

Omitting radiotherapy in women ≥ 65 years with low-risk early breast cancer after breast-conserving surgery and adjuvant endocrine therapy is safe[☆]



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ABSTRACT

Purpose: The aim of this study was to verify if radiotherapy (RT) safely can be omitted in older women treated for estrogen-receptor positive early breast cancer with breast-conserving surgery (BCS) and endocrine therapy (ET).

Patients and Methods: Eligibility criteria were: consecutive patients with age ≥ 65 years, BCS + sentinel node biopsy, clear margins, unifocal T1N0M0 breast cancer tumor, Elston-Ellis histological grade 1 or 2 and estrogen receptor-positive tumor. After informed consent, adjuvant ET for 5 years was prescribed. Primary endpoint was ipsilateral breast tumor recurrence (IBTR). Secondary endpoints were contralateral breast cancer and overall survival.

Results: Between 2006 and 2012, 603 women were included from 14 Swedish centers. Median age was 71.1 years (range 65–90). After a median follow-up of 68 months 16 IBTR (cumulative incidence at five-year follow-up; 1.2%, 95% CI, 0.6% to 2.5%), 6 regional recurrences (one combined with IBTR), 2 distant recurrences (both without IBTR or regional recurrence) and 13 contralateral breast cancers were observed. There were 48 deaths. One death (2.1%) was due to breast cancer and 13 (27.1%) were due to other cancers (2 endometrial cancers). Five-year overall survival was 93.0% (95% CI, 90.5% to 94.9%).

Conclusion: BCS and ET without RT seem to be a safe treatment option in women ≥ 65 years with early breast cancer and favorable histopathology. The risk of IBTR is comparable to the risk of contralateral breast cancer. Moreover, concurrent morbidity dominates over breast cancer as leading cause of death in this cohort with low-risk breast tumors.

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Introduction

Breast-conserving surgery (BCS) is the standard treatment for early breast cancer. The addition of postoperative radiotherapy (RT)

has, in a large meta-analysis, been shown to halve the rate of local recurrences and reduce the breast cancer death by about a sixth [1]. However, the absolute benefits from RT vary substantially according to patient- and tumor-characteristics. There are subgroups of women where the adverse effects of RT, for instance ischemic heart disease and lung cancer [2–4], may exceed the advantages of postoperative RT, especially for long-term smokers [5]. Moreover, some women may choose a mastectomy in order to avoid 3–5 weeks of RT. After adjustment for age, among women with breast cancer in USA, the likelihood of receiving RT following BCS decreased significantly with increasing travel distance to the

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nearest radiation-treatment facility [6]. Assessment of the consequences of omitting RT for patients diagnosed with early-stage breast cancer is therefore needed.

We defined a cohort of women with low-risk-tumors were we presumed that the risk of IBTR after breast-conserving surgery with the addition of endocrine therapy (ET), even in the absence of postoperative RT would be at most 1–2% per year or 10% at 10 years.

Methods

Study design and patient baseline characteristics

The study was designed as a multicenter national prospective cohort study. Between 2006 and 2012, 603 women from 14 Swedish centers were included in the study. Every woman was carefully informed about pros and cons of the treatment and after written informed consent, adjuvant ET for 5 years was prescribed. All women included were registered in a case report form (CRF), which was sent to a local manager at the Clinical Research Support, University Hospital Örebro. Two patients did not fulfill the inclusion criteria (due to age <65 years) and were excluded from the cohort.

Eligibility criteria were; consecutive patients with age ≥ 65 years, BCS (sector resection and sentinel node biopsy) with clear margins (no tumor cells at inked border for invasive cancer, 2 mm margin for in situ cancer), T1N0M0 non-lobular breast cancer tumor, Elston-Ellis histological grade [7] 1 or 2 and estrogen receptor (ER) positive and/or progesterone receptor (PR) positive tumor. For every woman, information was collected from the CRF regarding initial treatment and tumor characteristics; type of adjuvant endocrine therapy (tamoxifen (TAM) or aromatase inhibitors (AI)), tumor size, histopathological type, Elston-Ellis histological grade, ER, PR and human epidermal growth factor receptor 2 (HER2). All variables were prospectively registered in the CRF (Table 1).

Follow-up

The procedures included mammography performed annually or more often when indicated by clinical symptoms. Annual visit with a physician was not mandatory, but the women were instructed to contact the treating institution in case of suspicion of recurrence.

