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# Selection of treatment modalities and significance of oestrogen receptor status on the benefit of radiotherapy after breast conserving surgery for breast cancer

Degree Project in Medicine

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# Abstract

Degree project, Programme in Medicine

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**Introduction:** Radiotherapy (RT) reduces the risk of breast cancer recurrence after breast conserving surgery (BCS). Radiosensitivity may be influenced by tumour oestrogen receptor (ER) status. However, most patients do not develop recurrences even without adjuvant treatment.

**Aims:** This thesis aimed to describe the effect of RT on recurrence, and determine if ER status influenced this effect. A further aim was to identify patients with a sufficiently low recurrence risk without RT, and without endocrine therapy, that omission of this treatment may be considered.

**Methods:** 530 breast cancer patients treated with BCS were included in this retrospective study. Medical records were reviewed. Primary outcome was locoregional recurrence (LRR), secondary outcomes were distant recurrence, any recurrence and death. Cox regression was used to obtain hazard ratios. A LRR rate <10% in 10 years was considered a low risk.

**Results:** RT reduced the 10-year risk of LRR by 73%, any recurrence by 62%, and the 15-year risk of death by 48%. ER status did not influence the RT effect on LRR ($p_{interaction}$=

0.287). One small group was identified where none had a LRR without RT, and two groups with LRR rates of 7.4% and 8.3% without endocrine treatment.

**Conclusion:** RT reduced the risk of recurrence substantially. Overall survival improved, although this should be interpreted with care due to confounding factors. ER status did not predict RT effect. Two groups were identified where omission of endocrine treatment might be considered, but regarding RT the number of patients was too low to draw any conclusions.

**Key words:** breast cancer, radiotherapy, breast conserving surgery, breast cancer recurrence

# Background

## Breast cancer

Breast cancer is the most common cancer among women in Sweden today. It accounts for 30% of women's cancer, and affects about one in ten women before the age of 75 (1). The incidence has increased over the past decades, with 8986 new cases reported in 2016 (1). By contrast, the death rate is steadily decreasing, which may be due to earlier detection and public awareness, as well as the development of more effective treatments (2, 3). The relative 10-year survival is now at 86% (1). Around 60% of breast cancers in Sweden are detected via the mammogram screening program, in which all women aged 40-74 years are summoned to a mammogram every two years (1, 4).

Risk factors include higher age, alcohol consumption, ionizing radiation to the breasts, being overweight after menopause, and dense breast tissue (5). Hormonal factors such as early puberty, late menopause, no full-term pregnancies or high age at first pregnancy, and long use of hormone replacement therapy, also increase the risk (3, 5). Physical activity and several pregnancies might be protective factors (1, 3, 5). Hereditary breast cancer accounts for 5-10% of cases, 2.5-5% express oncogene BRCA1 or BRCA2 (1).

Common symptoms of breast cancer are a palpable lump in the breast or surrounding area, dimpling of the skin, inward-turning nipple, bloody or clear secretion from the nipple, redness or irritation of the skin, swelling of the breast or arm, and a lump in the axilla (1-3). Patients with suspected breast cancer are referred to a specialized physician and undergo investigation. This usually consists of clinical breast examination, visualization by mammogram and ultrasound (in some cases MRI), and fine needle aspiration or core needle biopsy (2, 3, 5).

**Classification of breast cancer**

Breast cancer is classified according to histological origin and growth pattern. Among invasive tumours, ductal carcinoma is the most common (75-80%), followed by lobular carcinoma (10-15%), Phyllodes tumour (1%) and other rare forms such as medullary and tubular carcinoma (2). Non-invasive tumours are categorized as ductal cancer in situ (DCIS), lobular cancer in situ (LCIS) and Paget´s disease of the nipple (2).

Intrinsic subtypes with different prognosis and treatment options are identified by immunohistochemical examination of cell surface protein expression (6). Levels of oestrogen receptor (ER), progesterone receptor (PgR), growth factor receptor HER2, and proliferation marker Ki-67 are measured, along with evaluation of malignancy grade. Grade is estimated by histologic examination according to the BRE scale (Bloom, Richardson, Elston), and reported as grade I-III (2). The subtypes are defined as follows: luminal A (ER /PgR positive, low Ki-67 and low grade), luminal B (ER /PgR positive, high Ki-67 or high grade), HER2 (HER-2 positive, either ER /PgR positive, called luminal B/HER2, or hormone receptor negative), and triple negative (negative for ER, PgR and HER2) (2, 5). Luminal A accounts for 40%, luminal B 35-40%, HER2 <15% and triple negative <10% of cases (2).

Tumour stage is stated according to the TNM system, considering tumour size (T), lymph node status (N) and distant metastases (M). T is defined as Tis (cancer in situ), T1 (<20 mm), T2 (21-50 mm), T3 (>50 mm) and T4a-d (overgrowth to thoracic wall, skin, both thoracic wall and skin, or inflammatory cancer) (2). N is divided into pN0 (no metastatic lymph nodes), pN1 (1-3 nodes), pN2 (4-9 nodes) and pN3 (>9 nodes, or engagement of sternal or clavicular nodes) (2). M is either M0 (no distant metastases) or M1 (at least one distant metastasis) (2). Based on these characteristics, the cancer is defined as stage 0 (Tis N0 M0),

stage I (T1 N0 M0), stage II (T2-3 N0 M0, or T1-2 N1 M0), stage III (T3 N1 M0, or T1-3 N2 M0, or T4 N0-2 M0, or T1-4 N3 M0) or stage IV (T1-4 N0-3 M1) (2).

