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Adjuvant treatments to prevent local recurrence after breast-conserving surgery for early breast cancer – radiation, endocrine- or brachytherapy

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Abstract

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Radiotherapy after breast-conserving surgery due to breast cancer is an established treatment, known to reduce the incidence of recurrence and even death from the disease. However some women are over-treated with sometimes serious adverse effects. De-escalating the treatment and find alternative adjuvant methods are becoming an important issue.

In study I, we present the outcomes from a long-term follow-up trial randomising 381 women with breast cancer to surgery alone or to surgery with the addition of radiotherapy. The incidence of any first breast cancer event was significantly higher without radiotherapy but the protecting effect lasted for only the first five years.

In study II, we collected the tissue samples from the tumours in study I to construct tissue micro-arrays. Immuno-histochemical analyses were performed and the tumours were classified into the intrinsic subtypes. The luminal B/HER2 negative subtype was found to be prognostic for ipsilateral breast cancer recurrence (IBTR). The intrinsic subtypes did not interact with radiotherapy.

Study III was a multicentre prospective cohort study where the 601 study participants with early breast cancer were treated with surgery and endocrine therapy alone without postoperative radiotherapy. The cumulative incidence of IBTR after five years was low -1.2% and only one woman died of breast cancer.

In study IV we evaluated the feasibility and treatment complications when introducing a new method for intraoperative brachytherapy (IOBT) using HDR equipment. We designed a pilot study including fifty women where half of them were treated during primary surgery and the others during a second procedure. The treatment was well tolerated and no logistic problems were reported. No acute adverse effects from IOBT were seen.

Keywords: breast-conserving surgery, radiotherapy, endocrine therapy, intraoperative brachytherapy

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To Simon

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Original papers

The thesis is based on four papers, which will be referred to in the text by their Roman numerals (Papers I-IV):

Paper I: Sector Resection with or Without Postoperative Radiotherapy for Stage I Breast Cancer: 20-year Results of a Randomized Trial.

Wickberg Å, Holmberg L, Adami H-O, Magnuson A, Villman K, Liljegren G

J of Clin Oncol. 32, 2014. Reprint permission granted by ASCO permission department, March 1, 2018, (order id 18-0014)

Paper II: Influence of the subtype on local recurrence risk with or without radiotherapy in a randomized trial.
Wickberg Å, Magnuson A, Holmberg L, Adami H-O, Liljegren G

Paper III: Omitting radiotherapy in women ≥ 65 years with low-risk early breast cancer after breast-conserving surgery and adjuvant endocrine therapy is safe
Wickberg Å, Liljegren G, Killander F, Lindman H, Bjöhle J, Carlberg M, Blomqvist C, Ahlgren J, Villman K
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Paper IV: Intraoperative high dose rate brachytherapy during breast-conserving surgery -a prospective pilot study
Wickberg Å, Liljegren G, Ahlgren J, Karlsson L, With A, Johansson B

Abbreviations

AI Aromatase inhibitors
APBI Accelerated partial breast irradiation
BCS Breast conserving surgery
CT Computed tomography
3D-CRT Three-dimensional conformal beam radiotherapy
EBRT External breast radiotherapy
ELIOT Electron-based intraoperative radiotherapy
EORTC European Organisation for Research and Treatment of Cancer
FISH Fluorescent in situ hybridization
QLQ-C30 Quality of Life core questionnaire, version 3.0
ER Estrogen receptor
EQ-5D EuroQol five-dimensional questionnaire
FISH Fluorescent-in situ hybridization
HER2 Human epidermal growth factor receptor- 2
HR Hazard ratio
IHC Immunohistochemistry
IMRT Intensity modulated radiotherapy
IOBT Intraoperative brachytherapy
IORT Intraoperative radiotherapy
NHG Nottingham Histological Grade
PAD Pathological anatomical diagnosis
PBI Partial breast irradiation
PR Progesterone receptor
RCT Randomized controlled trials
SE Standard error
TAM Tamoxifen
TMA Tissue micro-arrays
XRT Radiotherapy

Introduction

In 1970 3392 women in Sweden were diagnosed with breast cancer. Forty-six years later, in 2016, the number was 8923 [1]. While the incidence of new breast cancer tumors have increased, the 5-year overall survival has also increased and is today approximately 90 % (figure 1). Breast cancer is the most common type of cancer among women today. More than one woman out of ten will statistically be diagnosed with the disease. The introduction of mammography screening and increased public awareness has led to earlier diagnosis with smaller tumors being diagnosed. In Sweden a majority of patients with breast cancer tumors are treated with breast-conserving surgery (BCS) [2] and adjuvant radiotherapy (XRT). Standard treatment for XRT today is 40-50 G y delivered for 3-5 weeks. Due to this prolonged treatment, some women chose a mastectomy. Moreover, for some women, the risks of XRT may outweigh the benefits. It is time to develop a more individualized approach to adjuvant XRT [3]. The focus of this thesis is XRT after BCS, the need for it and alternative methods.

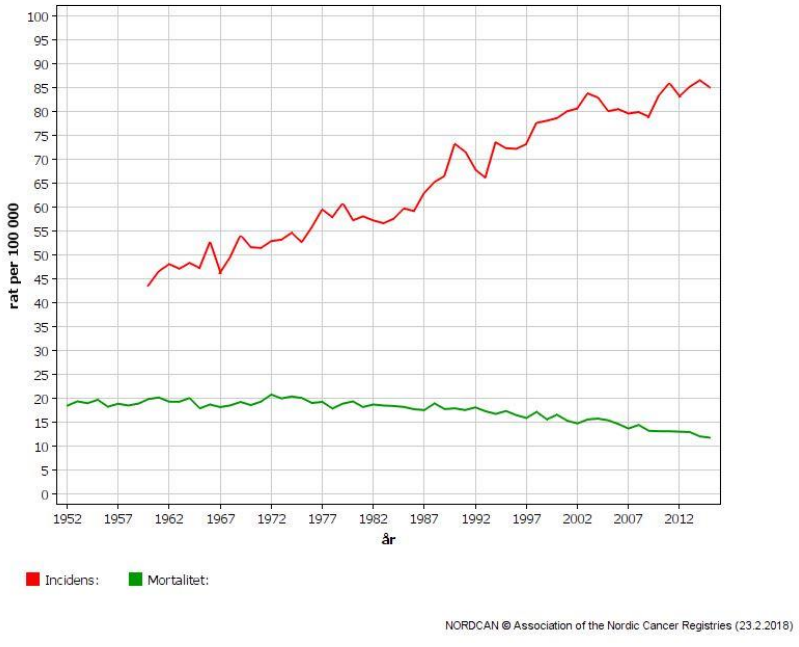


Figure 1 Time trends in incidence and mortality for female breast cancer I Sweden. Data from NORDCAN (Association of the Nordic Cancer Registries[4]

The surgical procedure

In 1902 Professor Morton, surgeon at the Bristol General Hospital, published the results from 54 women treated with mastectomy due to invasive breast cancer [5]. At that time the surgical procedure was extensive. Nineteen of the 54 women were free from recurrence 1-8 years after surgery but a majority died from the disease. Professor Morton carefully gave the details about his surgical procedure and whether or not it resembled the Halsted´s procedure [6]: "I have not adopted Halsted´s method of removing the great pectoral muscle unless it is involved in the growth, or the growth is fixed to it; nor his plan of removing the fatty tissue from the posterior triangle in all cases, though I have begun to do so now if I find the highest infra-clavicular glands are infected." In order not to divide any lymphatics containing cancer cells, the axilla content and the breast tissue is removed en bloc.

One of the earliest attempts to perform partial mastectomies was made by the American surgeon George Crile Jr [7]. In The American Journal of Surgery, one of his associates, Dr Hoerr, comments on possible eligible criteria for this new surgical procedure; the lesion should be located peripheral. A wide excision must be made with a wide margin of normal tissue. Finally, the breast must be sufficiently flaccid or large so that the resulting deformity will in no sense be worse than it would be after mastectomy [8].

In the seventies, the first segmental mastectomies were performed. However, there were some sceptics… Wolmark and Fisher wrote in 1981: "Although there is a sound scientific basis for the consideration of segmental mastectomy, there are no data available to justify the utilization of the procedure outside the context of a clinical trial. With the increased popularity and implementation of breast-preserving operations without the necessary supporting data, a potentially dangerous situation has been created which threatens to undermine the clinical trial process"[9].

In 1988 Aspegren et al proposed a classification system for the great number of different ways to perform breast-conserving surgery [10]. They also presented a standardized method of breast-conserving surgery, namely sector resection. The procedure consisted of dissection in the two planes (superficial layer and deep layer), include the periphery of the parenchyma in the breast specimen and a margin of one centimetre. Sector resection is the surgical method used in paper I, II and III.

Later controlled randomised studies have confirmed the safety of breast-conserving surgery with the addition of radiotherapy in comparison to mastectomy [11-13]. In the trial by Fisher B et al, 1851 women were randomised to lumpectomy (which is a less extensive surgical procedure than sector resection) alone, lumpectomy plus irradiation or mastectomy [14]. The cumulative incidence of local recurrence was highest for the lumpectomy alone-group but no differences between the three groups were seen with respect to overall survival or disease-free survival. Similar results were found in the trial by Veronesi et al where 701 women were randomised to radical (Halsted) mastectomy or quadrantectomy – a more extensive breast-conserving procedure, plus irradiation [13]. After 20 years no differences between the groups were seen concerning overall survival or death from breast cancer. The cumulative incidence of IBTR were 8.8 % in the BCS group and 2.3 % in the mastectomy-group ($p<0.001$). The author argued that the number of "true local recurrences" in the BCS group (i.e. that occur in the area were the primary tumour originated) were similar to the number in the mastectomy group (10/30 and 8/8 respectively). However, 20/30 local recurrences in the conserved breast occurred outside the primary tumour area and were thus classified as second ipsilateral carcinomas. Notably, the authors also point out intraoperative radiotherapy as a future treatment of choice, despite the relatively high incidence of local recurrences outside the primary tumour area.

The debate for and against the breast-conserving procedure at this time was extensive. In an editorial in New England Journal of Medicine, Monica Morrow strongly argued for the introduction of BCS and ended with the words: "It is time to declare the case against breast-conserving therapy closed and focus our efforts on new strategies for the prevention and cure of breast cancer.." [15].

Radiotherapy

Conventional/hypo-fractionated external radiotherapy

In the 1960s the cobalt cannons dominated the treatment field for breast cancer. They are nowadays replaced by other technologies, such as linear particle accelerators, which can generate higher-energy radiation. Since the

introduction of three-dimensional treatment planning in the 1980s the radiation therapy has changed dramatically and more precise radiation doses to the remaining breast tissue can be delivered. However, the surrounding organs still receives various amounts of irradiation.

Several randomized trials have confirmed the protective effect of postoperative radiotherapy after breast-conserving surgery [16-25]. It is known to substantially reduce breast cancer recurrence. It also reduces the absolute risk of breast cancer death significantly at 15 years but it is clear that this only applies if the difference in IBTR is >10% in ten years [23]. However, at least with older methods, there is a significant excess of non-breast cancer mortality in irradiated women. The excess mortality is mainly from radiation-induced heart disease (rate ratio 1.27; p=0.001) and lung cancer (rate ratio rate ratio 1.78, 2p=0.0004) [22]. A meta-analysis of published studies of cardiac toxicity demonstrated a decrease in cardiovascular events and cardiac death rate in more modern treatment eras [26], but even with modern regimens the heart still receives doses of 1-5 G y which may increase the risk of ischemic heart disease. In 2013, New England Journal of Medicine published a large population-based case-control study that attracted much attention. The study included 963 women with major coronary events and 1205 controls treated for breast cancer between 1958 and 2001 in Scandinavia [27]. Contrary to previous beliefs, the cardio-toxic side effects were found to begin within a few years after exposure and continued for at least 20 years. The mean heart dose, evaluated in this trial, was probably a better predictor of heart disease risk than other metrics, for example dose to the coronary arteries. The authors estimated that a 1 G y increase in mean heart dose equates to a 7.4% linearly increase in coronary events and the increase were constant with no apparent threshold [27]. The risk was highest in women with pre-existing cardiac risk factors and long-term smokers [26].

Postoperative radiotherapy after breast-conserving surgery due to invasive cancer is an established mode of treatment [11,12,20,24,28]. The therapy consists of 3-5 weeks of daily treatment, which for some patients, particular elderly and unhealthy persons with a long way to the hospital may imply a lot of inconvenience. Some patients might even chose a mastectomy in order to avoid this prolonged treatment.

At the latest St. Gallen conference 2017, the issue of escalating and de-escalating the treatment for early-stage breast cancer was highlighted [29].

The panel endorsed hypo-fractionated radiotherapy for women <50 years as presented by Whelan et al [30], as a way of avoiding the inconvenience with a prolonged treatment. Another alternative for de-escalating postoperative radiotherapy might be partial breast irradiation (PBI).

Partial breast irradiation

The rationale for delivering PBI is the observation that most local recurrences occur in the vicinity of the primary tumor [20,31]. According to the panel of experts at the St. Gallen breast conference 2017, PBI might be an alternative for a low-risk group of patients defined by the American Society for Radiation Oncology (ASTRO) and the European Society for Therapeutic Radiology and Oncology (ESTRO) [32]. The safety of partial breast- and reduced-dose radiotherapy is supported by a randomized, controlled, non-inferiority trial carried out in 30 radiotherapy centers in the United Kingdom published recently in the Lancet [33]. Two thousand and sixteen patients were randomly assigned to receive 40 G y whole-breast radiotherapy, 36 G y whole-breast radiotherapy and 40 G y to the part of the breast where the tumor had been localized (reduced-dose group), or 40 G y to that part of the breast only (partial-breast group) in 15 daily treatment fractions. In terms of local recurrence non-inferiority of partial-breast and reduced-dose radiotherapy compared with the standard whole-breast radiotherapy was found. However, a Cochrane Systematic review including 7 RCTs and 7586 women, found a worse local recurrence-free survival for women receiving PBI/APBI compared to whole breast irradiation [34]. Indeed, the difference was small and the evidence limited. There are different techniques of delivering PBI [34];

1. Intra-cavitary brachytherapy or MammoSite® - a balloon is inserted into the wound cavity either during primary surgery or in a second procedure.
2. Interstitial brachytherapy - inserting catheters into the surgical cavity and surrounding tissue to temporarily deliver radioactive sources.
3. Intra-operative techniques (IORTs or IOBTs) using electrons or x-rays at 50 k V p (using a dedicated machine to deliver a very lo-

calized radiation dose to the surgical cavity in the operating room or by moving the patient with an open wound to the radiation machine)

4. Intensity modulated radiotherapy (IMRT) or three-dimensional conformal beam radiotherapy (3D-CRT) which is external beam radiotherapy using three-dimensional conformal radiotherapy delivered in the postoperative setting to a volume of breast tissue around the tumor cavity using a standard linear accelerator.

Accelerated partial breast irradiation (APBI) with multicatheter interstitial brachytherapy has shown promising local control and cosmetic outcomes [26,35-37]. The longest follow-up is presented in a small single–center study by Polar et al [38] were 41 patients with non-lobular T1 breast cancer were prospectively selected and treated with interstitial HDR BR after BCS. After a median follow-up of 133 months, the recurrence rate were low – four IBTR and two regional nodal failure. Strnad et al presented a phase 3, randomized, non-inferiority trial including 1184 patients in the Lancet [35]. After five years of follow-up the cumulative incidence was 1.44% (95% CI 0.51–2.38) with APBI and 0.92% (95% CI 0.12–1.73) with whole-breast irradiation (difference 0.52%, 95% CI –0.72 to 1.75; p=0.42). The pre-specified acceptable absolute increase of IBTR by 3 percentage point was not met.

Several clinical trials have investigated the local control and cosmetic result after PBI using the intracavitary balloon technique. Although primary results are promising, most of the trials are non-randomized with short follow-up [39-41]. In an ongoing randomized, multicentre phase III trial from the NSABP-B39/RTOG [42] Mammosite® is one of the interventions.

The IORT procedure has in vitro been found to change the wound response. Normal wound fluid stimulates proliferation, migration, and invasion in breast cancer cell lines. IORT induces a downregulating cascade which prevents breast cancer cell growth and reduces local recurrence in mice models [43].

Two large randomized trials have evaluated the effects of IORT. The TARGIT-A trial [44] was designed as a non-inferiority trial enrolling 3451 patients, ≥ 45 years with invasive ductal carcinoma, to be treated with IORT or EBTR after BCS. The primary outcome was absolute difference

in IBTR in the conserved breast, with a pre-specified non-inferiority margin of 2.5% at five years. The results showed that IORT was non-inferior to EBRT overall (IORT 3.3%, 95% CI 2.1% to 5.1% vs. EBRT 1.3%, 95% CI 0.7% to 2.5%; $p = 0.04$) and in the pre-pathology group ($n = 2298$) when IORT was given concurrently with BCS (TARGIT 2.1%, 95% CI 1.1% to 4.2% vs. EBRT 1.1%, 95% CI 0.5% to 2.5%; $p = 0.31$). With delayed TARGIT post-pathology ($n = 1153$), the between-group difference was larger than 2.5% and non-inferiority was not established for this group (TARGIT 5.4%, 95% CI 3.0% to 9.7% vs. EBRT 1.7%, 95% CI 0.6% to 4.9%; $p = 0.069$). The trial has been criticized for short follow-up – only 1222 patients were followed for 5 years and the median time for follow-up was 2 years and 5 months. Another critic is misuse of the non-inferiority criterion with the confidence interval for the difference in IBTR for the pre-pathology group extending beyond 2.5% (absolute difference 1.0 percentage points 95% CI -0.68 to 2.68) [45,46]. Vaidya et al found significantly fewer non-breast-cancer deaths with IORT (1.4% versus 3.5%; p=0.0086), and assigned this to fewer deaths from adverse effects from EBRT, like cardiovascular causes, in the IORT group [47]. However, in a reply to Vaidya, Yarnold et al argue that this causation is unlikely [48]. Since the risk of a major cardiac event has been found to increase by 7% per G y of the mean heart dose [27], based on expected mean heart doses in the EBRT group of 1–5 G y, radiotherapy cannot explain more than one of the 11 cardiovascular deaths.

The TARGIT-A trial uses the IntraBeam® device with a point source of 50 kV energy x-rays at the center of a spherical applicator (figure2). The applicator is placed into the wound cavity after resection of the breast tumor, and a purse-string suture is inserted to adapt the breast parenchyma to the applicator. Radiation is delivered for 20-45 minutes. The surface of the wound cavity receives 20 G y that attenuates to 5-7 G y at one cm depth.

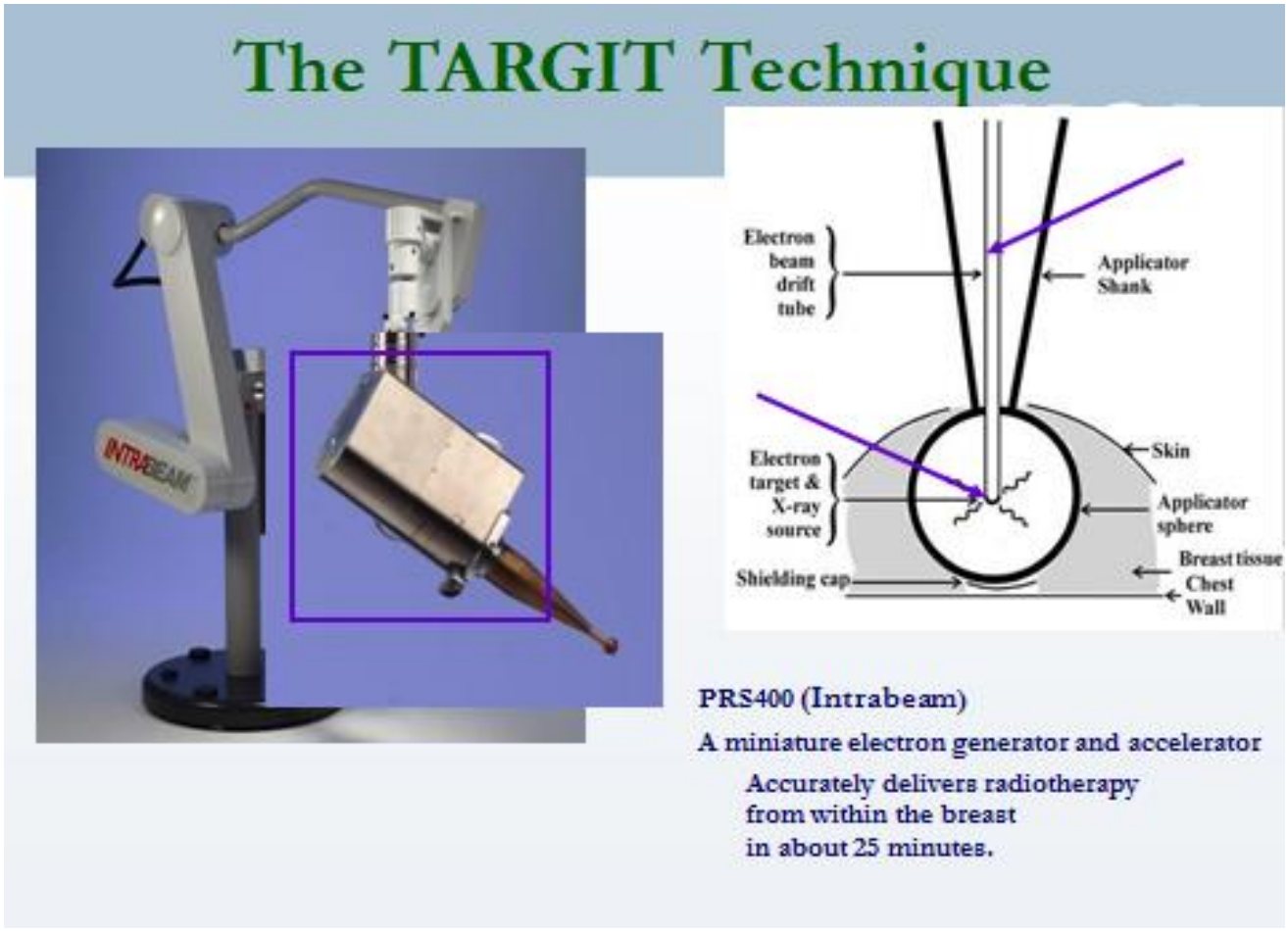


Figure2. The TARGIT Technique and the IntraBeam® eqiupment. Reproduced with permission from Professor Jeffrey S Tobias, University Collage Hospital, London, UK.