All IBTR's were confirmed by histopathology. Every year confirmed recurrences, cancers of other origin, discontinuation or change of ET or withdrawal from the study had to be reported to the CRS from each participating center.

A safety committee consisting of one statistician and two physicians, who were not involved in the study, examined all reported events once a year. If the IBTR exceeded 2% per year the study protocol recommended closure of the study.

The study was approved by the Regional Ethical Review Board at Uppsala University, D n r 2005:321. It was also registered in the data base "Research and Investigations in Sweden" (N r 53991).

Endpoints and outcome assessment

Primary endpoint was ipsilateral breast tumor recurrence (IBTR). Secondary endpoints were contralateral breast cancer and overall survival. Most of the women had a complete follow-up until 2017-03-01 (or could be followed until death), but 31 women were lost to follow-up. All women who were lost to follow-up were included in the analysis until withdrawal.

Statistics

It was decided that a ten year rate of IBTR of 10% would be acceptable. The number of included cases enabled estimation of IBTR with approximately 5% accuracy. E g, if 600 patients were enrolled with an estimated IBTR of 8% at ten years then the corresponding 95% CI would be 5.7% to 10.3%. The cumulative incidence of IBTR was estimated by a competing risk regression model implemented in Stata 12.1 (Stata/SE for Windows; Stata Corp, College Station TX), with regional recurrence, distant metastases, other types of cancers and deaths as competing risk [8]. The same procedure was done with respect to contralateral breast cancer. Overall survival was estimated with the Kaplan-Meier method. 95% confidence intervals (CI) were used for all calculations.

Results

Median age was 71.1 years (range 65–90) and the median tumor size was 11 mm. Only 1.8% of the women had tumors with over-expression of HER2 and 10.5% of the tumors were progesterone receptor negative. All tumors were ER-positive. The majority of the tumors were of ductal origin, low grade and PR-positive. Most of the patients received TAM (Table 1).

IBTR and other new primary tumors

At a median follow-up of 68 months (range 2 days–120 months) 16 IBTR, 6 regional recurrences (one combined with IBTR) and 2 distant recurrences both without IBTR or regional recurrence were observed. The calculated cumulative incidence of IBTR at five years was 1.2% (95% CI, 0.6% to 2.5%) (Fig. 1). Inclusion of the two excluded women did not change the estimate.

Thirteen women had a contralateral breast cancer; cumulative incidence at five years 1.8% (95% CI 0.9–3.2) (Fig. 3).

Thirty-four patients were diagnosed with tumors of other origins. Three of these tumors were ovarian cancer, three were lung cancer, nine were gastrointestinal cancer, eleven were other types of cancer and eight were endometrial cancers. Seven of the women with endometrial cancer were treated with TAM and one woman had an AI. However, one woman had TAM for only two weeks. For the others the duration range of intake was 1.5–7 years.

Table 1
Baseline characteristics. Calculated from the 601 participants.

	Median (range)
Age, years	71 (65–90)
Tumor size, mm	11.0 [3–20]
	N (%)
Endocrine therapy	
tamoxifen	534 (88.9)
aromatase inhibitor	67 (11.1)
Histopathology	
ductal	534 (88.9)
Other ^a	67 (11.1)
NHG	
grade I	342 (56.9)
grade II	258 (42.1)
unknown	1 (0.17)
Progesterone rec	
positive	536 (89.1)
negative	63 (10.5)
unknown	2 (0.33)
Her-2	
positive	11 (1.8)
negative	531 (88.4)
unknown	59 (9.8)

^a Mucinous, papillary, tubular.