**Primary treatment**

Nearly all patients undergo surgery – patients with small tumours are generally treated with breast conserving surgery (BCS) followed by radiotherapy (RT), while patients with larger or multi-focal tumours are recommended mastectomy (3, 7). To enable a good cosmetic result of BCS, the size of the tumour should be small compared to the breast (5). Several long-term follow-ups have reported equal survival rates and risks of distant recurrence of mastectomy and BCS (8, 9). This report will focus on patients that have been treated with BCS, rather than mastectomy. HER2-positive, triple negative, and tumours where radical excision cannot be ensured are often recommended neoadjuvant treatment (3, 5), which can also be used in order to shrink the tumour prior to BCS (3, 5).

To evaluate lymph node involvement, sentinel node dissection (SND) is often performed at the time of breast surgery (3). Axillary lymph node dissection (ALND), the removal of all lymph nodes in the axilla, is recommended if the sentinel node contains tumour cells, and combined with mastectomy in node positive, multi-focal or locally advanced cancer (7). Since SND is a relatively new procedure, ALND was more common a few decades ago than today.

**Breast cancer recurrence**

Breast cancer recurrence can be local, regional or distant. Local recurrences, IBTR (ipsilateral breast tumour recurrence), occur in the breast tissue remaining after BCS, the surrounding skin or the chest wall (10). Regional recurrences include metastases in axillary, supraclavicular or parasternal lymph nodes (11). The term locoregional recurrence (LRR) is

often used, and includes both local and regional recurrences. These are often discovered at follow-up mammograms, which are recommended for the first ten years after BCS (7), or noticed as new symptoms arise. Breast cancer, especially luminal types, can remain in remission for many years before recurring (12).

The risk of locoregional recurrence is dependent on tumour and patient characteristics. Young age at diagnosis and positive lymph nodes are strongly correlated to a higher risk (13-17). High ER-levels are associated with fewer recurrences (13). Luminal A generally has the best prognosis, while HER2 and triple negative subtypes have a higher risk of LRR (14, 15, 18). However, in many studies none of the patients received trastuzumab, a relatively new drug that improves the prognosis of HER2-positive tumours (14, 15, 18). Extent of surgery and margins, as well as adjuvant treatment, also influence disease outcome (17).

The prognosis after locoregional recurrence varies, but many patients attain long term remission. Recurrences can often be surgically removed (16), sometimes combined with RT or systemic therapies (11). IBTR increases the risk of subsequent distant metastases (19, 20), but the impact on mortality is debated (13, 20). Furthermore, a shorter time to IBTR is predictive of a higher risk of distant disease and death (13, 19, 20). Regional recurrence is associated with an even higher risk of distant metastases and a shorter overall survival (13).

Distant recurrence indicates advanced and, generally, incurable breast cancer (5). The risk of developing distant metastases varies. A 5-year cumulative incidence of 6.3% after BCS and RT has been reported, with an increased risk for HER2-positive and triple negative subtypes (18). Overall, skeletal metastases are the most common, primarily affecting the spine, ribs, pelvis and cranium, causing pain or pathological fractures (11). Luminal cancers often spread

to the lung and liver; HER2-positive tumours relatively frequently metastasise to the CNS (11). Triple negative cancer can metastasise early, often to the CNS, lungs and soft tissues (11). Metastatic breast cancer is not considered to be curable, and is therefore treated with a palliative intention. However, symptom control and prolongment of progression-free survival can still be achieved (5). Treatment consists of systemic drugs and in some cases surgery or targeted RT (11). In the last decades many new therapeutic options have been developed and the overall survival has increased, at least for some patient groups (21, 22).

**Post-operative radiation therapy**

Post-operative RT to the remaining ipsilateral breast is standard treatment after BCS (5). RT can also be given after mastectomy in high-risk patients, to regional lymph nodes in node-positive disease or as a palliative treatment (5). RT eliminates local tumour cells that might be left after excision of the clinical tumour, and therefore has its largest impact on locoregional disease control (17). The relative risk of local recurrence is reduced by approximately 50%, primarily in the first years after treatment (17). RT also reduces breast cancer mortality by 18%, a benefit most evident after ten years (17).

While the proportional effect of RT is rather consistent, the absolute risk reduction varies (16). Factors associated with a high recurrence risk, and therefore a large absolute effect of RT, are young age, metastatic lymph nodes, large tumour size, high grade, poor ER-status, and less extensive surgery (17). Young women with high grade tumours generally have a greater benefit from RT, while older women with small, ER-positive tumours benefit less (17). Additionally, systemic treatment influences the response to RT – tamoxifen may reduce the recurrence risk of ER-positive tumours even further (17), and trastuzumab may increase the radiosensitivity of HER2-positive tumours (23).