The ELIOT study [49], conducted by Professor Umberto Veronesi and colleagues, enrolled 1305 women (aged 48–75) diagnosed with early breast cancer, (tumor size ≤2.5 cm). The women were randomly assigned to receive either EBRT or electron-based intraoperative radiotherapy (ELIOT) after BCS. Patients in the ELIOT group received a single dose of electron radiation from two linear accelerators directly into the tumor bed after tumor removal. To minimize the radiation to the chest wall, a disc of lead and aluminum of different sizes was inserted between the gland and the pectoralis muscle. Veronesi's team found that ELIOT resulted in a significantly higher local recurrence rate of 4.4% versus 0.4% with conventional EBRT, although this difference was within the pre-specified non-inferiority margin of 7.5%.

PBI may also be delivered by external beam radiation therapy (IMRT or 3D-CRT). This technique is broadly available and easy to do. Unfortunately the reported results of trials using external beam radiation therapy either are disappointing or have low statistical power [50-52].

Endocrine therapy

There are two main types of endocrine therapy; tamoxifen (TAM) and aromatase inhibitors (AIs). TAM has been a safe and effective adjuvant therapy for breast cancer for more than 20 years, and was the first widely used endocrine therapy for postmenopausal women with estrogen receptor-positive metastatic breast cancer. It belongs to the SERMs (selective estrogen receptor modulators) which are characterized by their ability to act both as an agonist – for example in the uterus or the bone tissue, or as a competitive antagonist of estrogen at its receptor – in the breast [53]. However, resistance to the drug remains an obstacle in the treatment of hormone-dependent breast cancer. Up to one third of the patients are resistant to tamoxifen at the beginning of treatment and the majority of patients who initially respond to tamoxifen will later also become resistant [54]. Research is in progress to find biomarkers to predict tamoxifen-sensitivity [55]. Tamoxifen is associated with rare but potentially life-threatening side effects like pulmonary embolus and endometrial cancer, and the risk increases with longer treatment [56,57]. The risk of endometrial cancer is particularly attributed to postmenopausal women even though, in this subgroup of patients, the number of deaths from this type of cancer is small [57]. In premenopausal women, where aromatase inhibitors are not an alternative, the advantages of ten years of tamoxifen far outweigh the risks.

Aromatase is an enzyme expressed in several tissues in the body [58]. It is responsible for the conversion of the adrenal androgen substrate androstenedione to estrogen in peripheral tissue, which is the predominant source of estrogen in postmenopausal women. Aromatase inhibitors reduce the estrogen activity in peripheral tissue, but do not affect the ovaries, which makes it unsuitable for premenopausal women. Third generation of aromatase inhibitors is commonly used today and compared to the two first generations these drugs have increased specificity for aromatase. Third generation AIs are categorized as steroidal (type I) or non-steroidal (type

II), of which the former leads to irreversible inhibition of enzymatic activity and the latter are reversible competitive inhibitors [59]. Anastrozole® and Letrozole® belong to third generation type II AIs.
In estrogen-receptor-positive breast cancer the addition of five years of tamoxifen halves the risk of recurrence during the treatment period, and lowers the risk of breast cancer death by a third throughout the first 15 years [57,60]. The effects seem to be independent of age, nodal status, tumor grade, tumor size, chemotherapy use and timing. Aromatase inhibitors are more effective than tamoxifen to prevent breast cancer recurrences of any type during treatment but not thereafter [61-63]. The effectiveness of Anastrozole® and Letrozole® is evaluated in the Arimidex®, Tamoxifen Alone or in Combination (ATAC) trial and in the Breast International Group (BIG) 1-98 Collaborative Group study, where aromatase inhibitors prolonged disease-free survival compared to tamoxifen [64,65].

The sensitivity of breast cancer tumors to endocrine therapy seems to be restricted to ER-positive tumors, while tumors lacking PR expression have lower sensibility to this treatment [66,67].
Which treatment is most effective in preventing breast cancer recurrence – XRT or endocrine therapy or both? In a trial by Blamey et al [68] women with primary invasive breast cancer ≤2 cm, low grade and node negative were randomized to local excision with or without radiotherapy and local excision with or without tamoxifen. The risk of IBTR was reduced to a similar extent by either tamoxifen or radiotherapy. However, the results from a trial by Fisher B et al [25] suggest a better effect from radiotherapy than from tamoxifen. In this trial, after lumpectomy, 1009 women were randomly assigned to tamoxifen, XRT and placebo or XRT and tamoxifen. Cumulative incidence of IBTR through 8 years was 16.5% with TAM, 9.3% with XRT and placebo, and 2.8% with XRT and TAM. These results indicate that XRT is a better treatment than TAM, but that the combination of them both is the most effective for preventing IBTR. To my knowledge no corresponding trial has been performed with AI instead of TAM.
How about the prevention of contralateral breast cancer? According to some studies, TAM seems to be the most effective alternative [25,69], since it represent a systemic treatment. However, in our cohort study (paper III), where a majority of the study participants were treated with TAM, the incidence of contralateral cancer at five years was comparable to the inci-

dence of IBTR. Besides, no one in this study was treated with postoperative XRT, which could possibly induce a contralateral cancer.
What kind of adjuvant therapy would a woman prefer? Is endocrine therapy better tolerated than radiotherapy or is it the other way around? A woman stricken with substantial side effects from ET would surely prefer adjuvant XRT instead of taking anti-hormonal pills for 5-10 years. Tamoxifen may cause mood swings, low libido and vaginal dryness [70,71]. Aromatase inhibitors are associated with arthralgia, bone pain, osteoporosis and bone fractures [72,73]. Some of these symptoms can be addressed with specific interventions while others markedly affect quality of life. In a retrospective Swedish study, 31 % of the women stopped ET within three years, and half of them stopped within the first year [74]. Early discontinuation of and non-adherence to ET has been associated with increased mortality [75]. The best choice of ET is surely the treatment the woman is willing to take and she needs careful information in order to make a good decision.

Predictive and prognostic factors

Finding prognostic and predictive risk factors for breast cancer recurrence is an ongoing issue. A prognostic risk factor indicates the likeliness of recurrence; the absence or presence of this factor is associated with the patent´s clinical outcome. A predictive risk factor indicates a response probability in association with a specified treatment. The most well-established prognostic risk factors for IBTR after BCS are young age, positive margins, extensive in situ component, negative hormone receptor status, TNM staging, high histological type and grade, high mitotic figure counts and large tumor size [67,76,77]. Established predictive factors are ER status and HER2 status [57,78]. The predictive ability of the intrinsic subtypes and genomic testing is not fully understood.

The intrinsic subtypes

Since the establishment of classification into the intrinsic subtypes [79]focus has been on characterizing the intrinsic subtypes and evaluate their prognostic and predictive potential. The latest published consensus from the St Gallen breast cancer conference stresses the need for clinically applicable recommendations and is looking forward towards a more treatment-oriented classification of subtypes of breast cancer. While the intrinsic

subtype´s predictive properties for systematic therapy are rather well investigated, little is known about their radio-sensitivity properties, as emphasized in a review by Tsoutsou et al [80].

Genomic biomarkers are probably the most precise tools for predicting risk of breast cancer recurrence [81,82]. Today there are four main different gene expression test system available for this purpose; MammaPrint^{R}, Oncotype DX^{R}, Endopredict^{R} and PAM50 [83,84]. However, due to low availability and heavy expenses, surrogate subtypes based on immunhistochemical biomarkers are often used instead.

"True" ipsilateral recurrence

Most IBTRs occur in the same area where the original tumor was located [85,86]. But what constitutes a "true" breast cancer recurrence? To most breast cancer researchers´ a true ipsilateral recurrence typically appear in the same quadrant as the original tumor and a "new" second primary tumor develops elsewhere in the same breast. Professor Veronesi is very clear in the definition: "a local recurrence is the appearance of any new tumor in the breast within 2 cm of the surgical scar, and a second primary carcinoma as the appearance of any new tumor in other quadrants of the breast more than 2 cm from the scar" [24,87]. Smith et al investigated true recurrence (TR) versus new ipsilateral primary tumors (NP) and found that they differed in natural histories and prognoses. The tumours were classified as NP if the recurrence was distinctly different from the primary tumour with respect to the histologic subtype, the recurrence location was in a different location, or if the flow cytometry changed from aneuploid to diploid [88]. Patients who developed new primary tumor recurrences were significantly younger than those who developed true recurrences ($p<0.05$). Sixty (44%) recurrences were classified as TP and 70 (51%) were classified as NP. Six (4%) could not be classified. Fifty (71%) of the recurrences classified as NP changed location from the original site, 53 (76%) changed histology, and 4 (6%) changed flow cytometry. Thirty-four (49%) recurrences changed both histology and location and 3 (4.3%) recurrences changed histology, location, and flow cytometry. NP´s had a longer time to recurrence than those classified as TR (7.3 ± 0.6 years vs. 3.7 ± 0.3 years, $p < 0.0001$). Patients developed both NP and TR recurrences at similar rates until approximately 8 years, after which TR rates stabilized but NP rates continued to rise. NP relapse patients also had significantly

better 10-year distant disease-free survival. Krauss et al evaluated patterns of IBTR over time based on the type of recurrence (true recurrence, referring to those occurring in the same quadrant versus elsewhere) and compared these to rates of contralateral tumour in women treated with BCS and XRT [89]. The patients were followed up for 15 years. Median times for true recurrence, recurrence elsewhere in the breast and contralateral tumour were 5.7 years, 7.4 years and 5.2 years respectively. The rates of IBTR were found to vary with time and, after 5 years, approached the rates of development of a contralateral breast cancer.
If EBRT effectively would prevent new tumors to develop, the recurrence of these tumors would be lower than the incidence of tumors in the contralateral breast. Studies evaluating the risk of IBTR have not confirmed this. However, in a report from a workshop, Wallner et al present results from a study evaluating primary and re-excision breast conserving surgery specimens of 333 invasive carcinomas. Residual tumor was revealed 15 mm or less from the primary tumor in 91 % of the specimen [90]! Nevertheless, since EBTR does not seem to protect against new tumors and most true IBTRs occur in the same quadrant as the original tumor, PBI seems logical.

Aims of the thesis

The overall aim of this thesis was to find more effective and convenient methods to administer radiotherapy to women treated with breast-conserving surgery due to early breast cancer. We also wanted to find risk factors and predictive factors for recurrence in order to individualize the treatment. The specific aims of each study were:

I. To present the 20-year follow-up of a randomized trial evaluating the incidence of recurrence and death after breast-conserving surgery with or without postoperative radiotherapy and to identify a low-risk group were the radiotherapy might be omitted.
II. To investigate the intrinsic subtypes´ prognostic and predictive risks for IBTR with or without radiotherapy by recollecting the

tissues from the tumors in study I, constructing TMA´s, performing immunohistochemistry, classify them into the intrinsic subtypes and perform a risk factor analysis.

III. To evaluate if adjuvant endocrine therapy alone is a safe alternative to postoperative radiotherapy in a cohort of women with early breast cancer treated with breast-conserving surgery.

IV. To evaluate the feasibility and treatment complications when introducing a new method for intraoperative brachytherapy using HDR equipment. For this purpose, we designed a pilot study including fifty women were half of them were treated during primary surgery and the others during a second procedure.

Patients and methods

The Uppsala/Örebro trial

Study I and II are based on the Uppsala/Örebro study[86,91,92] , Results from the 10-year follow-up was published in 1999 [20]. From 1981 to 1988 381 women ≤80 years old with a unifocal invasive breast cancer, T1, N0, from six participating centers were randomized to breast-conserving surgery with or without postoperative radiotherapy. The XRT-group was treated with a total dose of 54 G y in 27 fractions from a 4 to 50 MV linear accelerator or from a cobalt 60 unit. Data for the long-term follow-up was collected from The National Cancer Registry, The Hospital Discharge Registry and The National Causes of Death Register at The National Board of Welfare, Stockholm, Sweden. These registers hold validated information of nationwide cancer incidence, admission and diagnosis at discharge from hospitals and surgical interventions in Swedish hospitals and causes of death respectively. In the 10-year follow-up the breast tumors had been classified according to the Bloom-Richardsson´s system [93]. For the 20-year follow-up we collected the paraffin blocks from the primary tumors and reclassified them into Nottingham histological grade (NHG) [94]. In 51 cases the grading was not possible due to lack of material from the original paraffin blocks or bad quality of the samples obtained. In these cases we estimated the NHG using the results from the 10-year analysis [20]. Six women lacked information about histopathological grade

and were excluded in this variable. One woman was diagnosed with cancer in situ at re-evaluation and was excluded in all variables.
We were able to collect 270 blocks of tissue from the original 381 primary tumors. Representative areas from each tumor were punched and brought into recipient paraffin-blocks to produce tissue micro-arrays (TMA). We stained for hormone receptors, HER2 and Ki-67 at two pathology departments according to a standardized protocol. The threshold for ER and PR to be considered positive was set to 10%. One hundred and fifty-one (40%) of the ER-values were missing and when appropriate replaced by values from the 10-year analysis (10). The same procedure was done with NHG and PR. Ki-67 cut- off to discriminate between high and low proliferation was set to 20%. This decision was made after consensus among the analyzing laboratories. Antibodies to identify the HER2/neu protein were applied to the samples and classified by one pathologist. The tumor was considered positive when more than 10% of the tumor cells showed strong membrane staining (3+) (11 tumors). Tumors exhibiting 0, 1+ or 2+ staining for HER2 protein over-expression were considered HER2 negative. Fluorescent in situ hybridization (FISH) was not used in our analyses. Fourteen tumors showed moderate staining (2+) and were consequently classified as HER2-negative.

The cohort trial

In the prospective cohort trial (paper III), 601 women were included from fourteen Swedish hospitals between 2006 and 2012. Inclusion criteria were age ≥65 years, tumor size ≤2 cm, non-lobular tumor, NHG 1 or 2, estrogen- and/or progesterone positivity. The women were treated with sector resection and sentinel node biopsy. After surgery, tamoxifen or an aromatase inhibitor was prescribed for five years and no adjuvant radiotherapy was given. A majority of the study participants were prescribed tamoxifen (89%) (table1). Median age was 71.1 years. All tumors were ER-positive and a majority of the tumors were of ductal origin, low grade and PR-positive (table1). The results from the proliferation analysis should be interpreted with caution, since fourteen hospitals contributed to data to this trial and the criterion for high/low proliferation at this time varied according to the method used. Moreover, in approximately 20% of the

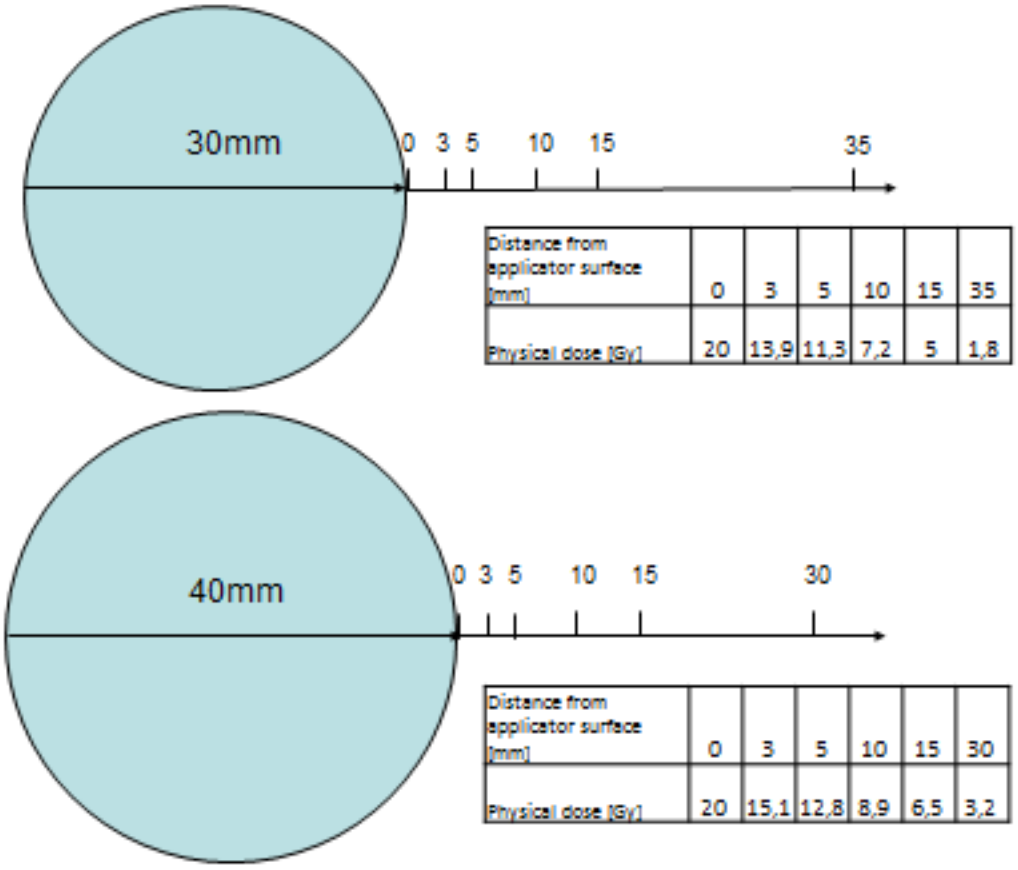
study participants, the proliferation status was unknown.

	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*	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)
Proliferation	
Ki-67	467 (77.8)
high	43 (7.1)
low	424 (70.3)
S-phase	10 (1.7)
high	1 (0.2)
low	9 (1.5)
Other	5 (0.8)
Unknown	119 (19.7)

Table 1 Baseline characteristics from the cohort study in paper III. Calculated from the 601 study participants.

Intraoperative radiotherapy with HDR-technology

In order to perform intraoperative brachytherapy (IOBT) we used equipment already available at the department of brachytherapy – high dose radiotherapy (HDR). Apple-shaped applicators of different sizes were developed, which could be connected to a MicroSelectron® HDR machine (Elekta, AB, Stockholm, Sweden). The current isotope was Iridium 192, which is the most commonly used isotope for HDR brachytherapy. The applicator delivered a dose of 20 G y at its surface in the wound cavity. The dose-fall from the surface varied due to the diameter of the applicator, forming a surrounding "10 G y-shell" where the dose was halved. Distribution of the radiation dose for the 30-mm applicator and the 40-mm applicator is illustrated in figure 3.



Distance from applicator surface [mm]	0	3	5	10	15	35
Physical dose [Gy]	20	13,9	11,3	7,2	5	1,8

Distance from applicator surface [mm]	0	3	5	10	15	30
Physical dose [Gy]	20	15,1	12,8	8,9	6,5	3,2

Figure3. Two of the applicators and distribution of the dose fall from the surface

Fifty women were included in a pilot study. Inclusion criteria were invasive, non-lobular, unifocal breast cancer T1-T2 (≤ 3 cm) N0 and age ≥ 50 years. Twenty-five of the study participants received their IOBT during the primary procedure. The others had their treatment during a second procedure, after definitive histopathological report. All study participants went through a computed tomography (CT) scan before radiotherapy. In this manner we wanted to check the applicators adherence to the breast parenchyma. The computer software (Oncentra Brachy®, Elekta AB Stockholm) was used to calculate the volume of the applicator and the volume of a simulated surrounding shell - the "10 G y tissue shell". We manually marked the empty spaces where the applicator and the breast parenchyma disconnected and could then calculate the amount of empty spaces/air in the shell.

Health questionnaires

Two questionnaires were used to estimate the women´s quality of life in the pilot study – EORTC-QLQ-C30 and EQ-5D-3L.

EORTC-QLQ-C30 is an integrated system to assess the health-related quality of life of cancer patients participating in clinical trials [95]. The questionnaire includes five functional scales (physical, role, cognitive, emotional and social), four symptom scales (fatigue, nausea, appetite and pain), five single items (constipation, diarrhea, sleep, dyspnea, financial) and a global scale. The scoring was performed according to the EORTC scoring manual and the results was compared to reference values in the Swedish population [96].

EQ-5D-3L, 3-level EuroQoL group´s 5-dimension questionnaire, is a generic instrument for health outcome assessment [97]. It contains five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The woman is also asked to indicate her health on a scale called the EQ VAS (visual analog scale). The results were compared with reference scores from the Swedish population [98].

Statistical analyses

The Kaplan-Meier method for estimating survival function and the Cox proportional hazards model for estimating the effects of covariates on the hazard of the occurrence of the event are commonly used statistical methods for the analysis of survival data [99]. Paper I - III represent different methods of monitoring breast cancer recurrence over time in the presence of competing risks. In a Kaplan-Meier analysis, the study subjects are censored if the study ends before the subject had the event of interest, are lost to follow-up or drops out. Censoring means that the subject is no longer at risk and does not affect the cumulative incidence at the time of censoring [100]. A censored study participant is assumed to have a similar chance of experiencing the event of interest as those still at risk.