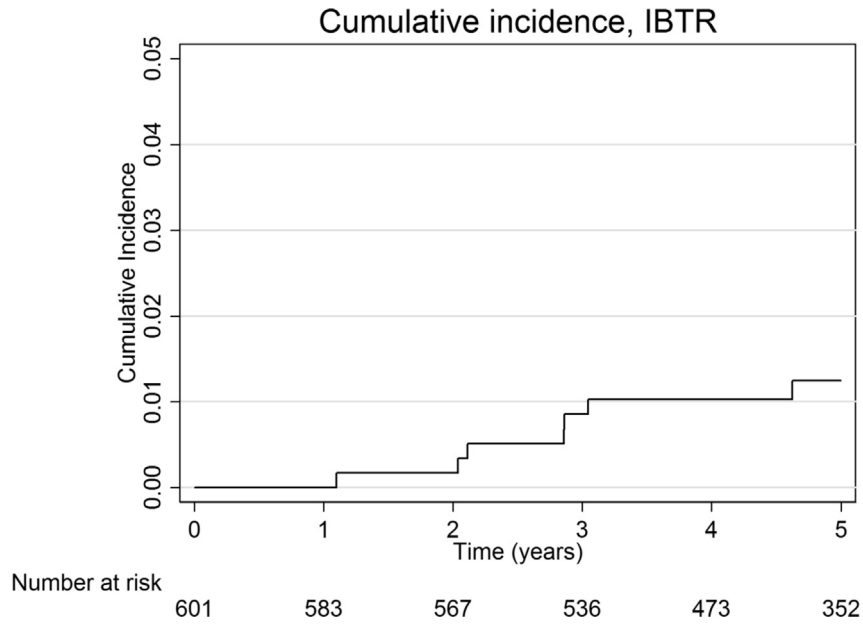


Fig. 1. Cumulative incidence of IBTR at 5 years of follow-up: 1.2% (95% CI 0.6–2.5%). Competing risk; regional recurrence, distant metastases, other types of cancers, deaths.

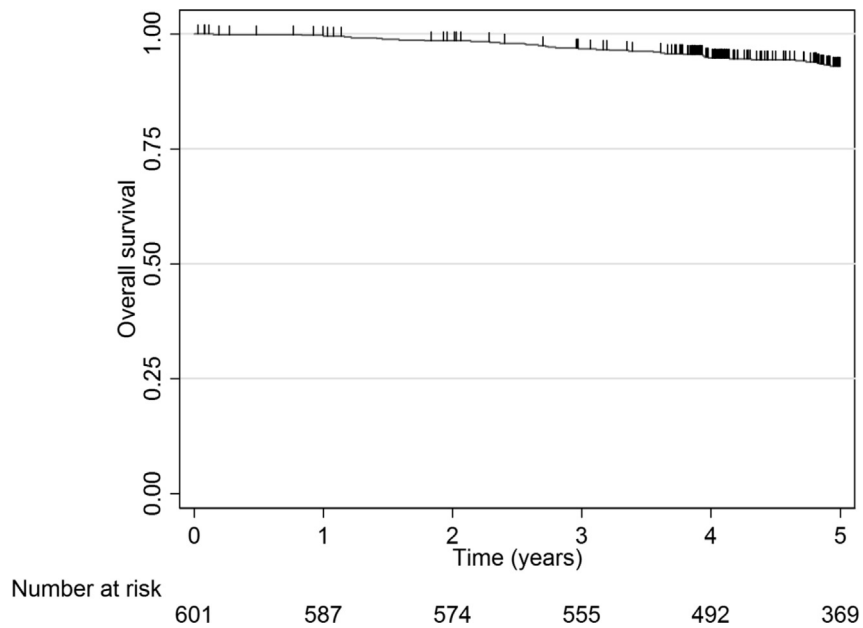


Fig. 2. Five-year overall survival (hash marks indicate censored data): 93.0% (95% CI 90.5–94.9%).

Overall survival

There were 48 deaths. Only one death was due to breast cancer. Two women died from endometrial cancer and 11 were due to other cancers. Overall survival at five years was 93.0% (95% CI 90.5–94.9%) (Fig. 2).

Withdrawal from follow-up and ET

Thirty-one women withdrew from follow-up or ET ahead of schedule. Three women withdrew due to serious illnesses (generalized cancer of different origin) and four women due to advanced age or dementia. Three women were lost for follow-up as they

moved abroad or to other parts of Sweden. In twelve cases the reason for withdrawal was unknown.

Eleven out of thirty-one women stopped their ET due to adverse effects. Nine of these women were lost to follow-up. Two of these eleven women changed from TAM to AI which they did not tolerate either. Compliance to ET with a median follow-up of 68 months (range 2 days–120 months) was 96%.

Discussion

The cumulative incidence of IBTR at five years was 1.2% in this cohort treated with BCS and ET. Only one out of forty-eight deaths was attributable to breast cancer, which means that other diseases