However, RT is also associated with adverse events. Acute side effects that may occur during or shortly after treatment include skin irritation and redness, swelling of the breast or arm, and pneumonitis (7). The most serious long-term risks are cardiac disease and second malignancies, lung cancer being the most common (24). A particularly large risk of serious events is observed among smokers (24). Early studies failed to observe a survival benefit to RT, primarily due to a slightly increased risk of death from lung cancer and cardiac disease (16, 25). In recent years, however, there have been significant advances in RT. With improved technology and use of breath-holding technique, radiation doses to inner organs have decreased substantially (24, 25).

**Adjuvant systemic treatment**

Most patients receive adjuvant systemic treatment after surgery. The most common options are chemotherapy, anti-HER2 drugs or anti-hormonal therapy. Chemotherapy is, in short, recommended to patients with triple negative, HER2 and luminal B tumours, and other patients with high recurrence risk, such as those with positive lymph nodes (7). HER2-positive tumours are treated with trastuzumab, a monoclonal antibody that blocks the growth factor receptor HER2 and approximately halves the recurrence risk (3, 5, 26). The length of treatment with trastuzumab is one year, initially combined with chemotherapy (5).

Anti-hormonal treatment is recommended to ER-positive patients for at least five years, up to ten years in high-risk patients (5). Premenopausal women receive tamoxifen, a selective ER modulator, and postmenopausal women are given either an aromatase inhibitor, which reduces production of oestrogen, or an aromatase inhibitor followed by tamoxifen (5). According to a meta-analysis, five years of tamoxifen reduces the annual recurrence rate by 41% and the rate of breast cancer death by 31% (27). Aromatase inhibitors may be even more

beneficial (28). Side effects include menopausal symptoms such as sweating, tiredness and hot flashes; tamoxifen can cause thromboembolism and endometrial cancer; and aromatase inhibitors can lead to joint pain and osteoporosis (7). Moreover, with an ongoing treatment of five years or longer, there is a risk of discontinuation of treatment (29).

**Omission of adjuvant treatment in low-risk patients**

RT following BCS reduces the risk of locoregional recurrences and increases overall survival, but is associated with both acute and long-term adverse events. Furthermore, while the beneficial effect is evident on a population level, most patients with early breast cancer do not develop a LRR even without RT and thus do not benefit from it (17).

A number of studies have attempted to find a group of patients with sufficiently low risk of recurrence that they can be spared RT altogether (30-34). Old age, small tumour size, low grade, negative lymph nodes and ER-positivity are frequently linked to a low recurrence risk, and, therefore, a small absolute benefit from RT. Several studies have investigated the possibility to omit RT in a low-risk population of older women with small, ER-positive breast cancer treated with BCS (30, 31, 34). An increased risk of IBTR of between 4% and 10% has been reported with adjuvant tamoxifen, compared to between 1% and 2% with tamoxifen and RT, but no difference in overall survival or distant recurrence (30, 31). A Swedish study by Wickberg et al (34) found a 5-year cumulative incidence of IBTR of 1.2% among women >65 years with hormone receptor positive tumours and favourable histopathology treated with BCS and endocrine therapy. Moreover, breast cancer is likely to have a relatively small impact on life-expectancy in older women, most deaths being due to comorbidities (30, 34). With that in mind, omission of RT might be a reasonable option for some patients (31, 34). By contrast, Sjöström et al (35) found that even in a clinical low-risk group, the benefit of RT

was still substantial and the recurrence risk without RT relatively high (although the use of systemic treatment was sparse). They proposed that instead of omitting RT, some patients could be treated with only RT and not endocrine treatment after BCS (35).

**Radiotherapy response dependent on ER-status**

As previously mentioned, the absolute effect of RT varies depending on prognostic factors, but the relative benefit may also vary depending on breast cancer subtype. In a post-mastectomy study, patients with positive ER/PgR and negative HER2 who received RT had a larger improvement of LRR risk and overall survival than other patients (36). A similar finding was observed in a study of BCS and RT, where luminal cancers had a significantly better prognosis than HER2 and basal subtypes (18). This suggests that cancers that do not express hormone receptor respond less to RT than those that do (18, 36). One possible mechanism could be that oestrogen speeds up the cell cycle in luminal cancers, rendering the tumour more vulnerable to radiation-induced DNA damage (36).

Not all studies confirm this possible predictive value of subtype to RT response. A Swedish study found that RT reduced the risk of recurrence in all subtypes except HER2, and that breast cancer death was only reduced in triple negative disease, thus contradicting the theory of a better RT effect in receptor positive cancers (35). On the other hand, trastuzumab, which was not used in this study, may increase the radiosensitivity of HER2-positive tumours (23, 35). Liu et al (32) found that subtype was not predictive of RT response, and that high-risk subtypes had a good effect of RT. Furthermore, HER2 and basal subtypes are associated with other negative prognostic factors such as high grade and young age at diagnosis, that may explain the high recurrence risks even after RT (18, 37).

There is currently no consensus as to whether hormone receptor positivity increases the sensitivity to RT, calling for further research on the topic. Extended knowledge of this relationship, as well as information regarding low-risk patients that may be spared the inconvenience of RT or endocrine treatment, would enable tailored treatment approaches for early breast cancer.