First breast cancer event of any type

In the large meta-analysis by Early Breast Cancer Trialists´ Collaborative Group (EBCTCG) [23], the main emphasis is time to first breast cancer event, defined as locoregional or distant recurrence, rather than time to IBTR as first event. The reason for this is that the probabilities of an IBTR and a distant recurrence are not statistically independent; IBTR may increase the risk of distant recurrence which may increase the risk of breast cancer death. Thus, valid estimates of the separate effects of radiotherapy on IBTR and distant recurrences cannot be obtained [101]. In paper I, Kaplan –Meier curves estimate time to breast cancer event and log-rank tests are used to evaluate differences between the XRT and the non-XRT groups. The first two analyses compose composite endpoints, similar to the analyses by EBCTCG [23]. The other analyses are cause-specific, which means analyzing one endpoint at a time. All women received follow-up until December 31, 2010. All breast cancer events and deaths were registered, which is necessary in a cause-specific analysis.

Cox regression and interaction test

In paper II we wanted to find out if the intervention (XRT) would affect the association between etiology (the different subtypes) and outcome (IBTR). To evaluate this matter, we used adjusted multivariate cause-

specific proportional hazards models, Cox regression [102-104]. The association measure was hazard ratio (HR) with 95% CI and the significance level was set to 5%. None of the independent variables showed evidence of non-proportional hazards, tested by phtest [105] in STATA using the Schoenfeld residuals. We adjusted for the following prognostic variables; tumor size (on continuous scale), lobular/non-lobular tumor and NHG. Since NHG was incorporated into the intrinsic subtypes, HR´s were calculated with and without adjusting for NHG. All women in the Uppsala/Örebro trial were followed up for 20 years except for four women who emigrated and were censored at that time. One of these women, however, could be reached by letter and received follow-up until 1997.
The Kaplan-Meier method with log-rank test was used to visualize the unadjusted cumulative risk of IBTR. The intrinsic subtypes´ association with radiotherapy and the risk of IBTR were investigated in an interaction test. We also calculated the absolute risks for IBTR for each intrinsic subtype. According to uneven distribution of age, particularly in the high-risk group, adjustment was made for age using binominal regression. Due to low numbers of events, this adjustment was possible only for age over and under 55 years.

Competing risk

In paper III we dealt with prognostic research, e.g. we predicted the probability of breast cancer recurrence at a given time for an individual patient [103]. The cumulative incidence of IBTR and contralateral cancer were here estimated using a competing risk approach [104]. A competing risk is an event that either hinders the event of interest or modifies the risk for this event to happen [103]. Time to IBTR/contralateral cancer was estimated and visualized as a cumulative incidence. All study participants received follow-up until their first IBTR/contralateral cancer and were censored for mortality/loss of follow-up by March 1, 2017. Regional recurrence, distant metastases, other types of cancer and deaths were regarded as competing risks [106,107]. Even if a negative breast cancer event, for example regional metastases, were registered, the study participant was followed until her first IBTR or contralateral cancer. At five years no study participant had an IBTR or contralateral cancer proceeded by a regional or distant recurrence.

Overall survival was estimated with the Kaplan-Meier method.

Fisher´s exact test

Data from the QLQ-C30 health questionnaire were analyzed using Statistical Package for Social Science (SPSS)-Version 22, IBM, Armonk, NY. The scores from the QLQ-C30 health questionnaire were linearly transformed into a 0-100 scale according to the manual [108]. The data were continuous and presented in mean, range and standard deviation. Differences in mean values for the women in the study at one-year of follow-up were compared to the reference values of the Swedish population [96]. Unpaired t-test was used to compare the continuous QLQ-C30 scores.
Fisher´s exact test was used to compare the categorical EQ-5D-3L proportions of the study group with reference values from the Swedish population [98]. The unpaired t-test analyses were performed with STATA release 14 (Stata Corp, College station, TX) and Fisher´s exact test with SPSS version 22. In order to evaluate the effect size, Cohen´s d was calculated for every difference in mean between the groups [109]. According to this concept a low Cohen's d indicates the necessity of larger sample sizes, and vice versa. “Low” are values <0.2, “moderate” are values around 0.5 and “high” are values >0.5.

Results

Paper I

Figure 5A shows the cumulative probability of first breast cancer event of any type. At 20 years 49 events occurred in the XRT group compared with 81 in the non-XRT group. The cumulative probability after 20 years was 30.9% in the XRT group and 45.1% in the non-XRT group (total hazard ratio [HR], 0.58; 95% CI, 0.41 to 0.82) (figure 5A). Twenty-five point eight per cent of the women in the non XRT group had a local recurrence compared with 11.5 % in the XRT group, yielding an absolute risk difference of -14% (95% CI,-22% to -7%). Regression analyses re-

vealed that the protective effect of radiotherapy was confined to the first 5 years after diagnosis (HR, 0.35; 95% CI, 0.21 to 0.59).

Thirty-eight women in the XRT group and 36 in the non-XRT group were diagnosed with other types of cancer (including contralateral cancer) as a first event. Absolute risk difference was 2% (95% CI, -6% to 11%) (figure5B). Thirty-two women in each group died of generalized breast cancer (XRT group: cumulative proportion, 20.1%; non-XRT group: cumulative proportion, 19.0%; absolute risk difference, 1%; 95% CI, -7% to 9% (figure 5C). Fifty-nine women in the XRT group (cumulative proportion at 20 years, 37.6%) and 74 women in the non-XRT group (cumulative proportion at 20 years, 43.2%) died from other causes (absolute risk difference, 6%; 95% CI,-15% to 4%) (figure5D).

At the end of the follow-up period, 92 of 184 women in the XRT group and 106 of 197 women in the non-XRT group died. The cumulative proportion of overall mortality after 20 years was 50.4% in the XRT group and 54.0% in the non-XRT group (absolute risk difference, 3.6%; 95% CI,-14% to 6%) (figure5E). Forty-six women in the non-XRT group and 34 women in the XRT group died from cardiovascular disease. The difference was non-significant.

In a postulated low-risk group including women without lobular or comedo-type cancer and age ≥ 55 years, the cumulative proportion of breast cancer event of any type in the XRT group was 24.8% and 36.1% in the non-XRT group; absolute risk difference, -11% (95% CI, -20% to -2%).

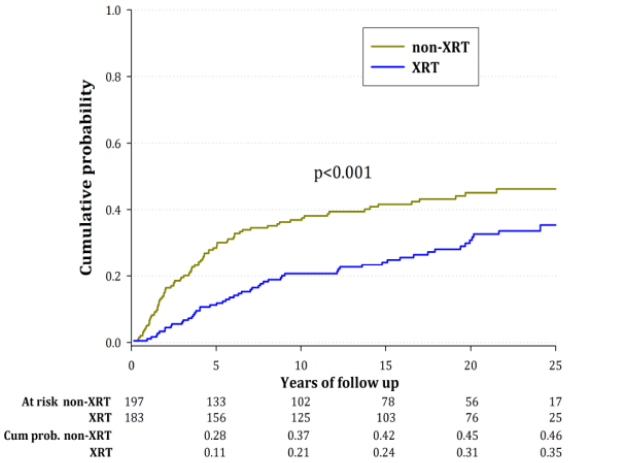


Figure5A

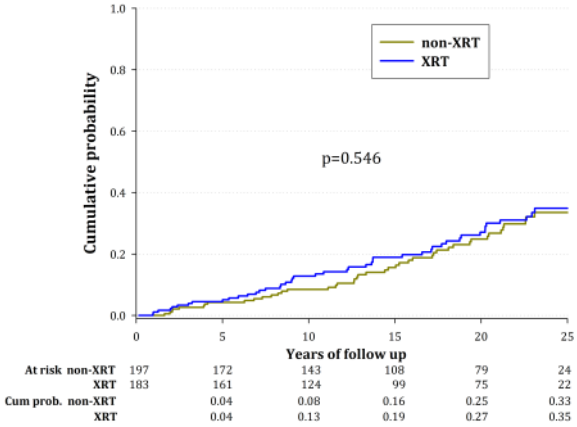


Figure5B

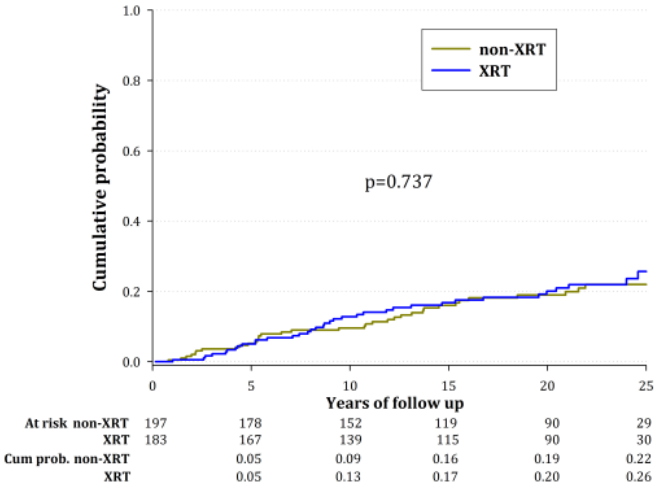


Figure5C

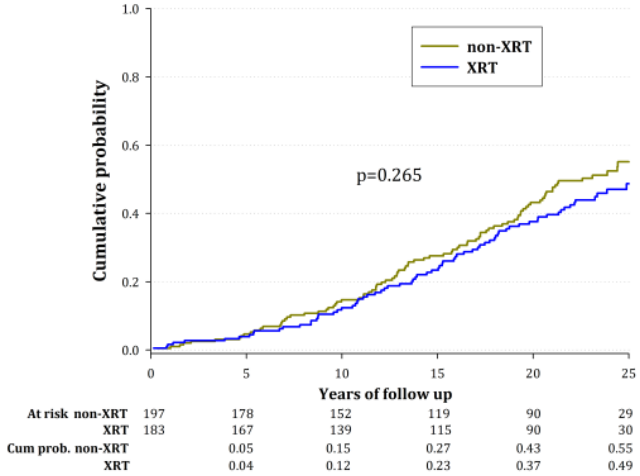


Figure5D

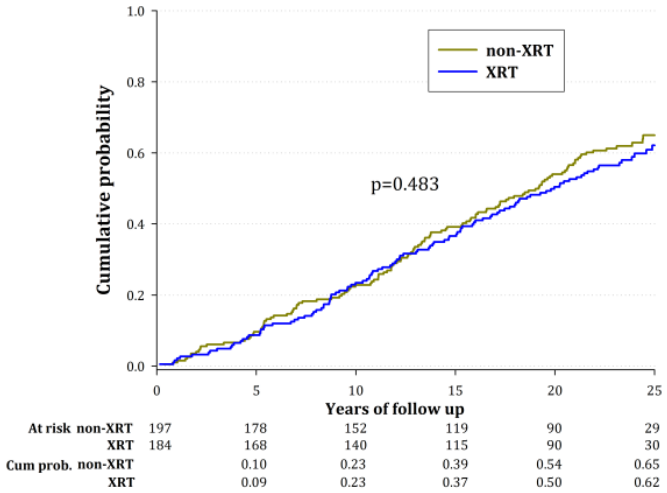


Figure5E

Figure 5A.First breast cancer event of any type: local recurrence, distant/regional metastases or death as a result of generalized breast cancer. Figure 5B.First event of contralateral cancer or death as a result of cancers other than breast cancer. Figure 5C.Death as a result of generalized breast cancer. Figure 5D.Death as a result of causes other than breast cancer. Figure 5E.Death as a result of all causes. Numbers at bottom of each graph indicate patients at risk and cumulative probability. Non-XRT; women randomly assigned to surgery alone, XRT; women randomly assigned to surgery and radiotherapy.

Paper II

Immuno-histochemical data were complete for 223 of the original 381 study participants. Their tumors were classified into the intrinsic subtypes according to the St. Gallen International Expert Consensus recommendations 2011 [110] and Swedish guidelines based on Sorlie´s classification [111] (table2). Fifty-seven tumors were classified as luminal B/HER2-negative of which 24 graded as NHG 3. Eighteen of these tumors had low Ki-67 and were PR-positive and would have been classified as luminal A tumors if the NHG status had not been considered. Due to low numbers, luminal B/HER2 positive, HER2-positive and triple negative tumors were grouped together to form a "high-risk group".

Luminal B /HER2-negative tumors showed an about 3-fold higher risk for IBTR in the Cox regression analysis with luminal A tumors as reference, no matter if XRT was given or not (HR 2.58 95% CI 1.07-6.20 and HR 5.08 95% CI 1.31-19.7 respectively). The absolute risk of IBTR at 20 years was to the benefit of XRT in all intrinsic subtypes but the differences showed no statistical significance in any subtype. Moreover, evaluation if the risk of IBTR with or without radiotherapy differed between the subtypes, revealed no interactions.

In a postulated low-risk group (luminal A tumors, ≥55 years old, without lobular cancer, n=83) log-rank test revealed no statistical difference between the XRT and non-XRT group (p=0.27; absolute risk difference 7.5% 95% CI -6.6% to 21.6%).

	ER	PR	HER2	Ki-67	NHG
Luminal A	+	+	-	low	
Luminal B/HER2-neg	+	- or low*	-	high*	grade 3*
Luminal B/HER2-pos	+	+ or -	+	high or low	any grade
HER2-pos	-	-	+	high or low	any grade
Triple negative	-	-	-	high or low	any grade

*Table2. Classification into the intrinsic subtypes – how it was done. *One or more.*

Paper III

At a median follow-up of 68 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%). Thirteen women had a contralateral breast cancer; cumulative incidence at five years 1.8% (95% CI 0.9 to 3.2). 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 was treated with AI. However, one of these women had TAM for only two weeks. For the others the duration range of intake was 1.5 to 7 years. There were 48 deaths. Only one death was due to breast cancer. Two women died from endometrial cancer and 13 were due to other cancers. Overall survival at five years was 93.0 % (95 % CI 90.5 to 94.9 %). Thirty-one women withdrew from follow-up or ET ahead of schedule. Eleven out of thirty-one women stopped their ET due to adverse effects. Compliance for ET with a median follow-up of five years was calculated to 96%.

Paper IV

The clinical procedures worked out well logistically. Seven women received additional external radiotherapy. Six of them belonged to the pre-pathology group and in all cases final histopathological report showed in situ component with insufficient or indistinct margins. One of these seven women belonged to the post-pathology group. Due to a large wound cavity the breast tissue could not be adapted to the applicator and she was treated with external XRT instead of IOBT. Mean total surgical time (time in operating room + IOBT time + time for wound-closure) for the pre-pathology group was 75 minutes and for the post-pathology group (time to open the wound and place the applicator + IOBT time + time for wound-closure) 38 minutes. Mean time in the operation room for the pre-pathology group was 62 minutes.

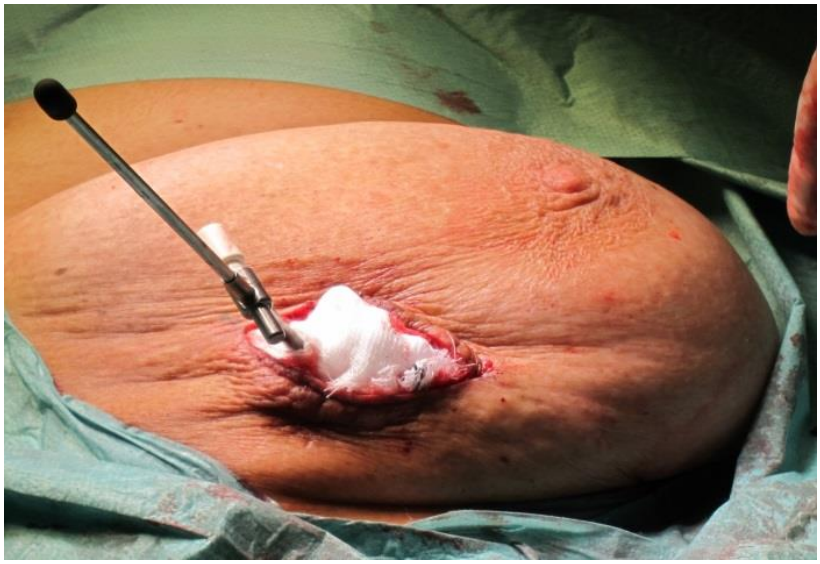


Figure6. The IOBT procedure. Applicator in the wound cavity.

No acute toxic effects from IOBT were recorded. Three women had a wound infection, which in two cases needed antibiotic treatment. At the 2-4 week-follow-up 11 women had no symptoms at all and 37 women had mild 1-2 side effects according to the LENT-SOMA scale. At 6 months all women had a satisfying outcome and most of the 1-2 side effects were gone.

The results from the EORTC-QLQ-C30 questionnaire showed that the women in our study in general reported high scores on functional scales and low scores on symptomatic scales. Compared with a reference group from the Swedish population, an unpaired t-test showed a significant difference for "cognitive functioning", where the study participants scored lower than the reference group. The women in the pilot study also reported a significantly higher score on fatigue, insomnia and appetite loss. The results from the EQ-5D questionnaire were similarly compared with a reference group from the Swedish population using Fisher´s exact test. No significant differences were found.

One year after initial treatment 14 women in the pre-pathology group and 11 women in the post-pathology group had a good ("G") result according to the BCCT software tool. Only one woman in each group was registered with "poor" cosmetic result. Two women were excluded in the

one-year follow-up, one due to incomplete photographing and the other because she was diagnosed with subcutaneous skin metastases.

Results from the CT scan showed that the median air proportion inside the 10 G y-shell, for the pre- and post-pathology groups were 0.9% and 1.2 % respectively. The median size for the applicator was 25 mm in the post-pathology group and 30 mm in the pre-pathology group. The median values for irradiated tissue (e.g. the 10 G y-shell) were 25 cm^3 in the pre-pathology group and 15 cm^3 in the post-pathology group.

Figure7. CT scan shows the location of the applicator.

Discussion

Paper I

The addition of radiotherapy after BCS conferred an absolute risk reduction of first breast cancer event of 14 % at 20 years. No differences were found between the XRT group and the non-XRT group concerning breast cancer death or overall mortality. In the postulated low-risk group, the absolute risk difference between XRT and non-XRT group was 11%.

The majority of IBTR´s occurred in the non-XRT group during the first five years, and after this time period, the protective effect of radiotherapy ceased to exist. Similar trends have been found in other trials [14,17]. In 2016 Killander et al published a trial where a total of 1187 women with invasive T1-2N0M0 breast cancer were randomized, after standardized sector resection, to postoperative whole breast XRT or no local treatment. After 15 years of follow-up their results resembles ours - a significant higher incidence of IBTR was observed in the non-XRT group compared to the XRT group *(*$p < 0.001$). Overall survival was not significantly lower for the XRT-group. Moreover, the main effect from XRT was seen during the first five years. The authors were unable to find a subgroup which could be spared XRT.

In a large meta-analyses by EBCTCG [22] a significant excess incidence of contralateral breast cancer (rate ratio 1.18, SE 0.06, 2p=0.002) were seen in irradiated women. In our trial a contralateral breast cancer was diagnosed in 52 women; 30 women in the XRT group (cumulative incidence at 20 years, 16.4%) and 22 in the non-XRT group (cumulative incidence at 20 years, 11.2%), corresponding to an absolute risk difference of 5% at 20 years (95% CI, -2% to 12%). The absolute difference almost reached statistical significance.

In the same meta-analysis a significant excess incidence of non-breast cancer mortality in irradiated women was found (rate ratio 1.12, SE 0.04,

2p=0.001). The excess mortality was mainly from lung cancer (rate ratio 1.78, SE 0.22, 2p=0.0004) and heart disease (rate ratio 1.27, SE 0.07, 2p=0.0001). The larger number of cardiovascular death in the non-XRT group in our trial is probably due to lack of power since the trial was not designed to evaluate this matter. In addition, cardiovascular death in our study included death from stroke, bowel ischemia, and other events unrelated to breast irradiation. Thus, the numbers of acute/subacute cardiac events are not calculated and any conclusion from these findings should be drawn with caution.

Several trials have tried to find a subgroup of women where the risk of local recurrence is so low that radiotherapy might be omitted [20,112-115]. In selected subgroups of patents the risk of IBTR without XRT after BCS is in general low. However, no trial so far has been able to identify a subgroup where XRT can be safely omitted.

Paper II

Luminal B/HER2 negative subtype increased the risk of local recurrence 3-5-fold. No subtype benefitted from radiotherapy more than the other. In the low-risk group, the risk of IBTR at 20 years was 7.5%.

The prognostic ability of luminal B/HER2-negative subtype has been investigated in several trials [116-118] but little is known about the intrinsic subtypes´ risk of recurrence with or without radiotherapy [80].

Two recently published randomized trials investigated the different subtypes´ risk for recurrence with or without radiotherapy, and tried to identify a low-risk group [119,120]. In both these studies the primary objective was to define intrinsic subtyping as a predictive biomarker of the benefit of radiotherapy.

Liu et al randomly assigned 769 patients after BCS to tamoxifen plus breast irradiation or to tamoxifen alone [119]. IHC analysis was conducted on 501/769 available blocks. Median age was 68 years, 83% had pT1 tumors, 94% were estrogen receptor–positive or unknown and 83% were pathologically or clinically node negative. The median follow-up time was 10 years. The authors found intrinsic subtyping to be prognostic for IBTR; (10-year estimates of IBTR in univariable analysis: luminal A, 5.2%; luminal B, 10.5%; high-risk subtypes, 21.3%; P < 0.001). Luminal A and luminal B subtypes seemed to derive less benefit from radiotherapy (lu-

minal A; RH 0.40, 95% CI 0.12-0.29, luminal B; RH 0.51, 95% CI 0.19-1.36) than the high-risk subtypes including HER2 positive-, basal like-, and triple-negative tumors (RH 0.13 95% CI 0.03-0.54). However, a subtype-treatment interaction test revealed no significant differences between the subtypes. A low-risk group was also defined (age older than 60 years, T1, grade 1 or 2) where the risk of IBTR without irradiation but with the addition of tamoxifen, was low; 1.3 % in 10 years.