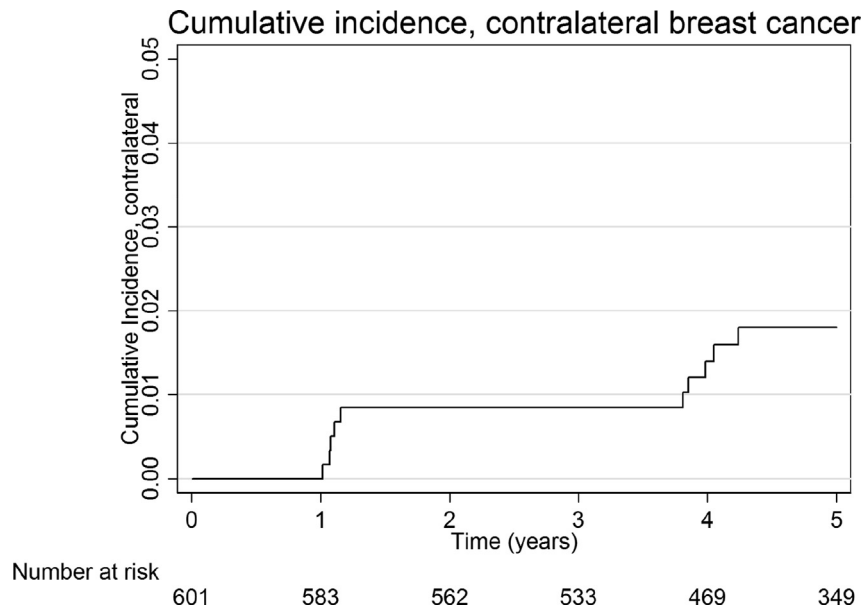


Fig. 3. Cumulative incidence of contralateral cancer at five-year of follow-up. 1.8% (95% CI 0.9–3.2%). Competing risk; regional recurrence, distant metastases, other types of cancers, deaths.

pose a larger threat to the survival of women in this age group during the first five years after a low-risk breast cancer.

Postoperative RT after BCS is still a general recommendation [1,9] although efforts have been made to identify a group of low-risk tumors for which this treatment may be omitted. The Oxford overview of studies of adjuvant RT after breast-conserving surgery included 10 801 women [1]. In pN0 patients (7287 women), the first recurrence was locoregional for a higher proportion of women allocated to surgery alone (22.8%) than for women allocated to surgery and RT (7.3%), while the numbers of distant recurrences were the same (8.2% and 8.3%). The group with pN0 disease was divided into three categories based on the absolute reduction in the 10-year risk of any recurrence with RT; high (>20%), intermediate (10–20%) or low (<10%). The categorization was based on age, tumor grade, ER-status, tamoxifen use, and extent of surgery. Patients with $\geq 20\%$ reduction in recurrence had a 7.8% (95% CI 3.1–12.5) improvement in 15-year breast cancer mortality, which was in line with pN + disease. However, for the intermediate risk reduction group, the decrease in mortality did not reach significance 1.1% (95% CI –2.0 to 4.2), and for the group with <10% improvement, there was no decrease in mortality, point estimate 0.1% (95% CI –7.5 to 7.7). This supports the notion that it should be possible to define a subgroup of patient for which RT after BCS safely can be omitted.

Although modern imaging and dose planning have reduced the risks of RT, adjacent organs are still burdened by irradiation to some extent. The magnitude of the risk of heart disease increase linearly with whole-heart radiation dose [10] and there is a small but statistically significant risk of lung cancer [4]. For a majority of the patients the benefits of RT far outweigh the risks, while in elderly women with a shorter life expectancy, RT after BCS for low-risk breast cancer can impose a non-justifiable risk for serious adverse effects.

Several previous studies have assessed the risk factors for IBTR in women treated with breast-conserving surgery without irradiation [11–19]. Documented risk factors for IBTR in these studies were low age [11–14,18], large tumor size [14,20], extensive cancer in situ [18], and lobular histology [11]. Based on these analyses low age, large tumors, extensive cancer in situ, and invasive lobular histology were decided to be exclusion criteria in our study.

Three studies have studied populations of elderly breast cancer patients treated with BCS with an anticipated low risk of local recurrence, even without RT [15,16,20,21]. The Cancer and Leukemia Group (CALGB) 9343 randomized study tested omission of adjuvant whole-breast RT in women aged ≥ 70 years with T1 tumors (≤ 2 cm) receiving adjuvant TAM after BCS. A 3% gain in locoregional control from RT was observed after 5 years of follow-up (1% vs 4%) and a 7% gain in locoregional control after 10 years (2% vs 9%) [15,16]. No difference was found concerning overall survival or distant metastatic disease. The authors concluded TAM alone to be a reasonable adjuvant treatment for this group.

In the Prime II-study [21] 1326 women aged >65 years with early breast cancer judged as low-risk patients, were randomized to TAM plus whole breast RT or TAM alone. After 5 years the cumulative incidence of IBTR was 1.3% and 4.1% respectively. Even though the difference is statistically significant the absolute risk difference is small. The authors considered the incidence of IBTR low enough to omit RT for some patients.