# Aim

The aim of this thesis was to describe the prognosis after BCS and RT, regarding the risk of locoregional recurrence, distant recurrence and overall survival, in a retrospective population-based cohort at the Department of Oncology at Sahlgrenska University Hospital. An objective of the study was to examine the relationship between ER-status and response to RT. The thesis further aimed to investigate whether it is possible to identify patients within this cohort with a sufficiently favourable prognosis without RT, or without endocrine therapy, that omission of this treatment may be considered.

# Research questions

Does ER-status affect the response to radiotherapy, in breast cancer patients <80 years treated with breast conserving surgery, concerning the risk of locoregional recurrence, distant recurrence or death? Can we, based on clinical variables, retrospectively identify patients with a sufficiently low recurrence risk (<10% in 10 years without RT) that omission of RT is reasonable? Can we, correspondingly, identify patients with a sufficiently low recurrence risk (<10% in 10 years without endocrine treatment) that omission of endocrine treatment is reasonable?

# Ethical considerations

Application for ethical approval of this study was filed and approved by the Swedish Ethical Review Authority prior to the start of the study (application no. S164-02). The study was retrospective and observational, hence there were no risks of potential exposure or endangerment of the patients included. Reviewing medical records could be an ethical problem. To reduce potential harm to patient integrity, only notes that were relevant to the study, i.e., from the Departments of Surgery and Oncology, were reviewed. Once all information was gathered, the ID numbers of the patients were deleted from the dataset.

# Material and methods

**Population and data collection**

This study was carried out as a retrospective cohort study. The study population consisted of 675 patients with breast cancer diagnosed in the Swedish region of Västra Götalandsregionen (VGR) between January 1989 and December 1999, who were included in the bio bank of frozen tumour material at Jubileumskliniken (Department of Oncology) at Sahlgrenska University Hospital. The inclusion criteria were age < 80 years at diagnosis, no distant metastases and having undergone treatment with BCS. Approximately two thirds of the patients had received post-operative RT. Medical records were reviewed in the digital system Melior. Where no digital records were available, printed medical records were retrieved from the archives of concerned hospitals within VGR, i.e., Sahlgrenska University Hospital (SU), Norra Älvsborgs Länssjukhus (NÄL) and Kungälvs Sjukhus (KS). Data was collected through systematic review of medical records from the Departments of Oncology and Surgery from the date of diagnosis up until the latest date of available records or death of the patient.

**Patients included**

Out of 675 tumours in the bio bank of frozen tumour material from patients who were diagnosed with breast cancer and underwent BCS between 1989-1999, we were able to retrieve medical records for 412 patients, and register data with follow-up for 141 patients. Hence, 122 patients were excluded due to lack of follow-up. A further eleven patients were excluded because their breast cancer was found to be non-invasive, five patients where it could not be determined whether or not they had received RT, and four patients who had undergone mastectomy and not BCS. Two patients where the current tumour was interpreted as a recurrence, and one patient where the information from medical records was extremely limited, were also excluded from analysis. 530 patients were included in the baseline and LRR analyses. This number includes 19 patients who were diagnosed with breast cancer and treated with BCS in both breasts between 1989 and 1999, and therefore occur twice in this analysis. For simplicity, every tumour will henceforth be referred to as one patient, unless stated otherwise.

For the endpoints of distant recurrence and any first recurrence, 11 patients with bilateral cancer at diagnosis and 15 patients with a previous contralateral breast cancer were excluded from analysis, since it would be impossible to determine the tumour of origin of a potential distant metastasis. Thus, 504 patients were included in these analyses.

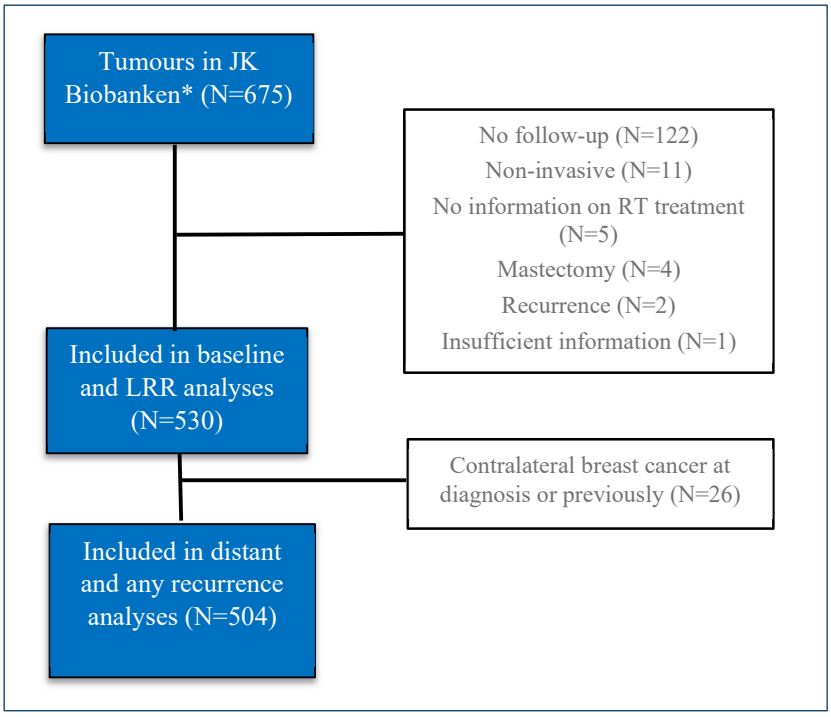


*Figure 1. A flowchart of patients excluded from analyses. *Frozen tumour material gathered from patients diagnosed with breast cancer and treated with breast conserving surgery between 1989-1999 in VGR. Abbreviations: JK Jubileumskliniken at Sahlgrenska University Hospital. LRR locoregional recurrence.*