Sjöström et al randomized 1003 patients with node-negative, stage I and II breast cancer in the Swedish Breast Cancer Group 91 Radiotherapy trial to breast conservation surgery with or without XRT [120]. Systemic therapy was used in 8% of the study participants. Just like in our trial and in the trial by Liu et al, the authors found subtyping not to be predictive of response to XRT even though HER2-positive tumors seemed to be less sensitive to radiotherapy. Contrary to our findings the low-risk group had an excellent benefit from XRT – the cumulative incidence at 10 years with and without XRT was 6% and 20 % respectively.

Thus, results from these trials are conflicting. Several retrospective studies have confirmed the low rate of recurrence associated with the luminal A subtype [116,121,122] and the worse prognosis for the triple-negative subtype [123,124], even though their response to adjuvant XRT are not fully elucidated. The introduction of trastuzumab has substantially lowered the risk of recurrence for the HER2- positive subtype [125].

Our trial has several limitations. Firstly, only 223/381 (59 %) tumors were available for TMA preparation and IHC. Secondly, 7 tumors exhibited 2+ and 11 tumors exhibited 3+ staining for HER2 protein overexpression. The 7 tumors exhibiting 2+ were all considered negative. Ideally, all these tumors would have been analyzed by fluorescent-in situ hybridization (FISH). However, due to low numbers, the lack of this analysis should not affect the final results.

The combination of old and modern biochemical analysis may contribute to uncertain results. However, cross tabulation showed no difference between the group where tissue samples were available compared to the group where samples were missing.

Classification into the intrinsic subtypes is an approximation of genotype-based subtypes accepted at the 13th St Gallen breast cancer conference [79]. Gene expression tests are found to be more precise in predicting recur-

rences, but heavy expenses and low availability still limit their usefulness [81,111,126,127].

Strengths of our trial are the randomization, the long follow-up and that the analyses were made without interference with systemic therapy. There are different policies in how the classification into the intrinsic subtypes should be done. In our trial we have taken NHG into account to differ between luminal A and luminal B/HER2-negative subtype (table 2). The strong prognostic value of NHG has been confirmed by a multidisciplinary group of American clinicians, pathologists, and statisticians [76], in a trial by Ehinger et al [128] and in a large retrospective trial of T1-T2 breast cancer tumors with long follow-up [129].

Since our classification was performed, the Swedish guidelines for breast cancer treatment have been updated. The current recommendation is to separate Ki-67 into a low (<14%), intermediate (14-19%) and high (≥20%) group before classification into the luminal A och luminal B subtypes. The threshold for PR to be considered positive should be 20%. These recommendations are based on findings from Maisonneuve et al [130].
In summary this randomized trial showed that luminal B/HER2-negative subtype entailed a 3-5 fold higher risk for IBTR compared to the luminal A subtype. This finding was not significantly modified by adjuvant radiotherapy. In the low-risk group defined by combining luminal A with clinical characteristics, the incidence for the non-XRT group was less than 1% per year.

Paper III

In our cohort the cumulative incidence of IBTR at 5 years was low. The incidence of contralateral cancer was comparable to the incidence of IBTR. Only one woman died from breast cancer.
Even though postoperative radiotherapy is known to substantially reduce breast cancer recurrence and moderately reduce breast cancer death, several randomized trials indicate that there are subgroups were the addition of radiotherapy can be questioned. The proportional benefits of adjuvant radiotherapy are similar for different prognostic risk groups of patients, while the absolute benefits depend on the risk of recurrence and therefore vary considerably between prognostic groups. The Oxford overview of trials of adjuvant XRT after BCS included 10 801 women [23]. In pN0 pa-

tients, the first recurrence was an IBTR for a higher proportion of women allocated to surgery alone (22.8%) than for women allocated to surgery and XRT (7.3%), while the proportion of distant recurrence was the same (8.2% and 8.3%). The group with pN0 disease (7287 women) were divided into three categories based on the absolute reduction in the 10-year risk of any recurrence with XRT; high (>20%), intermediate (10-20%) or low (<10%). The categorization was based on age, tumor grade, ER-status, use of TAM, and extent of surgery. Patients with ≥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. For patients in the intermediate category the breast cancer mortality reduction was only 1.1% (95% CI -2.0 to 4.2) and for patients with <10% absolute reduction, the absolute improvement was only 0.1% (95% CI -7.5 to 7.7). Thus, in these groups, addition of XRT did not add any benefit concerning breast cancer deaths, which indicate that there exist a subgroup of women where XRT may be omitted.

Where a treatment benefit is known but is considered to be so small not to be clinically relevant, then alternatives to RCTs may be considered to answer the question of the need for postoperative XRT. Our prospective cohort is one such example. The design of this trial may have facilitated more rapid accrual compared to a RCT, as patient acceptance of randomization is recognized to negatively affect recruitment. Moreover, the protective effect of postoperative radiotherapy is well-known and need not to be confirmed by an additional RCT. This is the rationale to our study design. Inclusion criteria in our trial are based on previous established risk factors for breast cancer recurrence; estrogen receptor negativity [18], large tumor size [76], extensive cancer in situ [24,131], poor tumor nuclear grade[76,131], lobular cancer [20], age [19,20,24,131,132] and clinically detected tumor [19]. Previous trials have set different inclusion criteria for age since there is no agreed age cut-off as to what constitutes an older patient. Our inclusion criterion was age > 65 years.

Similar to our results the low incidence of IBTR has been confirmed in other trials. The CALGB 9943 trial randomly assigned 636 women ≥70 years with stage I estrogen receptor-positive disease and tumor size ≤2 cm to receive BCS and tamoxifen with or without radiotherapy. Neither the five-year follow-up [114] nor the ten-year follow-up [112] revealed any survival advantages with XRT and the absolute risk benefits from XRT were

small. More recently, Kunkler et al published their PRIME II study where 1326 women aged ≥65 years with estrogen receptor-positive pN0 tumors and tumor size ≤3 cm, were randomized to receive BCS and endocrine therapy with or without radiotherapy. At a median follow-up of 5 years, similar local control rates to CALGB concerning IBTR and survival were found [113]. In an unplanned subgroup analysis, the five-year ipsilateral breast tumor recurrence incidence in estrogen receptor-rich patients receiving endocrine treatment without radiotherapy was 3.3%. However, in a study conducted by Fyles et al [115] a planned subgroup analysis of 611 women with T1, estrogen receptor-positive tumors indicated a substantial benefit from radiotherapy. All these trials rely on clinicopathological parameters to identify a group of patients with anticipated low risk of IBTR. However, improved techniques will most likely be required to select this group of patients.

Liu et al [119], as previously mentioned, carried out intrinsic subtyping on tissue samples from the study by Fyles and colleagues. The authors´ found a low rate of local recurrence in luminal A patients with or without radiotherapy. Just as in our trial, presented in paper II, they used immunohistochemical (IHC) tumor markers to classify the tumors into different intrinsic subtypes. The ongoing prospective cohort studies PRIMETIME [133] and LUMINA use the so-called IHC4+C score and IHC respectively to classify their tumors. Nevertheless, gene profiling techniques like Oncotype-DX or PAM-50 used in IDEA, PRECISION and EXPERT might be better prognostic and predictive tools [84,134].

The yearly risk for a woman treated for breast cancer of developing a contralateral cancer has been estimated to 0.7 % [135] and that risk is five times higher than for a woman in Sweden to develop a primary breast cancer tumor. Today most postmenopausal women are prescribed aromatase inhibitors instead of tamoxifen which might further reduce the risk of breast cancer recurrences, including contralateral cancer [136,137]. The use of tamoxifen may also have contributed to the relatively high incidence of endometrial cancer in this study [138]. The incidence of contralateral cancer in our trial at five years was comparable to the incidence of IBTR, even though radiotherapy was omitted and endocrine therapy prescribed. In the large meta-analysis from EBCTCG including 78 randomized trials comparing XRT versus no XRT, there was a significant excess of contralateral cancer in the XRT-group [22]. The excess appeared 5-14 years after

randomization. One may speculate whether XRT protect against contralateral cancer the first five years but not in the long-run. In a large Swedish-populations-based study the risk of dying from breast cancer was high for women with a short interval time to contralateral cancer, which stresses the need of reducing the risk of this event [69]. Would this justify a more intense treatment of the contralateral breast, or even a prophylactic mastectomy? According to the Surveillance Epidemiology and End Results database (SEER) in the United States, the incidence of prophylactic mastectomy has increased markedly during the last two decades [139].

In paper I we conclude that radiotherapy protects against any first breast cancer recurrence during the first five years of follow-up. After this time-span the difference between the XRT- and non-XRT - group seem to disappear. Similar results are presented in the large meta-analyses by EBCTCG [23], even though they found that the proportional reduction was still substantial during years 5–9 (rate ratio 0·59, 0·50–0·70). In this perspective, five years of follow-up would be sufficient to consider omission of radiotherapy to women with similar tumor characteristics as in our cohort. On the other hand, results from a meta-analysis indicate that a longer follow-up is needed [140]. In this meta-analysis the primary aim was to determine whether there are subgroups of women where endocrine therapy may be stopped after 5 years without substantially affecting the long-term risk of breast cancer recurrence. The authors found that the risk of distant recurrence was strongly correlated with TN status and that, even for T1N0 tumours, the cumulative risk of distant recurrence was 13% years 5 to 20.

In our trial only one breast cancer death was registered at five years, which indicates that breast cancer mortality in this low-risk cohort is of secondary importance compared to death of other malignancies or other causes.

The most apparent limitation of our study is the lack of a control group, which reduces the possibility to correlate for potential confounders. 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. While the multicenter design is a strength, it may also make it more difficult to collect data, due to lack of communication and local routines. A potential problem with a cohort design may be a big loss of study participants. In our study only 5 % (31 individuals)

of the women had withdrawn at five years. Almost half of them (12 individuals) did so for unknown reasons.
Even though one may argue that the median follow-up of 68 months is rather short, we find the cumulative incidence of IBTR of 1.2 % at five years promising.
To allow for more sophisticated analyses our trial needs complete data on immuno-histochemical tumor markers. The IBTR´s, which will increase in number with longer follow-up, might also allow for further research concerning true and secondary recurrences.

Paper IV

The procedures worked out well, both for the pre-and post-pathological group. No acute adverse effects from IOBT were registered. The results from the health questionnaires did not reveal any major differences compared to reference groups from the Swedish population. .

The TARGIT-A trial used IntraBeam®, described earlier, to deliver IORT. In 2017, 20 000 patients all over the world had been treated with IntraBeam®. In Germany and The United States more than 60 clinics in each nation use this method and in Australia IntraBeam® has been introduced as a standard treatment for a selected group of patients. In Scandinavia, IntraBeam® is in use at St. Olav´s Hospital in Trondheim, Norway, and at Herlves Hospital in Denmark. Our pilot trial represents the first attempt in Sweden to introduce IOBT.

The rationale for giving a single-dose of IOBT in the tumor bed is that most of the IBTR´s appear in the vicinity of the original tumor [31]. Since this is a fact in a majority of cases, it is also a matter of how to define true recurrences and secondary tumors, as discussed previously in "The surgical procedure" [13].

During the post-pathological procedure, it became clear that the breast tissue was compromised after previous surgery and was difficult to mobilize, which was also noticed by Vaidya et al when treating their patients in the post-pathology group [44]. In our trial, this observation was objectively confirmed by the CT scan, where the percentage air in the 10 G y-shell was larger in the post-pathology group compared to the pre-pathology group. We therefore decided to exclude the post-pathological surgical procedure, when planning a multicenter trial. To the best of our knowledge, no other IOBT trial has objectively evaluated the adherence of

breast tissue to the applicator in a CT scan. Hopefully, this will contribute to a better quality of IOBT.

Similarly to other studies evaluating PBI, we found no acute side effects from IOBT and the cosmetic outcome was satisfying for a majority of the study participants [44,49,141].

The results from the health questionnaires in our pilot trial should be interpreted with caution since the power is low. Quality of life was evaluated in a subgroup of women from the TARGIT-A trial´s post-pathological group. The women were asked to fill in the EORTC-QlQ-C30 questionnaire [97] including the Breast-Specific Module (BR23), and the Body Image after Breast Cancer Questionnaire (BIABC). This was done at baseline, before IORT, and then annually. Women in the IORT group were found to have better breast-related quality of life outcomes than patients treated with EBRT [142]. Contrary to the TAGIT-A trial, we did not have a control group and the health questionnaires were not filled in at baseline. However, reporting quality of life after a cancer diagnosis could also be misleading.

Results from the two large randomized trials TARGIT-A and ELIOT point towards a careful selection of patients to receive IOBT. The TARGIT-A trial included women aged ≥45 years with a tumor ≤ 35 mm. Lobular tumors were excluded. Inclusion criteria in the ELIOT trial were women ≥ 48 years with any invasive breast cancer ≤ 25 mm, lobular tumors included. In neither of these trials restrictions to axillary status were taken. In our pilot study, we excluded lobular tumors and the axilla had to be free from metastases.

The latest report from The National Institute of Health and Care Excellence (NICE) in England concludes that IntraBeam® can only be recommended if its use is accompanied by the gathering of additional information on clinical effectiveness by data collection [143]. They also conclude that there are some patients who could particularly benefit from IntraBeam®, but these patients should be fully informed of the evidence and treatment options. The report from NICE, the criticism against the TARGIT-A trial, and a recently published summary from the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) [46], may have contributed to a hesitation to introduce IOBT in a wider sense in Sweden. Moreover, the cost for the IntraBeam® equipment is high. At Örebro University Hospital, we have developed inexpen-

sive and easily accessible equipment for delivering IOBT. Waiting for the long-term results from further PBI trials, it would premature to introduce IOBT as a standard treatment. Nevertheless, in future it may be applicable to a group of selected women with early breast cancer.

Sammanfattning på svenska

I Sverige diagnosticerades 2016 8923 kvinnor med bröstcancer. Antalet insjuknade har mer än fördubblats över en period av 40 år. Samtidigt har bättre behandlingsmetoder och utvecklade diagnostiska instrument möjliggjort att dödligheten minskat. Denna avhandling fokuserar på att utvärdera huruvida strålbehandling skall ges efter operation av bröstcancer med bröstbevarande kirurgi, om det finns alternativa former av strålbe-

handling, eller om man kan avstå från den helt. Idag är det rutin att ge strålbehandling till kvinnor som genomgår bröstbevarande kirurgi. Detta skall minska risken för lokalt återfall i det kvarvarande bröstet. Standard är att ge en behandling om dagen i 3-5 veckor. För äldre och sjukliga patienter kan detta innebära långa, obekväma resor och frekventa sjukhusbesök. För att undvika detta väljer då en del patienter att operera bort hela bröstet.

I delarbete I randomiserades 381 kvinnor på 80-talet till att genomgå bröstbevarande kirurgi med eller utan efterföljande strålbehandling. Alla hade en välavgränsad tumör ≤ 2 cm utan spridning till armhålan samt var ≤ 80 år. Efter 20 år hade den grupp som inte fått strålbehandling signifikant fler återfall i bröstcancer jämfört med de som fått strålbehandling. Inga skillnader sågs mellan grupperna avseende död i bröstcancer eller annan sjukdom. I en mindre grupp av kvinnor med prognostiskt gynnsamma tumörer var återfallsrisken låg för de som inte fått strålbehandling, men skillnaden jämfört med strålbehandlingsgruppen var fortfarande statistiskt signifikant.

I delarbete II samlade vi in vävnadsproverna från tumörerna i delarbete I och omklassificerade dem enligt moderna metoder. Därefter delades tumörerna in i sk ”intrinsic subtypes”, vilka utgör ett nytt sätt att dela in bröstcancrar. Subtypernas förmåga att förutsäga återfall i bröstcancer är inte helt klarlagd, varför vi utförde en riskfaktoranalys med avseende på de olika subgrupperna. Vi fann att kvinnor som tillhörde subgruppen luminal B/HER2-negativ bröstcancer löpte en ökad risk för återfall jämfört med de andra grupperna. Vi fann ingen skillnad mellan subgruppernas risk för återfall med eller utan strålbehandling.

Delarbete III utgjordes av en kohortstudie där vi inkluderade 601 kvinnor med små, tidiga bröstcancrar. Alla genomgick bröstbevarande kirurgi och erhöll efterföljande tablettbehandling för att sänka östrogennivåerna i kroppen, men ingen strålbehandling. Efter en median uppföljning av 5 år var återfallsfrekvensen låg med 16 lokala återfall i det opererade bröstet, 13 cancrar i det andra bröstet samt en död i bröstcancer. Resultaten pekar mot att strålbehandling kan avstås från i en utvald grupp av tidiga, små bröstcancrar, men att längre uppföljningstid behövs.

En pilotstudie utgjorde delarbete IV. Syftet var att utvärdera införandet av en ny metod som syftar till att ge strålbehandling under själva bröstcanceroperationen (intraoperativ brachyterapi, IOBT). Vi utvecklade en

applikator som kunde anslutas till en redan befintlig utrustning på onkologiska kliniken, USÖ. Femtio kvinnor inkluderades i studien varav 25 erhöll IOBT under den första operationen och de övriga i en andra seans, efter att slutlig histopatologisk diagnos erhållits. Logistiken var god och inga akuta allvarliga sidoeffekter av behandlingen registrerades. Med reservation för att gruppen studiedeltagare var liten, sågs inga övertygande skillnader i hälsokvalitet i vår studiegrupp jämfört med en referensgrupp från Sveriges befolkning. Vår konklusion är att IOBT fortfarande skall ges inom ramen för forskning och till en utvald grupp av kvinnor med s k lågrisktumörer.

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ORIGINAL REPORT

Sector Resection With or Without Postoperative Radiotherapy for Stage I Breast Cancer: 20-Year Results of a Randomized Trial

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ABSTRACT

Purpose
To investigate how radiotherapy (XRT) adds to tumor control using a standardized surgical technique with meticulous control of surgical margins in a randomized trial with 20 years of follow-up.

Patients and Methods
Three hundred eighty-one women with pT1N0 breast cancer were randomly assigned to sector resection with (XRT group) or without (non-XRT group) postoperative radiotherapy to the breast. With follow-up through 2010, we estimated cumulative proportion of recurrence, breast cancer death, and all-cause mortality.

Results
The cumulative probability of a first breast cancer event of any type after 20 years was 30.9% in the XRT group and 45.1% in the non-XRT group (hazard ratio [HR], 0.58; 95% CI, 0.41 to 0.82). The benefit of radiotherapy was achieved within the first 5 years. After 20 years, 50.4% of the women in the XRT group died compared with 54.0% in the non-XRT group (HR, 0.92; 95% CI, 0.71 to 1.19). The cumulative probability of contralateral cancer or death as a result of cancer other than breast cancer was 27.1% in the XRT group and 24.9% in the non-XRT group (HR, 1.17; 95% CI, 0.77 to 1.77). In an anticipated low-risk group, the cumulative incidence of first breast cancer of any type was 24.8% in the XRT group and 36.1% in the non-XRT group (HR, 0.61; 95% CI, 0.35 to 1.07).

Conclusion
Radiotherapy protects against recurrences during the first 5 years of follow-up, indicating that XRT mainly eradicates undetected cancer foci present at primary treatment. The similar rate of recurrences beyond 5 years in the two groups indicates that late recurrences are new tumors. There are subgroups with clinically relevant differences in risk.

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INTRODUCTION

In the most recent meta-analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG),[1] postoperative radiotherapy after breast-conserving surgery (BCS) for early breast cancer halved the risk of any cancer recurrence over a 10-year-period. After 15 years, about one breast cancer death was averted for every four recurrences avoided by year 10. However, the reduction in breast-cancer-specific death is partly counterbalanced by an increase in nonbreast-cancer mortality owing to an increased risk of cardiovascular disease and lung cancer, particularly in the second decade after radiotherapy.[2-5] Because many women with early breast cancer are long-time survivors, these long-term adverse effects are clinically relevant, particularly among women with left-sided disease.[6,7]

The effect of adjuvant radiotherapy after BCS has been assessed in two randomized trials with 20-year follow-up. In the National Surgical Adjuvant Breast and Bowel Project B-06 trial[8] of women with stage I or II breast tumors, the cumulative probability of recurrence in the ipsilateral breast was 14.3% after lumpectomy and radiotherapy, as compared with 39.2% after lumpectomy alone.

In the Milan trial by Veronesi et al,[9] women were randomly assigned to undergo either the classic Halsted procedure or quadrantectomy plus postoperative radiotherapy. The cumulative probability of local recurrence after 20 years was 8.8% among women treated with BCS plus radiotherapy.

The Uppsala/Örebro study[10] was one of the first randomized trials to corroborate the benefit of adjuvant radiotherapy after 10 years of follow-up among women treated with BCS. We used a

standardized sector resection,[11] which is a more extensive procedure than lumpectomy but less extensive than quadrantectomy. Now, we report the 20-year event-free survival, death of any cause, and breast cancer mortality. We also try to identify a population with a low risk of recurrence even without the addition of postoperative radiotherapy.

PATIENTS AND METHODS

Study Design

The design of our randomized trial has previously been described in detail.[12] From 1981 to 1988, women ≤ 80 years old with a unifocal invasive breast cancer of histopathologic stage I were enrolled onto the study. Patients, doctors, and evaluators were not blinded to patient allocation. We assumed a priori that approximately 5 percent of the women randomly assigned to sector resection with postoperative radiotherapy (XRT group) would develop a local recurrence within 5 years, and we wanted to detect a local recurrence rate in women randomly assigned to sector resection without radiotherapy (non-XRT group) that would be 15% or higher at a 5% level of significance (two-sided test) and 90% power. With these considerations and 100% compliance, the predetermined sample size was 360 patients.

All women were treated with sector resection[11] and the axilla was dissected to levels I and II. Patients were then randomly assigned by telephone contact with the study secretariat at the University hospital in Uppsala to receive postoperative radiotherapy to the breast (XRT group, 184 women) or to surgery alone (non-XRT group, 197 women; Fig 1). No adjuvant systemic therapy was administered. Five central Swedish regional hospitals and one university hospital enrolled patients onto the study.