In our cohort of non-irradiated women, the cumulative incidence of IBTR was even lower at five years than the CALGB-study that also included stage I tumors [15]. In the Prime II-trial the incidence of IBTR was higher than in our study which could be due to larger tumor size, even though the age span was the same [21]. In both these studies lumpectomy was used rather than sector resection as in our study. Sector resection [22], represents a more extensive surgical approach, compared to lumpectomy. The procedure includes the periphery of the parenchyma and all tissue to the mamilla. The dissection goes down to the pectoral fascia and aims at a macroscopic or mammographic margin of one centimeter on the specimen. This probability contributes to the low incidence of IBTR in the present study.

The cumulative incidence of contralateral cancer was of the same magnitude as the incidence of IBTR, while in other studies, where radiotherapy was delivered, excess rates of contralateral breast cancer have been observed. In the Uppsala-Örebro study cumulative incidence of contralateral cancer in women treated with BCS alone was 11.2% at 20 years and in the group treated with both BCS and RT it was 16.4% (absolute risk difference 5%; 95% CI, –2% to 12%). None of these women were treated with ET [23]. In

a meta-analysis from EBCTCG [4] the excess rate of contralateral breast cancer after radiotherapy appears mainly during years 5–14 after randomization. After 5 years the incidence of contralateral breast cancer in the group treated with BCS alone was one per cent more than in our study (2.9%).

A majority of women in our cohort, 89%, were treated with TAM, the others with AI. TAM has shown substantial protective effect against IBTR (rate ratio 0.53, SE 0.03) and breast cancer death (rate ratio 0.71, SE 0.05) in estrogen receptor positive disease [24]. However, TAM as a selective estrogen receptor modulator (SERM) exerts a mixed estrogen receptor agonist and antagonist activity, depending on the target tissue. In the uterus TAM exhibits ER agonist activity and is associated with an increased risk of endometrial hyperplasia and malignancy. Five years of TAM was, in a large meta-analysis, associated with a small but significant absolute increased risk of dying from endometrial cancer [24], only seen in women older than 55 years. In a large systematic review and meta-analysis by Amir et al. [25], AI use was associated with a 66% reduction in the relative odds of endometrial carcinoma compared with TAM (OR = 0.34, 95% CI = 0.22 to 0.53, $P < .001$). In this cohort 8 women were diagnosed with endometrial cancer which corresponds to a five year incidence of 1.3% and two out of eight died from the disease. Although seven out of these eight women were treated with TAM, the low number of events in our cohort makes it inappropriate to test the difference between tamoxifen and aromatase inhibitors statistically. At present AIs have become standard adjuvant ET for postmenopausal women with estrogen receptor-positive breast cancer due to the superior efficacy of AIs compared with TAM. Speculatively, the incidence of breast cancer events could have been even lower if AI had been predominant in this study [26–28].

It is reasonable to believe that more than 11/601 women stopped their endocrine therapy due to adverse effects. Among the twelve study participants who stopped in advance for unknown reason some of them might have taken this decision due to side effects of the ET. In a retrospective Swedish study, 31% of the women stopped ET within three years, and half of them stopped within the first year [29]. Early discontinuation of and non-adherence to ET has been associated with increased mortality [30].

A limitation of this study might be the short follow-up. However, five years might be adequate to evaluate the risk difference of IBTR between patients treated with or without RT, since most of the local recurrences in non-irradiated patients occur during the first few years [1,23]. Ideally a cohort study should have a control group, which our study does not have. However, with the very low risk of recurrence in this study a randomized trial with an active treatment arm would have had a low power of detecting a clinically meaningful difference.

In conclusion, BCS and ET without RT seem to be a safe treatment option in women ≥ 65 years with early breast cancer and favorable histopathology. The risk of IBTR is comparable to the risk of contralateral breast cancer. Moreover, concurrent morbidity dominates over breast cancer as leading cause of death in this cohort with low-risk breast tumors. Clinicians need information on the absolute size of benefits and risks in order to recommend the best possible treatment for each individual.

Conflict of interest statement

The authors declare no conflicts of interest with regard to personal or financial relationships with other persons or organizations, except for Henrik Lindman who has had a consulting and advisory role to Astra-Zeneca, Novartis, Pfizer, Amgen and Daiichi and who have received honoraria from Servier, Amgen, Celgene, Astra-Zeneca and Roche.

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