## Variables

Baseline information sampled included patient characteristics (date of diagnosis, age), tumour characteristics (size, histological grade, ER status, PgR status, radicality of surgery), lymph node involvement (palpable lymph nodes pre-surgery, ALND, number of pathologically positive lymph nodes) and adjuvant treatment (RT, chemotherapy, endocrine treatment). Regarding recurrences, information was gathered about date, localization (local, regional or distant), method of diagnosis (cytology, imaging techniques or clinical suspicion). Contralateral breast cancer and other malignancies were noted. In cases where the patient was deceased, date and cause of mortality was obtained from medical records where possible. The primary endpoint was time to locoregional recurrence (LRR). The secondary endpoint was time to distant recurrence, any first recurrence (local, regional or distant) and death.

**Statistical methods**

The data was summarized in a Microsoft Excel document, and exported to SPSS where the analyses took place. In all analyses, a p-value of <0,05 was considered to be statistically significant. Baseline characteristics of the RT and no RT arms were compared with Chi-square test, Fisher's exact test and Mann-Whitney U-test.

Cox regression was used to estimate the effect of RT on time to LRR, distant recurrence, any first recurrence and death. LRR, distant recurrence and any first recurrence were measured up to 10 years after diagnosis, and death was recorded for the first 15 years. Distant recurrence was considered a competing event for the LRR outcome. For distant recurrence and any first recurrence, contralateral breast cancer was considered a competing event (since determining which tumour gave rise to the distant metastasis would be impossible). There were no competing events for death. Interaction terms were included to conclude whether the effect of RT differed depending on ER-status. Since the cohort was not randomized, adjustments were made for confounding factors. To determine which factors to adjust for, univariate Cox regression models were run for the individual variables that were hypothesized to have an effect on time to recurrence. Variables with a statistically significant hazard ratio (HR), as well as variables with a non-significant HR but known to be biologically relevant, were included in the final analyses.

To identify potential patient groups with a risk of recurrence of <10% in the first 10 years without RT or endocrine treatment, patients with characteristics commonly associated with a low recurrence risk were selected from the cohort, and their respective absolute risk of LRR calculated. Characteristics that were tested were high age (>50, >55, >60, >65, >70 years), small tumour size (<15, <18, <20, <25, <30 mm), luminal A tumour, ER positivity, a low

number of positive lymph nodes (no nodes, <2 nodes, <3 nodes, <4 nodes), radical surgery, chemotherapy, RT (when studying patients not given endocrine treatment) and endocrine treatment (when studying patients not given RT). These factors where combined to form groups of patients expected to have a low recurrence risk. Different combinations were tested, and absolute recurrence risks calculated for each of the combinations, to find the groups with the lowest recurrence risk.

# Results

### Patient and tumour characteristics

The total number of patients included in the study was 530, of which 353 (66.6%) had received RT and 177 (33.4%) had not. Median follow-up time was 9.6 years, with an interquartile range of 4.1-16.1 (min-max 0.07-30.75).

Patient and tumour characteristics are presented in *table 1.* The median age at diagnosis was 53 years in the RT group and 67 years in the no RT group ($p<0.01$). In general, patients treated with RT had a larger tumour size (median 20 mm for both groups, $p=0.008$). The RT group had a significantly higher frequency of ALND, and more positive lymph node metastases compared to the no RT group (no RT v. RT; no ALND 24.9% v. 4.5%; 1-3 positive nodes 9.6% v. 31.4%; ≥4 positive nodes 4.5% v. 8.8%; $p<0.01$). Additionally, the use of adjuvant treatment differed between the two groups, as 9.0 % of non-RT treated and 36.2% of RT treated had received chemotherapy ($p<0.01$), and 46.9% of non-RT treated and 39.9% of RT treated had received endocrine treatment ($p=0.002$).

Table 1. Patient and tumour characteristics for the no RT and RT groups.