Stratification at the time of randomization was made for each center, mode of detection (mammography screening or not), and tumor size (≤ 10 mm or > 10 mm). Allocation to treatment group was performed in blocks of four within each center; the block size was unknown to the investigators.

A total dose of 54 Gy in 27 fractions was delivered to the target volume, defined as breast parenchyma plus 1 cm. Two opposing tangential fields with an open angle of 185 degrees were applied. We used photons from a 4 to 10 MV linear accelerator or from cobalt 60.

Subgroup Analysis

In our 10-year report,[10] a risk factor analysis was performed with multiple regression identifying young age (≤ 55 years), lobular cancer, and comedo-type cancer as risk factors for local recurrence. We therefore analyzed a subgroup of women (n = 199) who were at least 55 years old without lobular or comedo-type carcinomas. This was a posthoc hypothesis, not predetermined in the original protocol.

Data Collection

Data for this long-term follow-up was extracted from The National Cancer Registry, The Hospital Discharge Registry, and The National Causes of Death Register at The National Board of Welfare, Stockholm, Sweden. These registers hold validated information of nationwide cancer incidence, admission, and diagnoses at discharge from hospitals and surgical interventions in Swedish hospitals and causes of death, respectively. Information was collected for each patient on newly reported tumors, diagnoses during hospital stays, and the date and causes of death.

Statistical Analyses

All analyses were intention-to-treat analyses. Time to first breast cancer event, defined as local recurrence, distant/regional metastases, or death as a result of generalized breast cancer, was estimated and visualized using the Kaplan-Meier method and was presented as a cumulative proportion. All patients received follow-up until their first breast cancer event and were censored for emigration and mortality by December 31, 2010. Log-rank test was used to evaluate differences between XRT and non-XRT groups. Absolute risk differences for cumulative probabilities at 20 years after operation was calculated with normal approximated 95% CIs. Cox regression was performed to compare the XRT group with the non-XRT group, both unadjusted and adjusted for the stratification variables at randomization. Hazard ratios (HR) with 95% CI were the measure of association. The proportional hazards assumption was evaluated and tested with Schoenfeld residuals and whether nonproportionality separate analyses were conducted at 0 to 5 and > 5 years

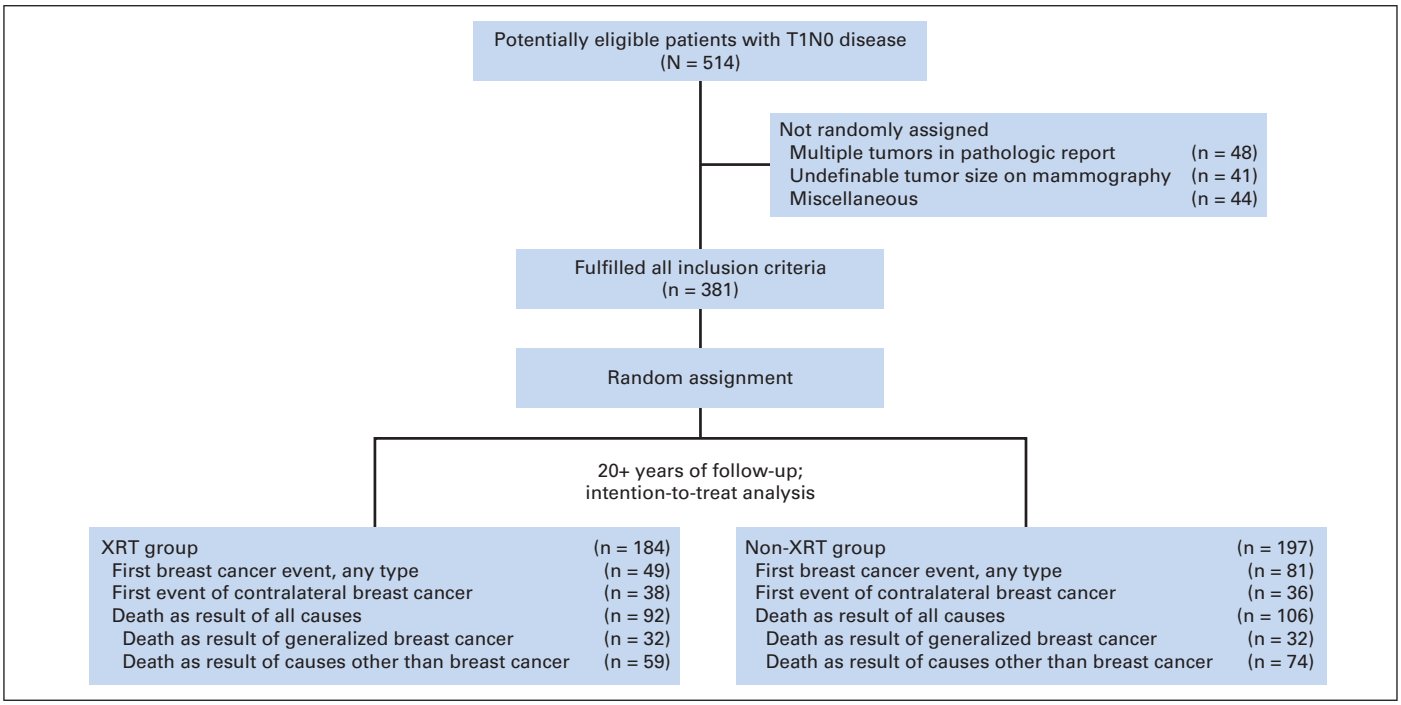

Fig 1. CONSORT diagram showing patient selection, random assignment, and all events in the trial. Non-XRT, women randomly assigned to surgery alone; XRT, women randomly assigned to radiotherapy.

Table 1. Baseline Characteristics of Treatment Groups

Characteristic	XRT Group (n = 184)		Non-XRT Group (n = 197)	
	No. of Patients	%	No. of Patients	%
Age, years				
Mean	59.0		60.9	
SD	11.5		11.0	
Postmenopausal	118	64.1	114	57.9
Tumor detected by screening	86	46.7	90	45.7
Largest tumor diameter on mammography ≤ 10 mm	70	38.0	80	40.6
Largest tumor diameter on pathology report ≤ 10 mm*	61	34.6	66	34.9
Median No. of lymph nodes investigated	7		7	

Abbreviations: non-XRT, women randomly assigned to surgery alone; SD, standard deviation; XRT, women randomly assigned to radiotherapy.
*Eight patients in the XRT group and eight patients in the non-XRT group had missing tumor diameter information from their pathology reports.

after operation, according to the concept of delayed entry. The same strategy of analyses was performed for the second outcome defined as time to first event of contralateral breast cancer or death from cancers other than breast cancer. Also time to death as a result of generalized breast cancer as well as time to all-cause mortality was evaluated. All statistical analyses were done using STATA software version 11 (STATA, College Station, TX).

Patients

We enrolled 381 patients onto to the study. Eleven women who did not accept radiotherapy were analyzed according to the assigned treatment group, as were four women who did not start the treatment because of complications. Between 1989 and 1994, four women who moved abroad were censored at the date of emigration, except for one woman who could be reached by mail. She received follow-up until 1997. For all other participants, we achieved complete follow-up on any type of relapse or death of any cause through December 31, 2010. Table 1 lists the distribution of selected clinical variables in the two treatment groups. The study protocol was approved by the local ethics committee at the Central Hospital in Falun on October 12, 1981. For the reanalysis with data based on the central registries at the National Board of Welfare, Stockholm, approval was given by the ethics committee in Uppsala, Sweden.

RESULTS

First Breast Cancer Event of Any Type

Table 2 lists the cumulative probability of first breast cancer event of any type. At 20 years, 49 events occurred in the XRT group compared with 81 in the non-XRT group. Absolute risk difference was 14% (95% CI, −24% to −5%; Table 2; Fig 2A). The difference between the groups was almost exclusively caused by the difference in local recurrence as a first event, with a cumulative proportion of 11.5% in the XRT group and 25.8% in the non-XRT group (data not shown). The absolute risk difference between the two groups at 20 years was −14% (95% CI, −22% to −7%). Results from the regression analyses show that the protective effect of radiotherapy to the breast on a first breast cancer event is confined to the first 5 years after diagnosis (HR, 0.35; 95% CI, 0.21 to 0.59; Table 3).

Contralateral Cancer As First Event or Death From Cancers Other Than Breast Cancer

A contralateral breast cancer was diagnosed in 52 women; 30 women in the XRT group (cumulative proportion at 20 years, 16.4%) and 22 in the non-XRT group (cumulative proportion at 20 years, 11.2%), corresponding to an absolute risk difference of 5% at 20 years (95% CI, −2% to 12%; data not shown). When we included other types of cancers as first events in the analyses, 38 women in the XRT group (cumulative proportion at 20 years, 27.1%) and 36 in the non-XRT group (cumulative proportion at 20 years, 24.9%) were affected with a corresponding absolute risk difference of 2% (95% CI, −6% to 11%; Table 2; Fig 2B).

Table 2. No. of First Breast Cancer Events, Deaths by Cause, No. of Other Events, Cumulative Probability, and Absolute Risk Difference With 95% CIs

Type of Event	XRT Group (n = 184)			Non-XRT Group (n = 197)			20 Years After Operation	
	No. of Events at 20 Years			No. of Events at 20 Years				
	No. After 20 Years of Follow-Up*	Total Follow-Up*	Cumulative Probability at 20 Years	No. After 20 Years of Follow-Up*	Total Follow-Up*	Cumulative Probability at 20 Years	Absolute Risk Difference†	95% CI
First breast cancer event, any type; local recurrence; distant/regional metastases; or death as a result of generalized breast cancer‡	49	53	0.309	81	83	0.451	−0.14	−0.24 to −0.05
Low-risk group‡§	19	21	0.248	31	32	0.361	−0.11	−0.20 to −0.02
First event of contralateral cancer or death as a result of cancers other than breast cancer‡	38	46	0.271	36	44	0.249	0.02	−0.06 to 0.11
Death as a result of generalized breast cancer‡	32	36	0.201	32	35	0.190	0.01	−0.07 to 0.09
Death as a result of causes other than breast cancer‡	59	74	0.376	74	91	0.432	−0.06	−0.15 to 0.04
Death as a result of all causes	92	111	0.504	106	126	0.540	−0.04	−0.14 to 0.06

Abbreviations: non-XRT, women randomly assigned to surgery alone; XRT, women randomly assigned to radiotherapy.
*Numbers are given with number after 20 years of follow-up and total number in entire available follow-up group until December 31, 2010.
†Absolute risk difference of cumulative proportion between XRT and non-XRT group.
‡One woman excluded owing to unknown cause of death.
§XRT group, n = 96; non-XRT group, n = 103.

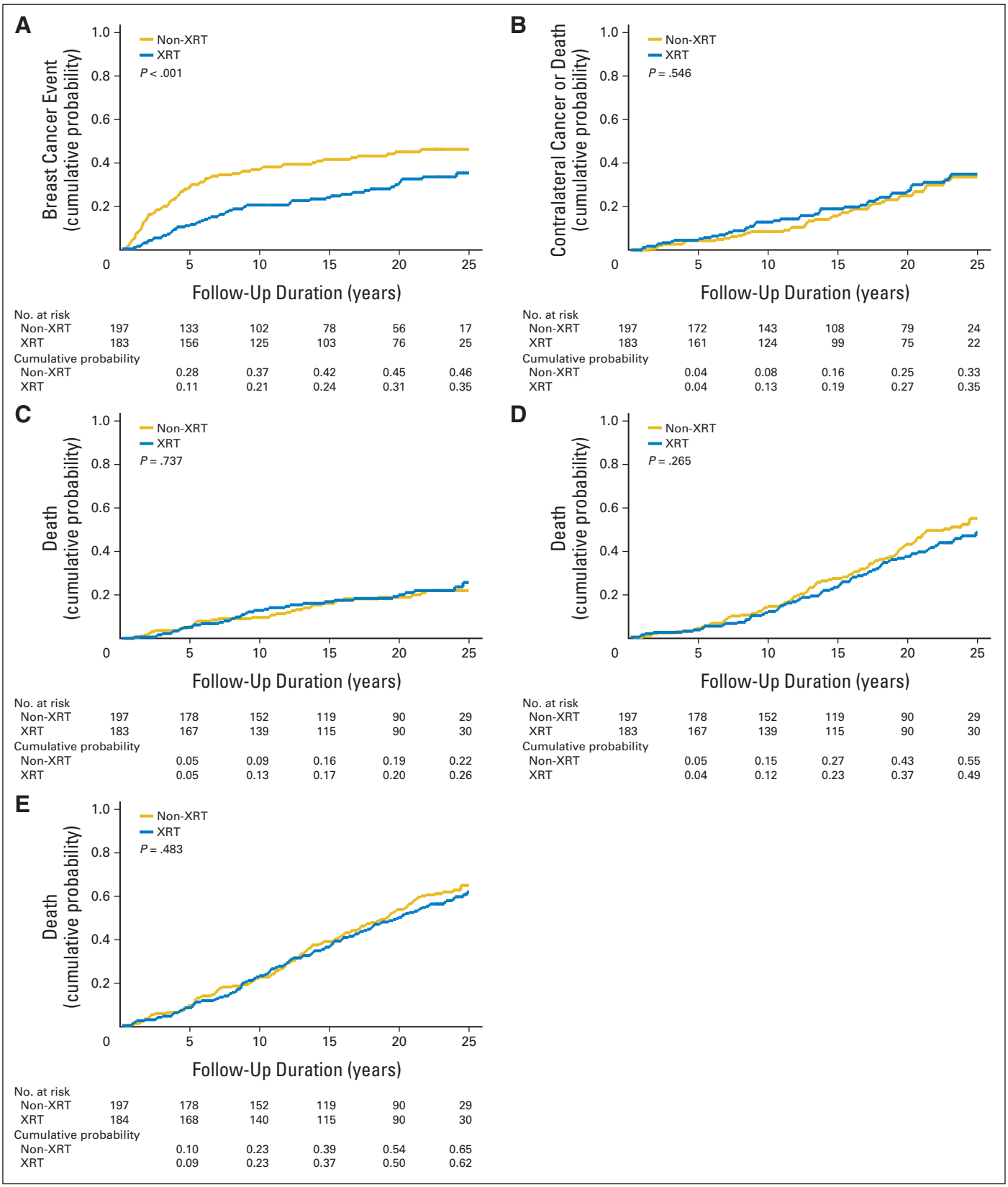

Fig 2. (A) First breast cancer event of any type; local recurrence, distant/regional metastases, or death as a result of generalized breast cancer. (B) First event of contralateral cancer or death as a result of cancers other than breast cancer. (C) Death as a result of generalized breast cancer. (D) Death as a result of causes other than breast cancer. (E) Death as a result of all causes. Numbers at bottom of each graph indicate patients at risk and cumulative probability. Non-XRT, women randomly assigned to surgery alone; XRT, women randomly assigned to radiotherapy.

Table 3. Regression Analysis of First Breast Cancer Event, Death As a Result of Generalized Breast Cancer, Death As a Result of Causes Other Than Breast Cancer, and All-Cause Mortality at 0-5 Years and ≥ 5 Years

	Total						0-5 Years						> 5 Years					
	Unadjusted			Adjusted*			Unadjusted			Adjusted*			Unadjusted			Adjusted*		
Event	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
First breast cancer event, any type; local recurrence; distant/regional metastases; or death as a result of generalized breast cancer†	0.56	0.40 to 0.79	.001	0.58	0.41 to 0.82	.002	0.35	0.21 to 0.58	< .001	0.35	0.21 to 0.59	< .001	0.93	0.56 to 1.54	.785	0.99	0.59 to 1.64	.965
Low-risk group†‡	0.60	0.34 to 1.04	.067	0.61	0.35 to 1.07	.084												
First event of contralateral cancer or death as a result of cancers other than breast cancer†	1.14	0.75 to 1.72	.546	1.17	0.77 to 1.77	.453												
Death as a result of generalized breast cancer†	1.08	0.68 to 1.72	.738	1.11	0.70 to 1.77	.654												
Death as a result of causes other than breast cancer†	0.84	0.62 to 1.14	.266	0.84	0.61 to 1.14	.254												
Death as a result of all causes	0.91	0.71 to 1.18	.483	0.92	0.71 to 1.19	.521												

Abbreviations: HR, hazard ratios; non-XRT, women randomly assigned to surgery alone; XRT, women randomly assigned to radiotherapy.
*Adjusted by study center, mode of detection (screening or not), and tumor size at mammography (≤ 10 mm or > 10 mm).
†One woman was excluded owing to unknown death cause.
‡XRT group, n = 96; non-XRT group, n = 103.

Death From Breast Cancer, Other Causes, and Overall Mortality

A total of 64 women died with breast cancer as the underlying cause of death, with 32 women in each group (XRT group: cumulative proportion, 20.1%; non-XRT group: cumulative proportion, 19.0%; absolute risk difference, 1%; 95% CI, −7% to 9%; Table 2; Fig 2C). Fifty-nine women in the XRT group (cumulative proportion at 20 years, 37.6%) and 74 women in the non-XRT group (cumulative proportion at 20 years, 43.2%) died from other causes (absolute risk difference, 6%; 95% CI, −15% to 4%; Table 2; Fig 2D). At the end of the follow-up period, 92 of 184 women in the XRT group and 106 of 197 women in the non-XRT group died. The cumulative proportion of overall mortality after 20 years was 50.4% in the XRT group and 54.0% in the non-XRT group (absolute risk difference, 3.6%; 95% CI, −14% to 6%; Table 2; Fig 2E). In the Cox regression analysis, no statistically significant difference in hazard ratios were detected (HR, 0.92; 95% CI, 0.71 to 1.19; Table 3).

Identifying a Low-Risk Population

We repeated our analysis of women older than age 55 years without comedo-type or lobular carcinomas (199 of 381women; a low risk group for local recurrence, even without radiotherapy),[10] but this time we used a first breast cancer event of any type as the event. After 20 years of follow-up, 19 events occurred in the XRT group (cumulative proportion, 24.8%) and 31 events in the non-XRT group (cumulative proportion, 36.1%; absolute risk difference, −11%; 95% CI, −20% to −2%; Table 2).

DISCUSSION

Adding postoperative radiotherapy to BCS conferred an absolute reduction of first breast cancer events by approximately 14% at 20 years, similar to the reduction rate in our study after 10 years of follow-up. The majority of cancer events, particularly in the non-XRT group, occurred during the first 5 years after primary treatment. After 5 years, the yearly rate of first breast cancer event was similar in the two treatment groups. Omission of radiotherapy in our trial neither affected breast cancer death nor overall mortality. In the subgroup of women older than 55 years who had no lobular or comedo-type carcinomas, the incidence of first breast cancer event was 11% less in the non-XRT group and 6% less in the XRT group, in absolute terms, compared with all patients in the respective groups.

We found no additional protective effect of radiotherapy against breast cancer events after 5 years of follow-up. Similar results were presented in the National Surgical Adjuvant Breast and Bowel Project B-06 trial[8] in which, in the group treated with lumpectomy alone, 73.2% of the local recurrences occurred within the first 5 years after surgery. In that trial, women received lumpectomies for tumors up to 4 cm, including patients with node-positive disease. In the group treated with lumpectomy and radiotherapy, the yearly rate of local events was more evenly distributed during follow-up.

A meta-analyses by EBCTCG[2]showed a 5.4% reduction of breast cancer mortality at 15 years attributable to postoperative radiotherapy. This benefit is partly counteracted by increased deaths from cardiovascular and lung disease.[3,5] In our trial, omission of radiotherapy did not significantly affect overall mortality, nor did we observe an increased risk of cardiovascular death after radiotherapy. Our study was not powered to further disentangle the nonsignificant excess number of deaths in the non-XRT group from cardiovascular disease and other cancers. Given the findings in the EBCTCG overview, the finding is unlikely to be because of treatment allocation. At 20 years, almost half of the women in each group were still alive, emphasizing the importance of minimizing late adverse effects among low-risk patients with early-stage disease.

In the most recent Oxford overview,[1] the absolute effects of postoperative radiotherapy on a first breast cancer event were larger in younger women than in older women. In our trial, in the subgroup of women older than 55 years who had no lobular or comedo-type carcinomas, the absolute difference in breast cancer events at 20 years was 11.0% between the groups, which is equal to a number needed to treat of nine. This is still a substantial protective effect of radiotherapy. Other studies have tried to define subgroups of older women in whom the risk of local recurrence is so low that postoperative radiotherapy can be questioned. Earlier, we showed a decreased risk of local recurrence of 3% per year of increasing age (95% CI, 1% to 6%), which corresponds to a reduction of almost 50% during 20 years of increasing age.[10] In a trial by Hughes et al,[13] which included 636 patients older than 70 years treated with lumpectomy plus tamoxifen with or without postoperative radiation, the investigators concluded that omitting postoperative radiotherapy would be an acceptable choice in older women treated with tamoxifen.

Two other randomized trials compared postoperative irradiation with surgery alone or surgery plus tamoxifen after breast-conserving surgery but did not restrict the study to older women.[13-15] Fisher et al[15] included more than 1,000 women of all ages with tumors less than 1 cm. Following lumpectomy, the women were then randomly assigned to tamoxifen, XRT, or XRT plus tamoxifen treatment. The results favored the use of XRT after surgery even in small tumors. In the trial by Fyles et al,[14] all 769 women, ages older than 50 years, received tamoxifen and their tumor size was up to 5 cm. Postoperative radiotherapy significantly reduced the risk of local recurrence. Thus, evidence does not show tamoxifen to be a universal substitute for XRT in preventing local recurrence and the trial by Hughes et al[13] has not led to general recommendations to omit XRT in higher age groups.

