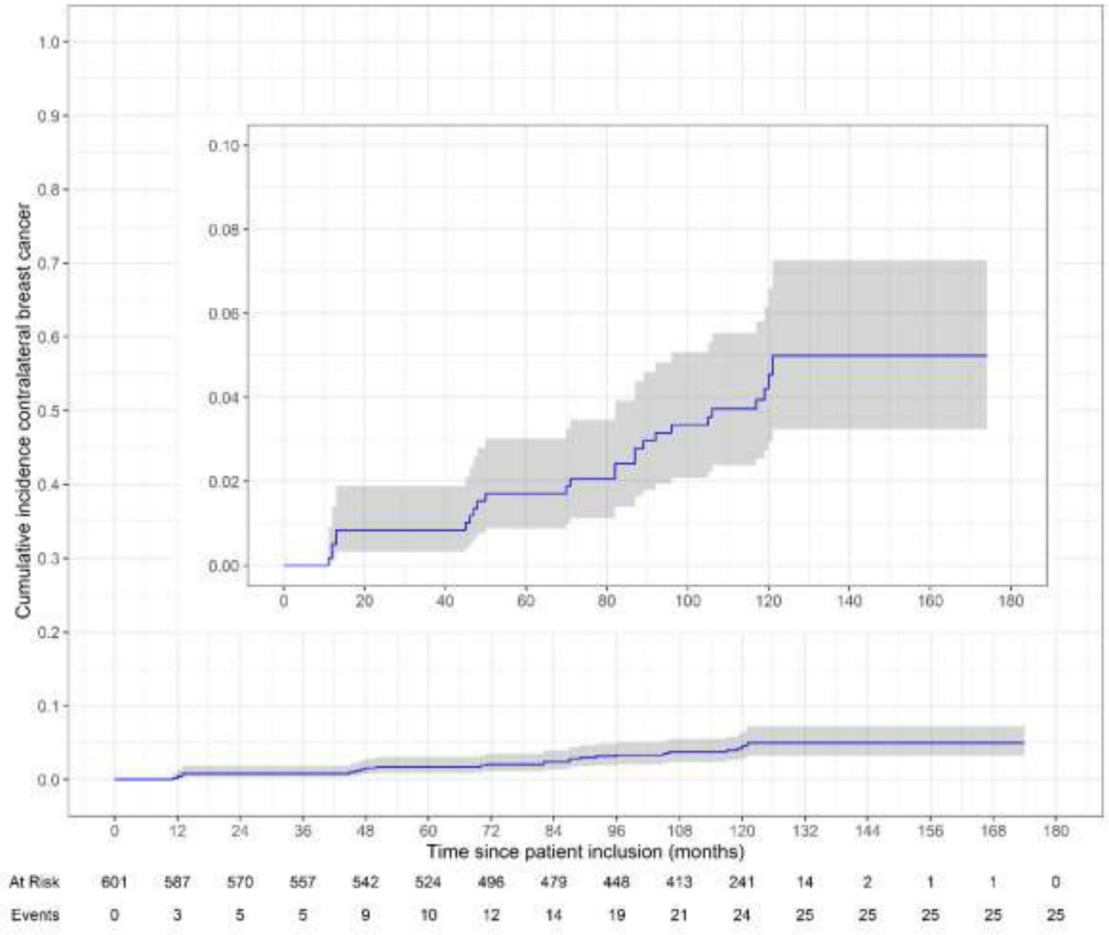

Figure 4. Cumulative incidence of contralateral breast cancer. The **shaded area** around the curve indicates the 95% confidence interval. The inset shows the same data on an expanded y axis.

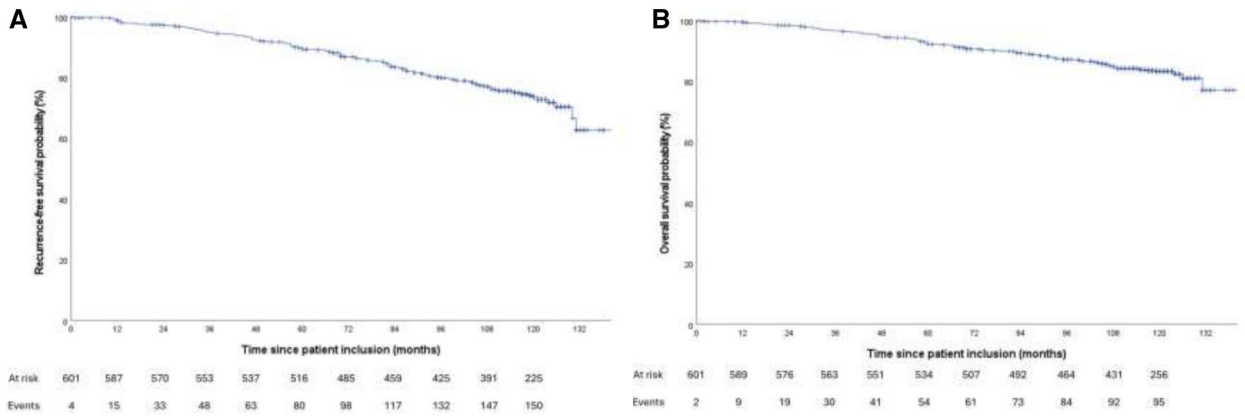

Figure 5. Kaplan–Meier curves showing (**A**) recurrence-free survival and (**B**) overall survival in the study cohort.

and avoid the, albeit smaller, risk of short- and long-term adverse effects, and the health-care systems can allocate resources to more impactful cancer care strategies. Omission of RT after breast-conserving surgery is endorsed in American[29] and European[30] guidelines as a treatment option that can be considered in well-defined groups of older patients with low-risk breast cancer, in line with the movement started by the Choosing Wisely initiative,[31] which fits well into the present era of patient-centered care and shared decision making.