| Variable | | No RT | RT | Total | P-value |
|---|---|---|---|---|---|
| **Total, No. (%)** | | 177 (33.4) | 353 (66.6) | 530 (100) | |
| **Age, median (min-max)** | | 67 (31–79) | 53 (25–78) | 57 (25–79) | <0.001 |
| **Age categories, No. (%)** | <40 | 4 (2.3) | 32 (9.1) | 36 (6.8) | |
| | 40-49 | 29 (16.4) | 111 (31.4) | 140 (26.4) | |
| | 50-59 | 31 (17.5) | 93 (26.3) | 124 (23.4) | |
| | 60-69 | 40 (22.6) | 86 (24.4) | 126 (23.8) | |
| | 70-79 | 73 (41.2) | 31 (8.8) | 104 (19.6) | |
| **Tumour size, mm, median (min-max)** | | 20 (2-70) | 20 (5-130) | 20 (2-130) | 0.008 |
| **Size categories, No. (%)** | < 10 mm | 16 (9.0) | 8 (2.3) | 24 (4.5) | |
| | 10-19 mm | 69 (39.0) | 131 (37.1) | 200 (37.7) | |
| | 20-29 mm | 61 (34.5) | 145 (41.1) | 206 (38.9) | |
| | 30-39 mm | 15 (8.5) | 39 (11.0) | 54 (10.2) | |
| | >40 mm | 11 (6.2) | 22 (6.2) | 33 (6.2) | |
| | Missing | 5 (2.8) | 8 (2.3) | 13 (2.5) | |
| **ER, No. (%)** | Positive | 140 (79.1) | 274 (77.6) | 414 (78.1) | 0.877 |
| | Negative | 33 (18.6) | 67 (19.0) | 100 (18.9) | |
| | Missing | 4 (2.3) | 12 (3.4) | 16 (3.0) | |
| **PgR, No. (%)** | Positive | 114 (64.4) | 218 (61.8) | 332 (62.6) | 0.485 |
| | Negative | 56 (31.6) | 123 (34.8) | 179 (33.8) | |
| | Missing | 7 (4.0) | 12 (3.4) | 19 (3.6) | |
| **Histologic type, No. (%)** | Lobular | 18 (10.2) | 41 (11.6) | 59 (11.1) | 0.911 |
| | Ductal | 138 (78.0) | 274 (77.6) | 412 (77.7) | |
| | Other | 16 (9.0) | 31 (8.8) | 47 (8.9) | |
| | Lobular and ductal | 3 (1.7) | 4 (1.1) | 7 (1.3) | |
| | Missing | 2 (1.1) | 3 (0.8) | 5 (0.9) | |
| **Subtype, No. (%)** | Luminal A | 97 (54.8) | 187 (53.0) | 284 (53.6) | 0.868 |
| | Luminal B | 40 (22.6) | 87 (24.6) | 127 (24.0) | |
| | Non-luminal | 33 (18.6) | 67 (19.0) | 100 (18.9) | |
| | Missing | 7 (4.0) | 12 (3.4) | 19 (3.6) | |
| **Endocrine therapy, No. (%)** | Yes | 83 (46.9) | 141 (39.9) | 224 (42.3) | 0.002 |
| | No | 68 (38.4) | 189 (53.5) | 257 (48.5) | |
| | Yes, discontinued | 10 (5.6) | 6 (1.7) | 16 (3.0) | |
| | Missing | 16 (9.0) | 17 (4.8) | 33 (6.2) | |
| **Chemotherapy, No. (%)** | Yes | 16 (9.0) | 128 (36.2) | 144 (27.2) | <0.001 |
| | No | 146 (82.5) | 208 (58.9) | 354 (66.8) | |
| | Yes, discontinued | 0 (0) | 2 (0.6) | 2 (0.4) | |
| | Missing | 15 (8.5) | 15 (4.2) | 30 (5.7) | |
| **Radical surgery, No. (%)** | Yes | 168 (94.9) | 334 (94.6) | 502 (94.7) | 0.816 |
| | No | 6 (3.4) | 10 (2.8) | 16 (3) | |
| | Uncertain | 3 (1.7) | 9 (2.5) | 12 (2.3) | |
| **Lymph nodes, No. (%)** | No ALND | 44 (24.9) | 16 (4.5) | 60 (11.3) | <0.001 |
| | No positive nodes | 50 (28.2) | 87 (24.6) | 137 (25.8) | |
| | 1–3 positive nodes | 17 (9.6) | 111 (31.4) | 128 (24.2) | |
| | ≥4 positive nodes | 8 (4.5) | 31 (8.8) | 39 (7.4) | |
| | Missing | 58 (32.8) | 108 (30.6) | 166 (31.3) | |
| **Grade, No. (%)** | Grade 1 | 20 (11.3) | 40 (11.3) | 60 (11.3) | 0.637 |
| | Grade 2 | 41 (23.2) | 95 (26.9) | 136 (25.7) | |
| | Grade 3 | 27 (15.3) | 75 (21.2) | 102 (19.2) | |
| | Missing | 89 (50.3) | 143 (40.5) | 232 (43.8) | |

*P-values were calculated with Chi-square tests for all variables except histoligic type, chemotherapy and radicality, where Fisher's exact test was used, and age and tumour size, where Mann-Whithney U-test was used. Abbreviations: RT radiotherapy; ER oestrogen receptor; PgR progesterone receptor; ALND axillary lymph node dissection.*

**Reviewed and non-reviewed patients**

We were able to retrieve and review medical records for 412 patients (of whom 21 were subsequently excluded), either in paper form from the hospital archives, or through the medical records system Melior. For 141 patients (of whom 2 were subsequently excluded), we were not able to retrieve any medical notes, and instead used information that was already registered in Cancerregistret. This register included some follow-up time during which any recurrences were noted. However, the median follow-up time for reviewed patients was notably longer, 12.0 years (interquartile range 7.35-17.73) compared to 3.7 years (interquartile range 2.31-5.66) for non-reviewed patients. In addition, for the reviewed patients we were able to check for any further recurrences after the first one had occurred, while the register data was limited to the first recurrence (although the follow-up time often proceeded beyond that point). Concerning patient and tumour characteristics, the register data had a low frequency of information about malignancy grade (71.2% of values missing) and lymph node status (72.7% of values missing), while it was often found in the medical records (34.0% and 16.6% missing, respectively). Since only 16 patients (3%) had a non-radical surgery, for patients where no information about radicality was available, it was assumed that the surgery was radical.