An increased risk of contralateral breast cancers after XRT has previously been described in a meta-analysis.[2] Our findings are compatible with the results of the meta-analysis, but our statistical power is too low to corroborate or rule out modest risks. Contralateral cancer as an adverse effect however continues to be relevant, as emphasized by a large Swedish cohort study[16] in which contralateral cancer, especially within the first 2 years after primary surgery, was associated with an increased risk of breast cancer death.

The strength of our trial is that it is population-based. Women were treated with a standardized surgical technique in routine settings—half of the women were recruited from a population-based routine mammography screening program—and with complete follow-up. Our trial was not dimensioned to study subgroups and all such analyses should be regarded as hypothesis generating.

In our trial, radiotherapy protects effectively against breast cancer events that are prone to develop during the first 5 years of follow-up. Hereafter, the yearly rate of recurrences is similar in the XRT and non-XRT groups. Thus, the protective effect of XRT seems mainly to eradicate subclinical, multifocal cancers that are undetectable by mammography and are present at the time of primary treatment. A long-term protective effect on local recurrences by sterilizing the breast parenchyma seems to be limited. The similar rate of recurrences beyond 5 years in the two groups

indicates that late recurrences are new tumors. The long-term occurrence of new tumors that may be curable has implications for follow-up. Our findings also imply that there is a possibility to find subgroups with clinically relevant differences in risk. Although we cannot reliably define a group with little benefit of XRT, the data implicate that searching for a group with modern biomarkers for either radiosensitivity or further risk stratification is of high priority.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Data analysis and interpretation: Åsa Wickberg, Lars Holmberg, Hans-Olov Adami, Anders Magnuson, Kenneth Villman, Göran Liljegren
Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

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Original article

Influence of the subtype on local recurrence risk of breast cancer with or without radiation therapy☆

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ABSTRACT

Purpose: To investigate if intrinsic subtypes of breast cancer predict different risks of ipsilateral breast tumor recurrence (IBTR) following breast-conserving surgery (BCS) with and without postoperative radiation therapy.

Patients and methods: We randomized 381 women with a unifocal T1N0M0 breast cancer to BCS alone (197 women) or BCS plus postoperative radiation therapy (XRT) (184 women). All available histopathological material was re-analyzed with modern immunohistochemical methods (223 women). After 20 years of complete follow-up we analyzed the risk of IBTR by intrinsic breast cancer subtypes (luminal A, luminal B/HER2-negative, luminal B/HER2-positive, HER2-positive and triple negative). We used Cox regression analyses to estimate hazard ratios (HR) with 95% confidence intervals (CI).

Results: In a multivariate analysis the luminal B/HER2-negative subtype, compared with the luminal A subtype, was associated with a higher risk of IBTR overall (HR 3.04; 95% CI 1.38–6.71) and in both the XRT-group (HR 5.08 95% CI 1.31–19.7) and the non-XRT-group (HR 2.58 95%CI 1.07–6.20); (p for interaction = 0.37). The risk of IBTR in the XRT- and non-XRT group, stratified by intrinsic subtype, revealed an absolute risk difference at 20 years to the benefit of XRT of 14% (95% CI 1.0%–26%) for luminal A, 17% (95% CI -6.0% to 39%) for luminal B/HER2 negative and 22% (95% CI -7.0–51%) for the high-risk group.

Conclusions: Among breast cancer patients treated with BCS, the luminal B/HER2-negative subtype predicts an about 3-fold higher risk for IBTR compared to other intrinsic subtypes independent of postoperative radiation therapy.

1. Introduction

The impact of intrinsic subtype on breast cancer recurrence has become better understood during the last 15 years. Several trials have evaluated the different subtypes and the risk of distant recurrence and lately, also ipsilateral breast tumor recurrence (IBTR) [1,2]. However, only a few trials have studied whether postoperative radiation therapy modifies the risk of IBTR among women with different subtypes [3–5]. Such information might allow for better individualized treatment [3].

In the Uppsala-Örebro-trial [6]of breast-conserving surgery with or without postoperative radiation therapy, a risk factor analysis following 10 years of follow-up revealed low age, lobular carcinoma and comedo cancer (similar to grade 3 tumors in the new classification) to independently increase the risk for IBTR. We here proceed with an analysis of the intrinsic subtypes as predictors of IBTR.

Tissue microarrays were constructed from the still available paraffin blocks and immunohistochemistry was performed. After classification into the intrinsic subtypes, we investigated if certain

☆ The study has previously been presented as a poster at The St Gallen breast cancer conference in Vienna, March 2017.

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subtypes are associated with an increased risk of IBTR, with or without radiation therapy.

2. Patients and methods

2.1. Patients

The trial design has previously been described in detail [6]. Between 1981 and 1988 we randomized 381 women ≤80 years old with a unifocal T1N0M0 invasive breast cancer to treatment with BCS alone (197 women) (non-XRT-group) or BCS with the addition of postoperative radiation therapy (184 women) (XRT-group). We used a highly standardized surgical technique to ensure radical removal of the primary cancer [7]. The axilla was dissected to levels I and II, and median number of investigated lymph nodes were seven in both groups. Radiation therapy was delivered by photons from a 4- to- 10-MV linear accelerator or a cobalt 60-unit. A total dose of 54 Gray (Gy) in 27 fractions was given at the rate of five fractions per week. No adjuvant chemotherapy or endocrine therapy was given. Baseline data of treatment groups are shown in Table 1. IBTR was defined as recurrence in the surgical field, new primary cancers in quadrants outside the surgical field, metastases in an intramammary lymph node or recurrence in the cuticular tissue. The results from the follow up have been published after 10 and 20 years [6,8] and the design of the study is illustrated in Fig. 1.

2.2. Histopathology and grade

In the 10-year publication, three histopathological types could be identified; tubule-ductal, and ductal (grouped together), comedo and lobular [6]. Tumor grade was analyzed according to the Bloom-Richardson classification system [9]. In this updated analysis with 20 years of follow-up, we retrospectively collected the paraffin blocks from the primary tumors and reclassified them into Nottingham histologic grade (NHG) [10], a modification of the Bloom-Richardson system. The reclassification was made by the same pathologist. In 51 cases the grading was not possible due to lack of material from the original paraffin blocks or poor quality of the sample obtained. In these cases we estimated the NHG using the results from the 10-year analysis [6]. Six women lacked information about histopathological grade and were excluded in this variable. One woman was diagnosed with cancer in situ at re-evaluation and was excluded in all variables (Table 1).

2.3. TMA construction and immunohistochemistry

Paraffin blocks of tissues from 270 of the 381 primary tumors were retrieved from the six participating centers. Representative areas from each tumor were punched and brought into recipient paraffin-blocks to produce TMA: s consisting of three cores (diameter 1 mm) per tumor. Three to four micro-mm thick sections were cut from the array blocks and transferred to glass slides. We stained for hormone receptors, HER2 and Ki-67 at two pathology departments according to a standardized protocol. The threshold for ER and PR to be considered positive was set to 10%. One hundred and fifty-one (40%) of the ER-values were missing and when appropriate replaced by values from the 10-year analysis (10). The same procedure was done with NHG and PR. (Table 1).

Ki-67 cut-off to discriminate between high and low proliferation was set to 20%. The decision was made after consensus among the analyzing laboratories.

Antibodies to identify the HER2/neu protein were applied to the samples and classified by one pathologist. The tumor was considered positive when more than 10% of the tumor cells showed strong membrane staining (3+) (11 tumors). Tumors exhibiting 0, 1 + or 2 + staining for HER2 protein over-expression were considered HER2 negative. The scoring was done by the same pathologist. Fluorescent in situ hybridization was not performed in our analyses. Fourteen tumors showed moderate staining (2+) and were consequently classified as HER2 negative (data not shown).

2.4. Intrinsic subtypes

For 223 of the original 381 trial participants IHC data were complete (Fig. 1). Their tumors were grouped into the intrinsic subtypes: luminal A, luminal B/HER2-negative, luminal B/HER2-positive, HER2-positive and triple negative according to the St. Gallen International Expert Consensus recommendations 2011 [11] and Swedish guidelines based on Sorlie's classification [12] (Table 2). The classification was done with respect to ER/PR-status, low/high Ki-67 and HER2-positivity- or negativity. We used NHG grade to discriminate luminal A from luminal B/HER2-negative.

Table 1
Distribution of Clinicopathological Characteristics among the original the 223 participants and baseline characteristics for tissue samples available/missing. 1 Missing values NHG n = 7, (but 223/223 have NHG status).

	Participants N = 381	Tissue sample available n = 223	Tissue samples missing n = 158	p
Treatment				
XRT-group	184 (48%)	105 (47%)	79 (50%)	
Non-XRT-group	197 (52%)	118 (53%)	79 (50%)	0.57
Age mean (SD)	60 (11)	61 (11)	60 (12)	0.48
Tumor size, mm mean (SD)	13 (4)	13 (4)	13 (4)	0.72
<11 mm	130 (34%)	73 (33%)	57 (36%)	
>11 mm	251 (66%)	150 (67%)	101 (64%)	0.50
NHG 1[1]	126 (34%)	76 (34%)	50 (33%)	
2	164 (44%)	99 (44%)	65 (43%)	
3	84 (22%)	48 (22%)	36 (24%)	0.87
Histopathology				
ductal	353 (93%)	206 (92%)	147 (94%)	
lobular	23 (6%)	13 (6%)	10 (6%)	
other	4 (1%)	4 (2%)	0	0.32
Intrinsic subtypes				
Luminal A		130 (58%)		
Luminal B HER2 negative		57 (26%)		
Luminal B HER2 positive		6 (3%)		
HER2 positive		5 (2%)		
Triple negative		25 (11%)		

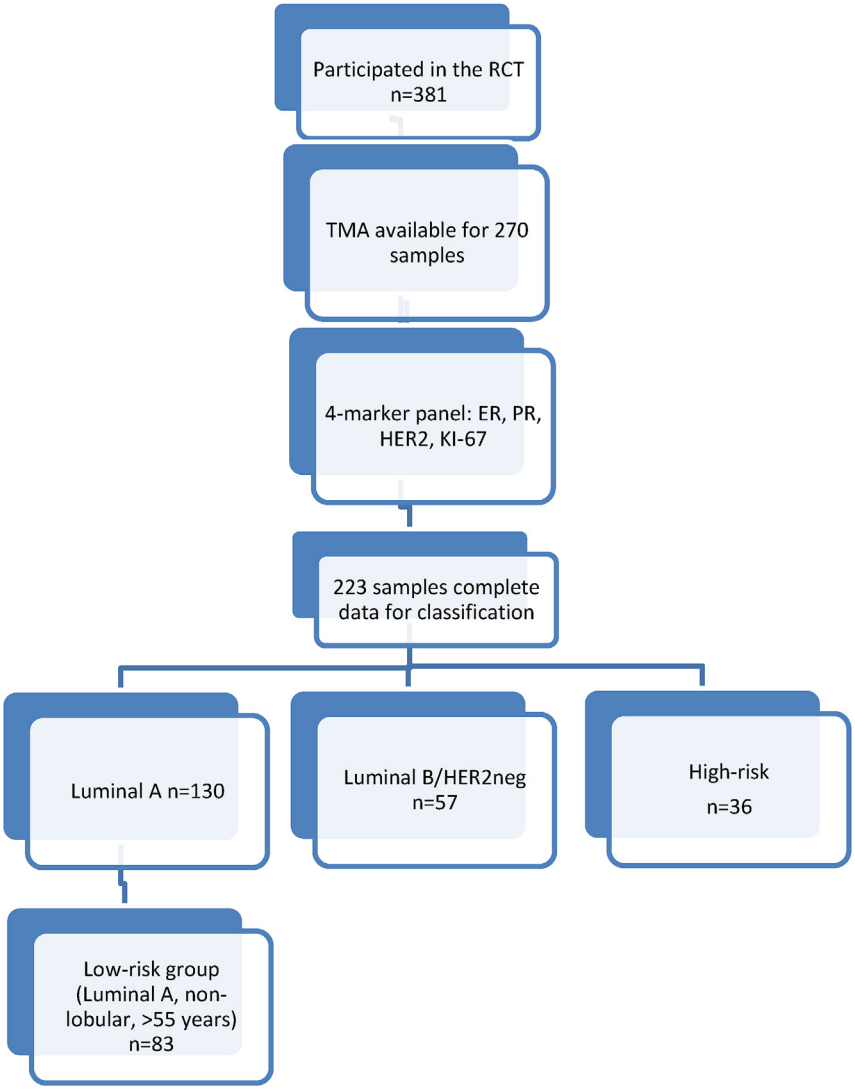

Fig. 1. Participant flow sheet. From the 381 participants in the original trial, tissue samples were available from 270 patients. TMA's were constructed and immunohistochemistry performed. 223 samples showed complete information (ER, PR, HER2, Ki-67, NHG) for classification in the intrinsic subgroups. The specific numbers of patient samples in each subtype is shown along with the low-risk group.

Table 2
Classification in the intrinsic subtypes – how it was done.

	estrogen receptor	progesterone receptor	human epidermal growth factor receptor 2 (HER2)	Ki-67	NHG
Luminal A	+	+	–	low	
Luminal B/HER2-neg	+	- or low[a]	–	high[a]	grade 3[a]
Luminal B/HER2-pos	+	+ or -	+	high or low	any grade
HER2-pos	–	–	+	high or low	any grade
Triple negative	–	–	–	high or low	any grade

[a] One or more.

2.5. Statistics

We stratified women into those treated with XRT or not, because the benefit from XRT has already been documented [6].

We used unpaired *t*-test (continuous variables) and chi-2 test (categorical variables) or Fischer's exact test when appropriate, to compare patient and clinical characteristics between patients with and without available tissue samples.

We analyzed the intrinsic subtypes as potential prognostic variables for time to IBTR using Cox regression. All 381 study participants were followed up until 20 years after diagnosis except for four women who were censored at emigration without IBTR. One of

Table 3
Regression analysis for patient characteristics, outcome: **IBTR,** n = 223. 1 Non estimatable. 2 If not adjusted by NHG then luminal B/HER2 negative HR = 3.03 (95%CI 1.50–6.14) and high-risk HR = 1.73 (95%CI 0.75–3.95) compared to luminal A.

			Unadjusted		Adjusted for age and XRT		Adjusted for all variables	
	n	events	HR	95% CI	HR	95% CI	HR	95% CI
Treatment								
XRT	105	13	0.41	0.21–0.78	0.39	0.20–0.75	0.36	0.18–0.70
Non-XRT	118	32	Ref.		Ref.		Ref.	
Luminal A	130	22	Ref.		Ref.		Ref. [2]	
Luminal B HER2 negative	57	15	1.77	0.92–3.42	2.53	1.28–5.03	3.04	1.38–6.71
High-risk	36	8	1.48	0.66–3.32	1.43	0.62–3.28	1.67	0.57–4.85
	Interaction tests, luminal status and XRT							
			Unadjusted		Adjusted for age		Adjusted for all variables	
	n	events	HR	95% CI	HR	95% CI	HR	95% CI
Among non-XRT	118	32						
Luminal A	75	17	Ref.		Ref.		Ref.	
Luminal B HER2 negative	29	10	1.71	0.78–3.73	2.23	1.00–4.98	2.58	1.07–6.20
High-risk	14	5	2.03	0.75–5.51	1.52	0.56–4.15	1.66	0.48–5.69
Among XRT	105	13						
Luminal A	55	5	Ref.		Ref.		Ref.	
Luminal B/HER2 negative	28	5	2.31	0.67–7.98	3.56	1.00–12.6	5.08	1.31–19.7
High-risk	22	3	1.62	0.39–6.79	1.37	0.32–5.79	1.91	0.40–9.21
Interaction test XRT*luminal B HER2 negative			P = 0.69		P = 0.53		P = 0.37	
Interaction test XRT*High-risk			P = 0.80		P = 0.91		P = 0.88	

these women, who moved abroad was reached by letter and was followed until 1997. We further adjusted for the following prognostic variables; tumor size on continuous scale, lobular (yes/no) and NHG. Because NHG status was partly incorporated in the intrinsic subtypes (separating luminal A from luminal B/HER2 negative), HRs were calculated with and without adjusting for NHG.

The intrinsic subtypes and XRT treatment were further evaluated in an interaction test. None of the independent variables showed evidence of non-proportional hazards, tested by phtest [13] in STATA using the Schoenfeld residuals. The association measure was hazard ratio (HR) with 95% confidence intervals (CI) and the significance level was set to 5%. We used Kaplan-Meier method with a log-rank test to visualize the unadjusted cumulative risk of IBTR.

We also calculated the absolute risks of IBTR at 20 years of follow up and estimated risk differences unadjusted and adjusted for age, over and under 55 years, with 95% CI between XRT and non-XRT groups combined with intrinsic subtypes using binomial regression with identity link. Only adjustment for age over and under 55 years was possible due to the low number of events.

All statistical analyses were performed with STATA release 14 (Stata Corp, College station, TX) or SPSS version 22 (IBM, Armonk, NY).

3. Results

3.1. Descriptive characteristics

Three hundred and eighty-nine women entered the study but eight were excluded due to ineligibility. One hundred and eighty-four women were randomized to postoperative radiation therapy and 197 women to surgery alone. Two hundred and seventy out of three hundred and eighty-one tissue samples were available for TMA construction and 230 samples were possible to analyze. We compared the baseline data in the group where the tissue samples were missing with the group where the tissue samples were available and found no major differences (Table 1).

Two hundred and twenty-three tumors had complete data in all four biomarkers including NHG status. One hundred and thirty tumors were classified as luminal A and they were all ER/PR positive, NHG 1 or 2 with low proliferation. Fifty-seven tumors were classified as luminal B/HER2-negative of which 24 tumors graded as NHG 3. Eighteen of these 24 tumors had low Ki-67 and were PR-positive. These tumors might have been classified as luminal A tumors if the NHG component had not been considered. Eleven tumors were classified as HER2-positive and 25 tumors were triple negative.

3.2. Cumulative incidence of IBTR

When we calculated the cumulative incidence of IBTR in each subgroup, HER2-positive and triple negative tumors were grouped together (high-risk group) due to low number of events (Table 3, Fig. 2A–C). Cumulative incidence of IBTR in the luminal A group at 20 years was 25% (95% CI 16%–38%) in the non-XRT group and 11% (95% CI 5%–25%) in the XRT group. In the luminal B/HER2-negative group the cumulative incidence of IBTR at 20 years was 41% (95% CI 24%–64%) in the non-XRT group and 25% (95% CI 11%–53%) in the XRT group. Cumulative incidence of IBTR in the high-risk group at 20 years was 41% (95% CI 18%–74%) in the non-XRT group and 18% (95% CI 6%–48%) in the XRT group.

3.3. Regression analysis and absolute risks of IBTR

In multivariate regression analysis by intrinsic subtype with luminal A tumors as a reference, the HR of IBTR was higher among luminal B/HER2-negative cancers overall (HR 3.04 95% CI 1.38–6.71) and both with (HR 2.58 95% CI 1.07–6.20) and without XRT (HR 5.08 95% CI 1.31–19.7) (Table 3). The risk of IBTR in the XRT- and non-XRT group, stratified by intrinsic subtype, revealed an absolute risk difference at 20 years to the benefit of XRT of 14%

(95% CI 1.0%–26%) for luminal A, 17% (95% CI -6.0% to 39%) for luminal B/HER2 negative and 22% (95% CI -7.0–51%) for the high-risk group. Following adjustment for age over or under 55 years the difference for luminal A was not statistically significant (Table 4 and Fig. 2A–C).

We used interaction test to evaluate if the risk of IBTR with or without adjuvant radiation therapy differed in the intrinsic subtypes, but no interaction was found (Table 3).

3.4. Low-risk group

In the postulated low-risk group (luminal A tumors, ≥55 years old, without lobular cancer, n = 83) the absolute risk of IBTR was 13% (95% CI 6.8%–23%) overall; 8.8% (95%CI 1.9%–24%) in the XRT-group (n = 34) and 16% (95% CI 7.3%–30%) in the non-XRT-group (n = 49). Log rank test revealed no statistical difference between the XRT and non-XRT group (p = 0.27); absolute risk difference 7.5% (95% CI -6.6% to 21.6%). Cumulative incidence of IBTR at 20 years was 12% (95% CI 4%–34%) in the XRT group and 21% (95% CI 10%–39%) in the non-XRT group (Fig. 3).

4. Discussion

In this randomized trial luminal B/HER2-negative subtype entailed an about 3-fold higher risk of IBTR than the luminal A subtype. This excess risk was not significantly modified by post-operative radiation therapy although the statistical power for the interaction analysis was limited.

While most previous studies have investigated the difference between adjuvant XRT and XRT plus endocrine therapy, the Uppsala-Örebro trial [6] is unique because half of the study participants were treated with surgery alone and none received adjuvant endocrine- or chemotherapy at the time of their primary treatment. The higher risk of IBTR in the luminal B/HER2-negative- and high-risk group compared to the luminal A group, would possibly have been reduced if systemic therapy had been given. Adjuvant systemic therapy is nowadays routine praxis and contributes to the reduced incidence of IBTR in the absence of radiation therapy.

Other strengths include the randomized design and the complete long term follow-up.

A limitation of our study is loss of tissue samples due to use of archival material which reduced statistical precision and hampered in particular our interaction analyses. Moreover, tumors exhibiting 2 + staining for HER2 protein overexpression should ideally have been analyzed by fluorescent-in situ hybridization. However, the lack of these analyses should not influence the results of our analyses because the total number of HER2 2 + was small. The combination of old and modern biochemical analysis may contribute to misclassification, which cross tabulation suggests would be non-differential (Table 1).