In the current landscape of personalized medicine and deescalation approaches in breast cancer treatment, the question of RT vs endocrine therapy is emerging as highly relevant in low-risk breast cancer. Research findings suggest that the adverse effects of endocrine therapy may have a negative effect on quality of life, especially in postmenopausal women,[32] raising the question of whether exclusive endocrine therapy or exclusive RT would be the preferable choice in the deescalation of treatment in low-risk breast cancer in older patients. This important

question is being investigated in the ongoing EUROPA trial,[33] where women aged 70 years and older with luminal A-like early stage breast cancer are randomly assigned between 5 years of endocrine therapy only and partial breast RT only, with patient-reported quality of life as well as time to ipsilateral breast tumor recurrence as primary outcome measures. The results of the EUROPA trial represent the missing piece in the current body of evidence on optimizing postoperative treatment strategies for older patients with low-risk breast cancer. Until these results become available, the omission of RT after breast-conserving surgery should be considered a valid treatment option for older patients with low-risk breast cancer, in accordance with current guidelines and supported by the growing body of evidence.

Our study has some limitations that need to be considered when interpreting the results. Adherence to endocrine treatment was not prospectively monitored, but this information was retrieved retrospectively from electronic medical records, which are generally considered reliable. Furthermore, there was no systematic collection of information on treatment toxicity and patients' quality of life in the study. As a result, we were unable to investigate the impact of this deescalating strategy on patients' quality of life. In addition, despite the substantial follow-up time of 10 years, an even longer follow-up period would be desirable because there is accumulating evidence that the risk of recurrence in estrogen receptor–positive breast cancer persists for several decades after diagnosis.[34,35] Finally, we lacked reliable information on cell proliferation biomarkers as this parameter was not considered in our low-risk definition, as opposed to the LUMINA trial.[23] However, we excluded histological grade 3 tumors that could serve as a proxy for highly proliferative tumors as well.

In conclusion, our study suggests that in women aged 65 years or older with T1N0 estrogen receptor–positive, grade 1 or 2, non-lobular breast cancer treated with radical breast-conserving surgery and adjuvant endocrine therapy, the risk of local recurrence at 10 years is low even in the absence of postoperative RT. The long-term results of this prospective cohort study add to the growing body of evidence indicating that withholding RT in a selected cohort of low-risk patients with breast cancer is safe and could be an option for patients fulfilling these criteria. Results from ongoing randomized trials will provide further evidence exploring the issue of patients' quality of life in relation to endocrine therapy and RT.

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The findings of this study have been presented as a poster at ESMO Breast Cancer 2024, held on May 13-15 in Berlin, and a conference abstract was published as part of the proceedings:

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Five-year results from this study have previously been published:

Wickberg A, Liljegren G, Killander F, et al. Omitting radiotherapy in women ≥65 years with low-risk early breast cancer after breast-conserving surgery and adjuvant endocrine therapy is safe. *Eur J Surg Oncol*. 2018;44(7):951-956.

Author contributions

Sofia Palmér, MD (Data curation; Investigation; Methodology; Validation; Writing—original draft), Antonios Valachis, MD, PhD (Data curation; Formal analysis; Methodology; Supervision; Visualization; Writing—original draft; Writing—review & editing), Henrik Lindman, MD, PhD (Conceptualization; Investigation; Methodology; Resources; Supervision; Writing—review & editing), Daniel Robert Smith, PhD (Data curation; Formal analysis; Methodology; Software; Writing—review & editing), Åsa Wickberg, MD, PhD (Data curation; Investigation; Validation; Writing—review & editing), Fredrika Killander, MD, PhD (Investigation; Resources; Validation; Writing—review & editing), Judith Bjöhle, MD, PhD (Investigation; Methodology; Validation; Writing—review & editing), Zakaria Einbeigi, MD, PhD (Investigation; Methodology; Validation; Writing—review & editing), Greger Nilsson, MD, PhD (Investigation; Methodology; Validation; Writing—review & editing), Johan Ahlgren, MD, PhD (Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing—review & editing), and Kenneth Villman, MD, PhD (Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing—review & editing).

Supplementary material

Supplementary material is available at *JNCI: Journal of the National Cancer Institute* online.

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Conflicts of interest

Antonis Valachis has received institutional unrestricted grants from Roche and MSD unrelated to current work. The other authors have no relevant conflicts of interest to report.

Data availability

The datasets analyzed during the current study are not publicly available because of data protection rules for sensitive

(pseudonymized) data but are available from the corresponding author on reasonable request.

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