**Events**

Out of 530 patients, 129 suffered a LRR within 10 years after diagnosis. In total, 102 patients had an IBTR, 36 patients had a RR, and 9 patients had both an IBTR and a RR within the first 10 years. Out of 504 patients included in the distant and any recurrence analyses, 94 patients had a distant recurrence and 186 patients had a recurrence of any location within 10 years. Thus, 37 patients suffered both a locoregional and a distant recurrence. Table 3 summarizes

the distribution of recurrences in the RT and no RT group, as well as the median time to recurrence. The RT group had a significantly lower rate of LRR and any recurrence than the no RT group ($p<0.01$ for both outcomes). In contrast, the rate of distant recurrence was essentially the same in both groups ($p=0.972$). The median time to LRR and any recurrence was more than one year longer in the RT group than in the no RT group, while the median time to distant recurrence was one year shorter in the RT group.

Table 2. Distribution of recurrences that occurred within 10 years, and the mean time to recurrence, in the no RT and RT groups.

| Recurrence type | No RT | RT | Total | P-value |
|---|---|---|---|---|
| **LRR, No. (%)** | 70 (39.5) | 59 (16.7) | 129 (24.3) | <0.001 |
| Median time to recurrence, years (interquartile range) | 2,48 (1.72-3.80) | 3,90 (1.98-6.32) | | |
| **Distant recurrence*, No. (%)** | 31 (18.6) | 63 (18.7) | 94 (18.7) | 0.972 |
| Median time to recurrence, years (interquartile range) | 4,12 (2.29-8.22) | 3,14 (2.03-5.02) | | |
| **Any recurrence*, No. (%)** | 80 (47.9) | 106 (31.5) | 186 (36.9) | <0.001 |
| Median time to recurrence, years (interquartile range) | 2,37 (1.60-3.83) | 3,41 (1.97-5.34) | | |

*P-values were calculated with Chi-square test. * 26 patients with previous or simultaneous contralateral BC excluded from analysis of distant and any recurrence. Abbreviations: RT radiotherapy; LRR locoregional recurrence.*

## Univariable analysis

Univariable analysis with Cox regression models were made for all outcomes. With LRR as outcome, chemotherapy and radical surgery were statistically significant ($p=0.006$ and $p=0.002$, respectively). For distant recurrence, lymph node status (≥4 positive lymph nodes), ER status and PgR status were statistically significant ($p <0.001$; $p=0.005$; $p=0.009$). For the outcome any first recurrence, lymph node status (≥4 positive lymph nodes) and radicality were statistically significant ($p=0.004$ and $p=0.026$, respectively). In univariable analysis for death within 15 years the following variables were statistically significant: age ($p <0.001$),

lymph node status ($p < 0.001$ for ≥4 nodes), ER status ($p=0.018$), PgR status ($p=0.011$), chemotherapy ($p=0.023$), radicality ($p=0.036$) and grade ($p=0.048$ for grade 3).

**Multivariable analysis**

The variables that were statistically significant in univariable analysis for each outcome were included in the multivariable Cox regression model. Factors that were thought to be of biological relevance (age, ER status, PgR status, chemotherapy, endocrine treatment and lymph node status) were included for all outcomes regardless of whether or not they were statistically significant in the univariable analysis.

Lymph node status was included for all outcomes despite the fact that 31% of the data was missing, thus reducing the number of patients included in the multivariable analyses from 472 to 344 for LRR and from 454 to 329 for distant and any recurrence. The variable was included primarily because lymph node status is known to be a strong clinical risk factor for both locoregional and distant recurrence. In our analyses, having >4 positive lymph nodes was statistically significant for LRR in the adjusted analysis (HR 3.84; 95% CI 1.53-9.65; $p=0.004$). The p-value for the entire model increased slightly (adjusted for lymph node status, $p=6.5*10^{-9}$; unadjusted for lymph node status, $p=1.5*10^{-9}$). For the outcomes of distant recurrence, any recurrence and death, lymph node status was significant in univariable analyses, and including the variable in a multivariable model resulted in a lower p-value for the entire model (the model for distant recurrence was insignificant unadjusted for lymph node status, $p = 0.079$). Furthermore, RT had a lower HR when adjusting for lymph node status, and lymph node status was significant for all outcomes, further supporting the decision to include the variable in a multivariable model. Malignancy grade was not included in the multivariable model for any outcome. This was due to the fact that the variable was missing

in 44% of cases, further reducing the number of patients included in the analysis to 285 for LRR, 255 for death and 243 for distant and any recurrence. Grade 3 was significant for death within 15 years in univariable analysis (HR 1.677; 95% CI 1.005-2.796; p=0.048), and in multivariable analysis (HR 2.195; 95% CI 1.169-4.122; p=0.015). The p-values for the entire models were slightly decreased when adjustment was made for grade, for all outcomes.