The classification into intrinsic subtypes is an approximation of genotype-based subtypes, still used in clinical practice at many centers, and accepted at the 13th St Gallen International Breast Cancer Conference [14]five years ago. The Swedish guidelines based on Sorlie's classification [12], is taking NHG into account, and our classification of intrinsic subtypes accommodated these recommendations. The strong prognostic value of NHG has further been confirmed by a multidisciplinary group of American clinicians, pathologists, and statisticians [15]and in a trial by Ehinger et al. [16]. However, gene expression tests might be more precise to predict breast cancer recurrence [12,17,18].

The potential of the luminal B/HER2-negative subtype as a risk factor for breast cancer recurrence has been investigated in several studies [19–21] but little is known about whether this risk is modified by adjuvant radiation therapy.

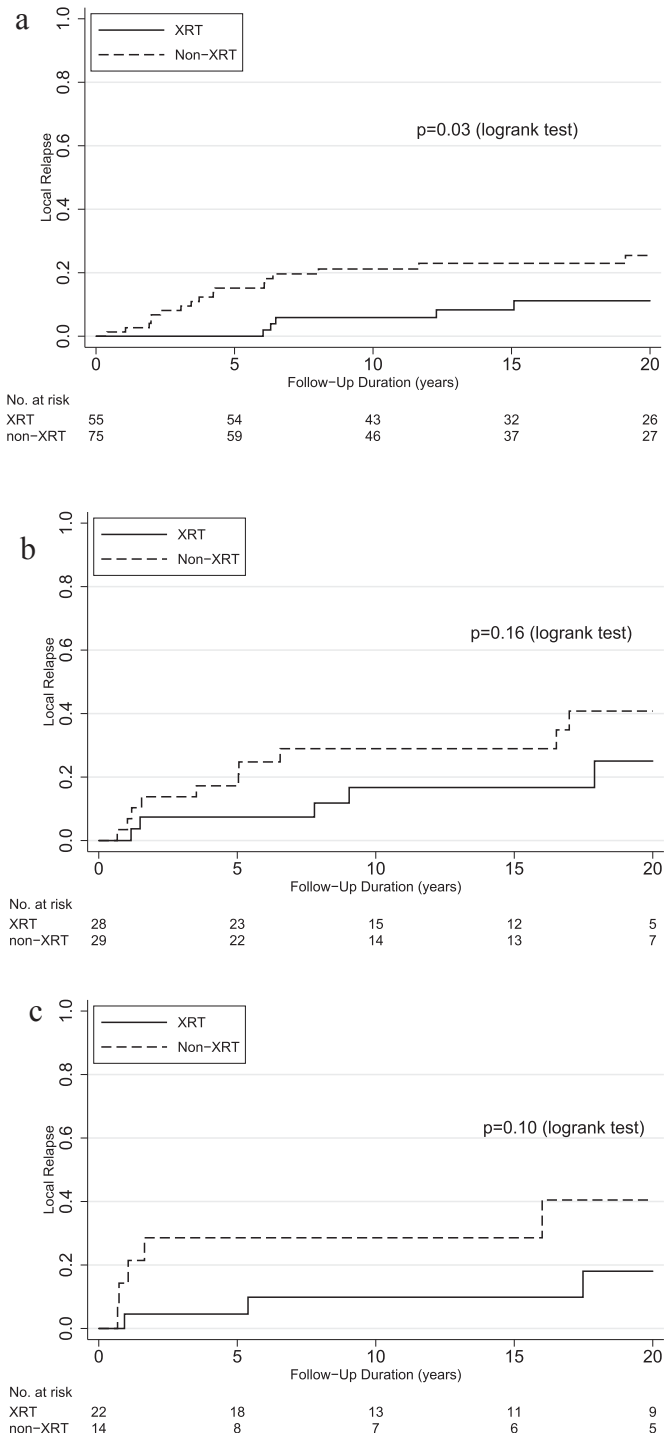

Fig. 2. A-C. Cumulative incidence of ipsilateral breast tumor recurrence for (fig. A) luminal A, (fig. B) luminal B/HER2 negative, and (fig. C) luminal B/HER2 positive, HER2 positive and triple-negative tumors. XRT; radiation therapy.

The absolute risk differences between the XRT and non-XRT group are clinically relevant for each intrinsic subtype judging by the point estimates. However, the results were statistically significant only for the luminal A group, but in all groups the point estimates had the same order of magnitude, suggesting that the difference in level of significance is a power issue rather than a qualitative difference. This is further borne out by the lack of

Table 4
The 223 tumors separated in intrinsic subtypes/XRT- and non-XRT-group calculating absolute risk with respect to IBTR (ipsilateral breast tumor recurrence). The risk difference were calculated using binominal regression unadjusted and adjusted for age <55, >55 years.

N = 223						
	N	Age distribution >55 years	Events (IBTR)	Absolute risk (95% CI)	Absolute Risk difference (95% CI) Unadjusted	Absolute Risk difference (95% CI) Adjusted for age <55, >55 years
N = 223:						
XRT	105	71%	13	0.12 (0.07–0.20)	Ref	Ref
Non-XRT	118	68%	32	0.27 (0.19–0.36)	0.15 (0.04–0.25)	0.14 (0.04–0.24)
Luminal A						
XRT	55	65%	5	0.09 (0.03–0.20)	Ref	Ref
Non-XRT	75	69%	17	0.23 (0.14–0.34)	0.14 (0.01–0.26)	0.11 (−0.01 to 0.23)
Lum B/HER2-neg						
XRT	28	89%	5	0.18 (0.06–0.37)	Ref	Ref
Non-XRT	29	79%	10	0.34 (0.18–0.54)	0.17 (−0.06 to 0.39)	0.16 (−0.05 to 0.38)
High-risk						
XRT	22	64%	3	0.14 (0.03–0.35)	Ref	Ref
Non-XRT	14	36%	5	0.36 (0.13–0.65)	0.22 (−0.07 to 0.51)	0.23 (−0.02 to 0.48)

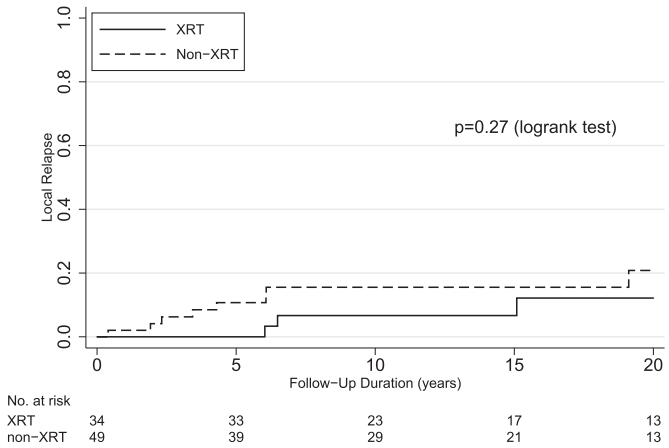

Fig. 3. Cumulative incidence of ipsilateral breast tumor recurrence for low-risk-group; (luminal A, >55 years, non-lobular). N = 83.

significance of the interaction test. Our analyses of the absolute risk differences were adjusted for age because, especially in the high-risk group, the numbers of study participants over and under 55 years were unevenly distributed (Table 4). However, the estimates did not change tangibly.

Two recently published randomized trials investigated the different subtypes' benefit from adjuvant radiation therapy and tried to define a low-risk group [4,5]. In both these trials the primary objective was to define intrinsic subtyping as a predictive biomarker of the benefit of radiation therapy. Liu et al. [4]randomly assigned 769 patients to adjuvant tamoxifen plus breast radiation therapy or to adjuvant tamoxifen alone with a median follow-up of ten years. The authors found intrinsic subtyping to be prognostic for IBTR. Luminal A and luminal B subtypes seemed to benefit less from radiotherapy, but a subtype-treatment interaction test showed no significant difference between the subtypes. Sjöström et al. [5] found results similar to ours in a cohort of 958 women with a median follow-up of 15–20 years. They analyzed the “high-risk group” separated in HER2-positive tumors and triple-negative tumors where the former was found to benefit less from radiation therapy. Our analyses identified the same prognostic pattern of risk for IBTR but did not have the power to answer the question whether the risk of IBTR differed between the intrinsic subtypes with or without adjuvant radiation therapy.

We tried to define a subgroup based on clinical and pathological risk factors identified after the 10-year follow-up. These risk factors were combined with the luminal A subtype. After 20 years of follow-up the difference in absolute risk of IBTR between the XRT and the non-XRT-group was halved compared to all patients. The trials by Liu and Sjöström [4,5] performed similar subgroup analyses. Only Sjöström found that the low-risk group benefited from radiation therapy. These conflicting results are most likely due to lack of power and stresses the need for additional large trials of this type or to merge data from randomized trials into a meta-analysis.

In conclusion the luminal B/HER2 negative subtype seem to be prognostic for the risk of IBTR. However we could not confirm that any subtype would respond better to radiation therapy nor identify a subgroup where XRT can be safely omitted.

Our findings may contribute to understanding the associations between intrinsic subtypes and clinical outcomes but calls for further research to understand the risk of IBTR for the different intrinsic subtypes with or without adjuvant radiation therapy.

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Disclaimers

Conflict of interest statement: The authors declare no conflicts of interest with regard to personal or financial relationships with other persons or organizations.

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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.

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

☆ The study has previously been presented as a poster at the breast cancer conference in San Antonio, December 2016.

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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.

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.

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 overexpression 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.

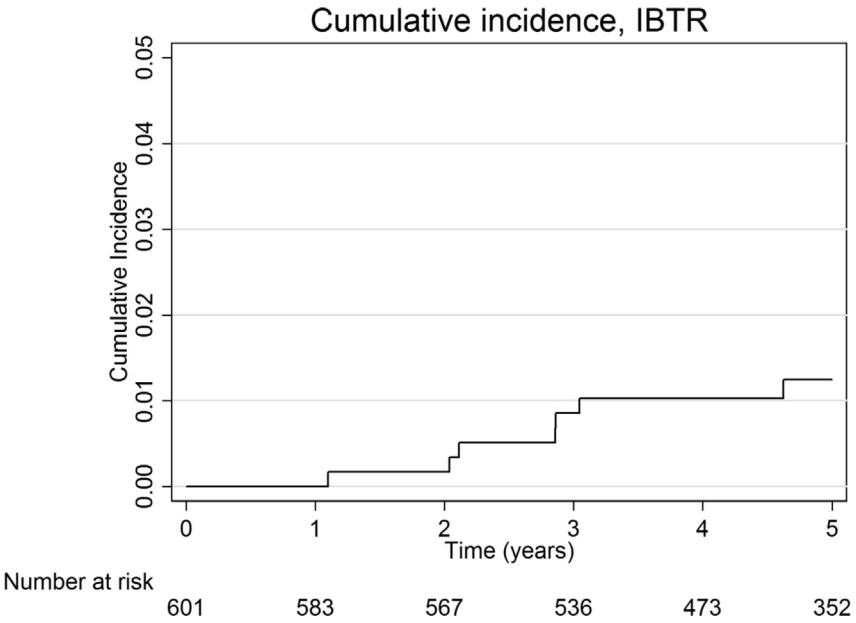

Fig. 1. Cumulative incidence of IBTR at 5 years of follow-up: 1.2% (95% CI 0.6–2.5%). Competing risk; regional recurrence, distant metastases, other types of cancers, deaths.

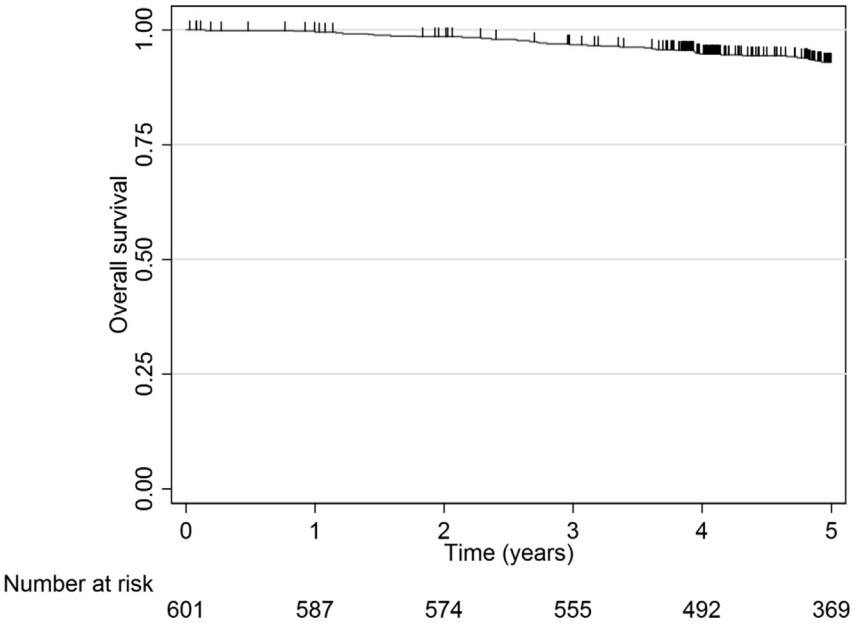

Fig. 2. Five-year overall survival (hash marks indicate censored data): 93.0% (95% CI 90.5–94.9%).

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

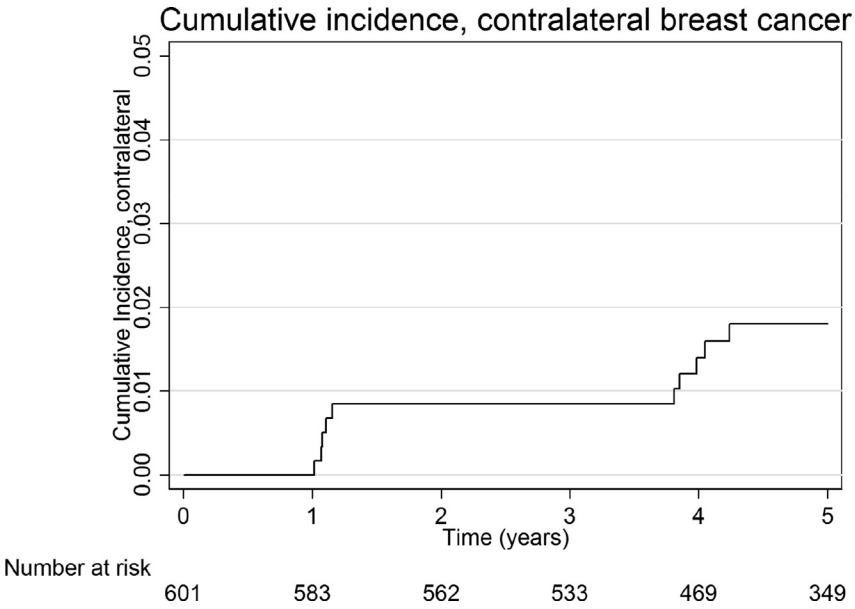

Fig. 3. Cumulative incidence of contralateral cancer at five-year of follow-up. 1.8% (95% CI 0.9–3.2%). Competing risk; regional recurrence, distant metastases, other types of cancers, deaths.

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 ≥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 mammilla. 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 organisations, 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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Intraoperative high dose rate brachytherapy during breast-conserving surgery -a prospective pilot study

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Abstract

Purpose
To evaluate feasibility, patient´s satisfaction, toxicity and cosmetic outcome for intraoperative breast cancer brachytherapy (IOBT) after breast-conserving surgery (BCS) using high does rate (HDR) therapy.

Methods and materials
Fifty-two consecutive women, ≥50 years old, diagnosed with a unifocal non-lobular breast cancer ≤3cm, N0, underwent BCS and sentinel node biopsy. Twenty-five women received IORT prepathology at primary surgery, and the others post-pathology, during a second procedure. A new applicator, connected to HDR equipment was used. Two of the women were excluded due to metastases found per-operatively at a frozen section from the sentinel node. Quality of life was evaluated using two validated health questionnaires. Treatment toxicity was documented according to the LENT-SOMA scale by two oncologists. The cosmetic result was evaluated using the validated software BCCT. Core 2.0.

Results
The clinical procedure worked out well logistically. Seven women received supplementary external radiotherapy due to insufficient margins and, in one case, poor adaptation of the breast parenchyma to the applicator. No serious adverse effects from irradiation were registered. The results from the health questionnaires showed no differences compared with reference groups from the Swedish population. Only two women were registered as having a "poor" cosmetic result while a majority of the women had a "good" outcome.

Conclusion
This pilot study shows that IOBT is a feasible procedure and encourages further trials evaluating its role in treatment of early breast cancer.

Introduction

Breast cancer is the most common type of cancer among women in Sweden and nowadays a majority of women is treated with breast-conserving surgery (BCS)[1]. The benefit of postoperative radiotherapy to the remaining breast tissue is well established in several randomized trials and in a large metaanalysis from Early Breast Cancer Trialists´Collaborative Group (EBCTG) [2]. Conventional external radiotherapy is delivered at a dose of 40-50 G y over 3-5 weeks postoperatively. In order to avoid the prolonged treatment and, for some patients, excessive travel time to the hospital, some women choose a mastectomy [3,4]. Moreover, screening programs and increased public awareness have led to earlier diagnosis, with many early and small tumors diagnosed. Using existing treatment routines may result in overtreatment of some of these breast tumors, which perhaps never would have been of any clinical importance.

At the latest St. Gallen-meeting in Vienna 2017, the issue of escalating/de-escalating breast cancer treatment was highlighted [5]. The panel suggested that partial breast irradiation (PBI) may be considered for a low-risk group of tumors defined by the American Society for Radiation Oncology, ASTRO [6] and the Breast Cancer Working Group of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) [7], especially when endocrine therapy is prescribed. In brief, this low-risk group would include women age ≥50-60 years with non-lobular T1 –T2 N0 tumors, even if the selection criteria differ between different national societies[8].

Since early local recurrences after BCS most commonly occur in the near vicinity of the primary tumor [9,10], it seems logical to concentrate radiotherapy to this volume of the breast parenchyma.. In the TARGIT-A trial [11] women with early breast cancer who underwent BCS were randomized to receive conventional external beam radiotherapy (EBRT) or intraoperative radiotherapy (IORT) using the Intrabeam® system. Feasibility and safety were reported after a median follow-up of 29 months. The treatment was well tolerated [8]. The estimated 5-year risk for local recurrence for the IORT group was 3.3% and 1.3% for the EBRT group, and so the pre-defined non-inferiority margin of a 2.5% increase was not reached. IORT concurrently with BCS (pre-pathology group) showed the same results (2.1% versus 1.1%) while with delayed IORT (post-pathology group), the difference between the groups were larger (5.4% versus 1.7%). The authors concluded that IORT should be considered as an option for carefully selected patients.

Partial breast irradiation (PBI) after BCS, as an alternative to conventional external radiotherapy, may be delivered in different forms. Pulse dose rate brachytherapy (PDR), is already in use at the University Hospital of Örebro and a previous clinical trial show promising outcomes after a median follow-up of 7 years [12]. PBI has also been delivered using a balloon device [13]. Intraoperative brachytherapy (IOBT) is in use in many countries all over the world, but so far no attempt has been made to implement this technique in Sweden. The breast team at the University Hospital of Örebro has taken advantage of the opportunity to use a novel brachytherapy applicator connected to a high dose rate afterloading machine (HDR) to treat 50 women with early breast cancer in a pilot study. Primary end-points were feasibility, treatment side-effects and expenses. Secondary end-points were patient´s satisfaction and quality of life, evaluated by two health questionnaires. We also evaluated the cosmetic outcome.

Methods and materials

Patients

The study was performed at the University Hospital of Örebro, Sweden. Fifty-two consecutive women, ≥50 years old, diagnosed with breast cancer who underwent breast-conserving surgery, were included. Written informed consent was obtained. Two of the women were excluded due to metastases found per-operatively at a frozen section from the sentinel node. All of the remaining women had a mammographically unifocal breast cancer, ≤30 mm and an axilla free from metastases. Patients with lobular cancer either on the preoperative biopsy or at final histopathological report were excluded. Patients with positive margins at the final histopathological report or extensive ductal cancer in situ, received conventional external beam radiotherapy as a complement to IOBT. Patients, tumors and treatment characteristics are shown in table 1.

Radiotherapy

HDR brachytherapy has for a long time been used for the treatment of prostatic- and gynecological cancer. The current isotope is Iridium 192, which is the most commonly used isotope for HDR brachytherapy applications. A reusable applicator of a plastic material, PEEK®, shaped according to the anisotropic radiation dose distribution was developed. The applicator was attached to a pole approved to be connected to a MicroSelectron® HDR machine (Elekta AB, Stockholm, Sweden). Four sets of applicators with a diameter of 25, 30, 35, 40 and 50 mm respectively, were constructed. A single dose of 20 Gy, prescribed at the applicator surface was delivered in the wound cavity. The dose fall from the applicator surface varied due to the diameter of the applicator (table 2). A hospital physicist calculated the treatment time from a dose-plan library depending on source strength and applicator dimension.

Using the pre-treatment CT study and the computer software Oncentra Brachy® (Elekta AB Stockholm, Sweden), the volume of the shell outside the applicator, enclosed by the 10 Gy-isodose, was determined. Air cavities inside this shell were outlined and their volumes were calculated as a measure of the tissue adaption to the applicator.

Clinical procedure

Twenty-five women were treated with IOBT during the primary surgery (pre-pathology group) and 25 women had IOBT during a secondary procedure, a few weeks after primary surgery when the full pathological report was known (post-pathology group). All IOBT-procedures took place at the department of brachytherapy.

In the operating room, wide local excision of the primary tumor and a sentinel node biopsy was carried out. Applicators of different sizes were tried out until the one that best fitted into the wound cavity was found. Two to four sutures were used to approximate the breast parenchyma to the applicator surface. A surgical gauze was inserted subcutaneously in order to protect the skin by creating a distance to the applicator. Local anesthesia with long duration was infiltrated around the surgical cavity. After bandaging, the patient was taken to the postoperative ward and shortly after that was transported to the department of brachytherapy. Before the start of brachytherapy, a CT-scan of the thorax was performed to visualize the applicator´s adaption to the parenchyma in the breast cavity. The patients were fully awake when transported from the postoperative care unit for the IOBT procedure. The applicator was then removed, the breast parenchyma adapted and the wound was closed. When receiving the IOBT during a secondary session, the whole procedure took place at the department of

brachytherapy. The wound was reopened under local anesthesia and the remaining procedure was the same as described above.

Follow-up

The women were followed-up with a clinical control which included filling in health questionnaires (EORTC-QLQ-C30[14] and EQ-5D, (see appendix) and photographing of the breasts, at 2-4 weeks and 6 months postoperatively and then annually.

Treatment toxicity

Classification and grading of surgical and radiation side effects were documented according to the LENT (late effects to normal tissue)-SOMA (Subjective, Objective, Management and Analytical evaluation of injury) scale subjectively by two oncologists [15] [16]. Symptoms were graded at a scale from 0-5 with the higher value the worse the outcome. Breast edema was defined as a swelling with an increased volume of the treated breast, either asymptomatic or symptomatic. Fibrosis was detected by palpation of the treated breast in comparison with the untreated side. The highest detectable grade of fibrosis in any quadrant of the breast was set as the final grade. Retraction and atrophy of the treated breast were defined as volume loss due to radiotherapy and surgery.

Quality of life

Patient´s satisfaction and quality of life after treatment were assessed by two health questionnaires – EQ-5D-3L and the European Organization for Research and Treatment of Cancer (EORTC) score 30item quality of life questionnaire QLQ-C30.

EQ-5D-3L, 3-level EuroQoL group's 5-dimension questionnaire, is a generic instrument for health outcome assessment [17]. It contains five dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension comprises three levels; no problems, some or moderate problems, and severe problems (see APPENDIX). In addition, the patient is asked to indicate her health on a scale called the EQ VAS (visual analogue scale). As a measure of health of the study group, the EQ-5D-3L scores were compared with the scores from the 1996-1997 Survey of Living Conditions, with a representative sample (16-84 years) of the Swedish population (n=11 698)[18].

EORTC-QLQ-C30 is an integrated system for assessing the health-related quality of life of cancer patients participating in clinical trials [19]. We used the latest version 3[20]. The EORTC-QLQ-C30 has been developed for several types of cancers, including a specific questionnaire for breast cancer (QLQ-BR23). Since this version includes several systemic therapy side effects such as hair loss, neurological symptom not applicable to our study group, we decided to use the general version consisting of 30 labels. This questionnaire evaluates five functional scales (physical, role, cognitive, emotional and social), four symptom scales (fatigue, nausea, appetite and pain), five single items (constipation, diarrhea, sleep, dyspnea, financial) and a global health scale. The scoring of the EORTC QLQ-C30 was performed according to the EORTC scoring manual [21]. All scores were linearly transformed to a 0 to 100 scale. A high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high quality of life, but a high score for a symptom scale / item represents a high level of symptomatology / problem.

Our results were compared to reference values for the EORTC QLQ-C30 in the Swedish population[22].

Cosmetic outcome

To evaluate the cosmetic outcome we used an objective assessment tool. Frontal digital photographs were taken 2-4 weeks, 6 months and then annually after surgery. The photographs were analyzed by BCCT. core 2.0, a validated software which produces a composite score based on symmetry, color and scar. Forty-eight patients were assessed one year after surgery. The scores were categorized into Excellent (E), Good (G), Fair (F) or Poor (P).

Statistics

We estimated a pilot trial of 50 women to be sufficient to implement the new procedure and to evaluate potential flaws. Data from the QLQ-C30 health questionnaire were analyzed using Statistical Package for Social Science (SPSS)-Version 22, IBM, Armonk, NY. All the scores from the QLQ-C30 health questionnaire were linearly transformed into a 0-100 scale according to the manual. The data were continuous and presented in mean, range and standard deviation. Differences in mean values for the women in the study at one-year of follow-up were compared to the reference values of the Swedish population (see table 4.)

We used unpaired t-test to compare the continuous QLQ-C30 scores. Fisher´s exact test was used to compare the categorical EQ-5D-3L proportions of the study group with reference values from the Swedish population [18,22]. The unpaired t-test analyses were performed with STATA release 14 (Stata Corp, College station, TX) and Fisher´s exact test with SPSS version 22. In order to evaluate the effect size, Cohen´s d was calculated for every difference in mean between the groups [23]. According to this concept a low Cohen's d indicates the necessity of larger sample sizes, and vice versa. “Low” are values <0.2, “moderate” are values around 0.5 and “high” are values >0.5.

The study was approved by the Regional ethics committee, Uppsala, Sweden, Dnr 2013/028.

Results

Feasibility

The clinical procedure worked out well logistically, both pre- and post-pathologically. Of the original 52 women, two were excluded due to metastases in the sentinel node, found peroperatively. Two women who received IOBT in a second procedure felt uncomfortable while positioning the applicator. One woman reacted with hypotension and nausea after administration of local anesthesia. A few women needed an extra injection of local anesthesia when closing the wound. In the post-pathology group one woman had a CT-scan were the applicator turned out to be separated from the breast parenchyma, due to a large wound cavity and difficulties to mobilize the tissue. This woman had conventional external beam radiotherapy instead of IOBT.

Six women in the pre-pathology group received additional external radiotherapy due to the final histopathology report. In all six cases the in situ component presented with insufficient or indistinct margins.

Mean total surgical duration (time in operating room + IOBT time + time for wound-closure) for the pre-pathology procedure was 75 minutes and for the post-pathology procedure (time to re-open the wound and place the applicator + IOBT time + time for wound-closure) 38 minutes. Mean time in the operating room for the pre-pathology group was 62 minutes.

The one-off cost for developing the applicators was 30 000 €. The cost for treating one woman with IOBT was 1950 €, which can be compared with a 3-weeks treatment of conventional external radiotherapy (15 sessions) - 5330 € or a 5-weeks treatment (25 sessions) – 7640 €, which are the costs according to the Örebro University hospital´s 2017 price list.

Treatment toxicity

Few acute side effects were recorded at the initial follow-up visits. According to the LENT-SOMA scale, 11 women had no symptoms at all at 2-4 weeks and 37 women had mild (grade 1-2) side effects. Among the women who underwent complementary external radiotherapy, one was diagnosed with a radiotherapy-related breast edema 2-4 weeks after treatment. The condition was successfully treated with cortisone. Three women had a wound infection, which in two cases needed antibiotic treatment. One of these women had a wound infection (treated with antibiotic) three months postoperatively. The woman with poor adaption of breast parenchyma, who received external radiotherapy instead of IORT, was missing in this first follow-up but not excluded. At the 6 and 12 months visit most of the grade 1-2 side effects had resolved and all the women had a satisfactory outcome (data not shown).

Quality of life

The one-year results from the EORTC-QLQ-C30 health questionnaires are illustrated in table 3. The numbers of missing items were low. At one-year of follow-up scores from three women were missing. For one additional woman three items from the scale were missing and for another woman two items. Four additional women missed one item each. Almost all missing items differed from each other, thus biasing should not be a matter of concern. Overall the women in the study reported a high score on the functional scales and quality of life and a low score on the symptomatic scales. The outcome was compared to a subgroup of women 60-69 years old in a random sample of adults from the Swedish population (table 4) [22]. Concerning global health and functional scales the women in our study scored higher than the reference population, but the difference showed statistical significance only for "cognitive functioning" (table 5). The study participants also reported a higher frequency of fatigue, insomnia and appetite loss. The unpaired t-test showed statistically significant differences in the "appetite loss", "pain" and "financial difficulties" parameters (table 5). Cohen´s d was low for almost all mean differences which indicates that larger samples are needed,

The EQ-5D analysis revealed for the study group better score on the EQ VAS (table 6). Fisher´s exact test showed no significant difference between the groups (p=0.22).

Cosmetic outcome

We decided to present the cosmetic results after one year when the wound and possible wound infections were healed. One woman was excluded due to an incomplete photographing at the one-year control. Another woman was diagnosed with subcutaneous metastases after one year and therefore was excluded. The woman with a large wound cavity described earlier did not receive IOBT due to poor adaption of the breast tissue to the applicator. She was still assessed in IOBT group according to the intention-to-treat concept and was assessed with "good" in the BCCT software. The pre-pathology group and the post-pathology group turned out to be evenly distributed among the five categories. The evaluation program reported "good" results in 14 women in the pre-pathology group and in 11 women in the post-pathology group (table 7). Only one woman in each group was registered as having "poor" cosmetic result.

CT scan results

The median of the air proportion inside the 10 Gy-shell were, for the pre- and post-pathology groups 0.9% and 1.2% respectively. The median value for the size of the applicator in the pre-pathology- and post-pathology groups was 25 mm and 30 mm respectively (data not shown). The results from one woman could not be found so the calculated number of study participants in the pre-pathology group was 24. The woman that received external RT instead of IOBT due to poor adaption to the applicator had a proportion of 32% air in her 10 Gy-tissue shell. She was still included in the calculation since she received the applicator. The median values for irradiated tissue (e.g. the 10 Gy-shell) were 25 cm^3 in the pre-pathology group and 15 cm^3 in the post-pathology group.

Breast cancer recurrence

After a median follow-up of 3.1 years, no study participant in the pre-pathology group had experienced a recurrence. One woman in the post-pathology group had an ipsilateral recurrence one year after primary treatment. The recurrence was located in a different quadrant than the primary tumor. She was treated with mastectomy. Another woman in this group had a contralateral cancer three years after IOBT. She was treated with BCS, sentinel biopsy and IOBT for a second time. An additional woman in the post-pathology group received IOBT to the left breast after earlier had been treated for a cancer in her right breast. She was shortly afterwards found to have a recurrence in her right breast with distant metastases.

Discussion

The trial shows that the procedure with BCS with pre- or post-pathology IOBT is feasible. No logistical problems were reported. No serious toxic side effects from IOBT were registered and the grade 1-2 side effects had almost disappeared six months after treatment. Three postoperative infections were noted. With the reservation of low power, quality of life did not differ significantly in this pilot group compared to reference groups from the Swedish population. The cosmetic outcomes were good in the vast majority of patients and evenly distributed between the pre- and post-pathology group.

There are different methods of delivering partial breast irradiation of which IOBT is one. The safety of partial- breast and reduced-dose radiotherapy is supported by a randomized, controlled, noninferiority trial done in 30 radiotherapy centers in the United Kingdom and published recently in the Lancet[24]. Patients were randomly assigned to receive 40 Gy whole-breast radiotherapy, 36 Gy wholebreast radiotherapy and 40 Gy to the partial breast (reduced-dose group), or 40 Gy to the partial breast only (partial-breast group) in 15 daily treatment fractions. In terms of local recurrence non-inferiority of partial-breast and reduced-dose radiotherapy compared with the standard whole-breast radiotherapy was found. However, the Groupe Europeen de Curie-therapie of European Society for Radiotherapy and Oncology (GEC-ESTRO) presented data from a non-inferiority, randomized trial. After a median follow-up of 6.6 years, the preset difference margin of 3 % was not reached [25].

In the TARGIT-A trial [11] 3451 patients were enrolled at 33 centers in 11 countries and randomized to IORT with Intrabeam® or external XRT. The 5-year risk for local recurrence overall was 3.3% (95% CI 2.1-5.1) for IORT versus 1.3% (95% CI 0.7-2.5) for external XRT (p=0·042).

Apart from the TARGIT-A trial, there is another large randomized trial - the ELIOT trial [26] . In this trial ipsilateral breast cancer recurrence after a median follow-up of 5.8 years was 0.4% in the group receiving external radiotherapy and 4.4% in the ELIOT-group. The non-inferiority margin of 4.5% was not exceeded but still, the numerical difference was 4 % which prompted the authors to

recommend an improved selection of patients to the ELIOT-method. Inclusion criteria in the ELIOT trial were invasive breast cancer tumor ≤2.5 cm with no restrictions regarding axillary nodal status. Lobular tumors were also eligible.

The techniques in these two trials are fundamentally different. Whereas Intrabeam® delivers irradiation from within the undisturbed tumor bed, in the ELIOT trial, the mammary gland is mobilized, a pre-pectoral lead shield is inserted, the edges of the tumor bed are joined, and radiation is delivered. Intrabeam® uses 50 kV x-rays delivering 20 Gy to the tumor bed surface and 5–7 G y at 1 cm depth, in 20–45 min. ELIOT uses electrons at 4–12 MeV delivering 21 G y in 3–5 min. The TARGIT-A trial has been criticized for its short follow-up – median time 29 months, only 611 (18%) patients had a 5-year follow-up, and for misinterpretation of the non-inferiority criterion, which requires the upper confidence interval (CI) to be less than the predefined non inferiority level of 2.5% (difference between IORT group and external XRT group 1.0 per cent unit (95 % CI, –0.68 to 2.68, pre-pathology group) [27]. Breast cancer mortality was much the same for IORT and external XRT, but significantly fewer non-breast-cancer deaths occurred in the IORT group than in the external XRT group. The authors´ explanation is fewer deaths from cardiovascular causes and other cancers in the IORT group.

The primary aim of this pilot study was to investigate feasibility and safety of a concept that was new for our breast surgical and radiotherapy team.

The Iridium 192 HDR source release photons of 374kV energy giving a deeper tissue penetration around the applicator although treatment has to be given in a shielded room. This differs from Intrabeam®, which uses 50 kV photons with lower penetration but with the possibility of delivering the treatment in an unshielded operating room. Both methods have the ability to deliver high doses to the tumor bed while reducing doses to nearby critical structures which makes them suitable for the purpose of PBI. Many centers already own a HDR equipment, which should reduce the cost of initiation of the procedure. However, a shielded (operating) room is mandatory. In our trial all IOBT treatments took place in a shielded room at the department of oncology. In this way, the duration time in the operating room for the pre-pathology group was prolonged for only 2 minutes which made room free for the next surgical procedure without delay. The TARGIT trial reports a prolongation of surgical procedure duration time of 30 minutes [11].

The TARGIT-A trial found a larger absolute risk of recurrence in the post-pathology group. The authors´ explanation is that the fresh tissue is compromised after several weeks of healing process and consequently that the treatment is not as effective as in the pre-pathology group. In our trial we objectively investigated the contact between the applicator and the target tissue through a CT scan and found a poorer adaptation between the applicator and the target tissue in the post-pathology group. To the best of our knowledge, no previous study has carried out a CT scan before start of IOBT. During the post-pathology procedure we experienced the same compromised tissue as in the TARGIT-A trial, which, together with our CT scan results, points towards performing IOBT only during primary surgery. However, waiting for definitive histopathological report could possibly limit the usefulness of the pre-pathological procedures since some patient will need the addition of complementary external XRT. In our trial there were six women (24%) in the pre-pathology group who underwent external XRT after the final histopathological report. In the TARGIT-A trial the corresponding percentage was 15%.

The frequency of additional external XRT after IORT depends on selection criteria [28] and the inclusion criteria differs between different radiotherapy societies [29]. Exclusion criteria in our trial were lobular cancer and metastases in the axilla. In this manner we wanted to reduce the need for additional external XRT. However, we did not succeed in our preoperative selection of patients to prevent this to happen for every fourth woman.

No serious adverse toxic effects were registered which is in line with previously reported results from IORT trials [30,31].

In the TARGIT-A trial IORT was found to significantly improve quality of life [32]. In our trial evaluation of the two health questionnaires should be interpreted with caution, due to potentially low power. While a few items in the QLQ-C30 health questionnaire showed statistically significant differences compared to the reference Swedish population, no signs of a lower state of health for the women in the study where found in the EQ-5D questionnaire. A drawback of this study is the lack of known state of health before treatment and cancer diagnosis. It is also fair to believe the results to be affected more by the diagnosis of cancer rather than by the IOBT procedure. Thus, giving a health questionnaire after the cancer diagnosis could also be misleading.

Since our trial was designed as a pilot study we did not include a control group. Instead, we compared the BCCT software results from the pre-pathology group with the results from the post-pathology group and found no differences. On the contrary, in the TARGIT-A trial, the cosmetic outcome for those treated with Intrabeam® was found to be superior to those patients who received conventional external beam radiotherapy [33].

One of the strengths with our trial is the CT scan images, which will possibly facilitate the identification and documentation of where the dose is delivered with respect to the excision cavity as well as the organs at risk including the skin and chest wall. It also improves surgical technique to avoid bad tissue adaptation. This will increase the quality of treatment or, in cases where re-treatment is needed, to identify previously delivered dose to organs at risk.

We also believe that our careful selection of patients and tumour characteristics are necessary when offering IOBT. The TARGIT-A trial had relatively wide inclusion criteria. We included tumors with smaller sizes and excluded lobular cancer and tumors presented with metastases in the axilla. Further trials are needed to find the best suitable group of patients for this treatment.

The National Institute of Health and Care Excellence (NICE) in England concludes in their latest report that there are some patients who could particularly benefit from Intrabeam®, but the patients should be fully informed of the evidence and treatment options available. Moreover, they conclude that Intrabeam® can only be recommended if its use is accompanied by the gathering of additional information on clinical effectiveness by data collection[34].

In conclusion, IOBT represents a promising alternative of postoperative radiotherapy for selected patients. In the absence of reliable data and longer follow-up it should remain as a technique under investigation. Our pilot trial urges for further larger trials using this concept, which already has started at our center.

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Table1. Patient, tumor and treatment characteristics

	Age	Tumor size(mm)	Applicator size(mm)	Distance to mamilla(mm)	Duration of surgery (min)	Duration of IORT(min)	Total time of surgery (min)
Mean	68,82	10,88	30,00	6,14	40,44	14,0	54,26
Median	68,50	10,00	30,00	6,00	37,50	12,0	55,00
Minimum	56	6	25	1	10	5	20
Maximum	84	22	40	12	100	24	112

Table2.The distance from the surface of the applicators with different diameters to the 10 G y isodose.

Diameter of the applicator (mm)	25	30	35	40	50
Distance from the surface to the 10Gy-isodose (mm)	5	6	7	8	10

Table 3Scores QLQ-C30 follow-up 12 months

	N	Minimum	Maximum	Mean	Std. Deviation
Global health	47	,0	100,0	80.7	19.6
Physical functioning	47	20,0	100,0	88.1	17.6
Role functioning	47	16,7	100,0	91.1	19.6

Emotional functioning	47	8,3	100,0	87,0	18,0
Cognitive functioning	47	66,7	100,0	92.9	10,3
Social functioning	47	,0	100,0	92.9	19.0
Fatigue	47	,0	100,0	19.9	22.9
Nausea	47	,0	83,3	5.7	14.4
Pain	47	,0	100,0	11.7	21.7
Dyspnoe	47	,0	100,0	15.6	23.9
Insomnia	47	,0	66,7	21.3	22,4
Appetite loss	47	,0	66,7	7.1	18.3
Constipation	47	,0	100,0	5.0	18.3
Diarrhoea	47	,0	100,0	5.0	17.0
Financial difficulties	47	,0	33,3	1.4	6.8
Valid N (listwise)	47				

Table4.Scores QLQ-C30 reference values from the Swedish population. Women 60-69 years old, N=1686[1].

	Mean	Std. Deviation
Global Health	77,2	15,1
Physical functioning	87,3	24,9
Role functioning	88,1	10,9
Emotional functioning	84,4	16,4
Cognitive functioning	89,0	8,0
Social functioning	91,1	7,8
Fatigue	19,1	22,3
Nausea	3,6	9,6
Pain	23,2	27,8
Dyspnoea	12,6	21,8
Insomnia	21,4	15,1
Appetite loss	3,7	1,7
Constipation	6,3	3,2
Diarrhoea	6,0	3,7
Financial difficulties	4,6	3,2

Table5.Scores QLQ-C30 reference values from the Swedish population compared to study group using unpaired t-test.

	Mean difference	95% CI interval	p-value	Cohen´s d^2
Global Health	3.5	-0.9 to 7.9	0.12	0.2
Physical functioning	0.8	-6.4 to 8.0	0.83	0.03
Role functioning	3.0	-0.2 to 6.2	0.07	0.3
Emotional functioning	2.6	-2.2 to 7.4	0.28	0.2
Cognitive functioning	3.9	1.5 to 6.2	<0.001	0.5
Social functioning	1.8	-0.6 to 4.2	0.14	0.2
Fatigue	0.8	-5.7 o 7.3	0.81	0.04
Nausea	2.1	-0.7 to 4.9	0.15	0.2
Pain	-11.5	-19.5 to -3.5	0.005	0.4
Dyspnoea	3.0	-3.0 to 9.3	0.35	0.1
Insomnia	-0.1	-4.5 to 4.3	0.96	0.1
Appetite loss	3.4	2.4 to 4.4	<0.0001	2.0
Constipation	-1.3	-2.6 to -0.1	0.04	0.4
Diarrhoea	-1.0	-2.3 to 0.3	0.14	0.3
Financial difficulties	-3.2	-4.2 to -2.2	<0.0001	1.0

Table6.EQ-5D-3L; Frequency of respondents (%) reporting moderate or severe problems in different dimensions, pilot study group n=50 and reference group n=4738, female aged 50-84 years, from a reference population in Sweden[3]. The numbers for the EQ VAS represent mean values for the respondents. Follow-up one year

Dimensions	N=50	N=4738
Mobility	5	944
Self-care	1	47
Usual activities	2	1532
Pain/discomfort	14	2332
Anxiety/depression	15	1040
EQ VAS (mean value)	82.1	69.5
Fisher exact test	P= 0.22	

Table 7.BCCT results. One year follow-up. The numbers represent number of patients in the different categories.

BCCT	Prepath.group	Postpath.group	Total

Excellent	2	3	5
Fair	8	9	17
Good	14	11	25
Poor	1	1	2
Missing	0	1	1
Total	25	25	50

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APPENDIX

EQ-5D-3L

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked **100**and the worst state you can imagine is marked **0**.We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.