**Locoregional recurrence**

Out of 344 patients included in the Cox regression analysis for LRR, 80 patients had suffered a LRR within 10 years after diagnosis. RT reduced the risk of LRR by 73% (HR 0.275; 95% CI 0.160-0.472; p <0.001), an absolute risk reduction of 22.8% (from 39.5% without RT to 16.7% with RT). Adjustment was made for age, ER status, PgR status, radicality, chemotherapy, endocrine treatment and lymph node status. Variables that were associated with a decreased risk of LRR were adjuvant endocrine treatment (HR 0.415; 95% CI 0.234-0.736; p = 0.003) and radical surgery (HR 0.243; p = 0,001). ER status was not associated with the risk of LRR (p=0.140).

Table 3. Multivariable Cox proportional hazards model for LRR.

| Variable | Category | HR (95% CI) | P-value |
|---|---|---|---|
| **RT-treated** | Yes | 0.275 (0.160-0.472) | <0.001 |
| **Age in years** | | 0.999 (0.978-1.021) | 0.947 |
| **Lymph node status** | 1–3 | 1.884 (0.939-3.782) | 0.075 |
| | ≥4 | 3.842 (1.530-9.650) | 0.004 |
| | No ALND | 1.225 (0.646-2.321) | 0.534 |
| **ER status** | Positive | 0.531 (0.229-1.231) | 0.140 |
| **PgR status** | Positive | 1.293 (0.624-2.605) | 0.472 |
| **Chemotherapy** | Yes | 0.419 (0.240-1.004) | 0.051 |
| **Endocrine treatment** | Yes | 0.415 (0.234-0.736) | 0.003 |
| **Radicality** | Yes | 0.243 (0.107-0.555) | 0.001 |
| | Not certain | 0.345 (0.085-1.399) | 0.136 |

*Adjusted for age, ER status, PgR status, chemotherapy, endocrine treatment and radicality. 344 patients were included, 80 had a LRR. Abbreviations: HR hazard ratio; RT radiotherapy; ALND axillary lymph node dissection; ER oestrogen receptor; PgR progesterone receptor.*

### Distant recurrence

The multivariable Cox regression model for distant recurrence included 329 patients and 67 events. Adjustment was made for age, ER status, PgR status, chemotherapy, endocrine treatment and lymph node metastases. In total, 18.7% of RT-treated and 18.6% of non-RT treated had a distant recurrence. RT was not significantly associated with the risk of distant recurrence (p=0.341), neither was ER status (p=0.457). Only lymph node status was statistically significant, both 1-3 nodes and ≥4 nodes increased the risk of distant recurrence (HR for 1-3 nodes 2.202; 95% CI 1.021-4.751; p=0.044; HR for >4 nodes 7.324; 95% CI 3.091-17.351; p <0.001).

Table 4. Multivariable Cox proportional hazards model for distant recurrence.

| Variable | Category | HR (95% CI) | P-value |
|---|---|---|---|
| **RT-treated** | Yes | 0.741 (0.399-0.741) | 0.341 |
| **Age in years** | | 1.012 (0.986-1.039) | 0.362 |
| **Lymph node status** | 1–3 | 2.202 (1.021-4.751) | 0.044 |
| | ≥4 | 7.324 (3.091-17.351) | <0.001 |
| | No ALND | 1.701 (0.698-4.146) | 0.242 |
| **ER status** | Positive | 0.751 (0.353-1.599) | 0.457 |
| **PgR status** | Positive | 0.750 (0.392-1.432) | 0.383 |
| **Chemotherapy** | Yes | 0.790 (0.392-1.593) | 0.510 |
| **Endocrine treatment** | Yes | 0.544 (0.291-1.016) | 0.056 |

*Adjusted for age, lymph node status, ER status, PgR status, chemotherapy and endocrine treatment. The model included 329 patients, 67 were diagnosed with a distant recurrence. Abbreviations: HR hazard ratio; RT radiotherapy; ALND axillary lymph node dissection; ER oestrogen receptor; PgR progesterone receptor.*

### Any first recurrence

The multivariable Cox regression model for any first recurrence within 10 years included 329 patients and 115 events, and was adjusted for age, ER status, PgR status, chemotherapy, endocrine treatment, radicality and lymph node status. RT reduced the risk of any recurrence by 62% (HR 0.378; 95% CI 0.238-0.600; p <0.001). In absolute terms, the rate was 31.5% among RT treated and 47.9% among non-RT treated, an absolute reduction of 16.4%. Chemotherapy, endocrine treatment and radicality each lowered the risk of recurrence

substantially (HR for chemotherapy 0.571; 95% CI 0.328-0.994; p=0.047; HR for endocrine treatment 0.463; 95% CI 0.287-0.747; p=0.002; HR for radicality 0.343; 95% CI 0.253-0.766; p=0.009). Having 1-3 positive lymph nodes doubled the risk and having ≥4 positive nodes increased the risk five-fold (HR for 1-3 nodes 2.225; 95% CI 1.254-3.946; p=0.006; HR for ≥4 nodes 5.485; 95% CI 2.729-11.026; p <0.001). ER status was not statistically significant (p=0.192).

Table 5. Multivariable Cox proportional hazards model for any first recurrence.

| Variable | Category | HR (95% CI) | P-value |
|---|---|---|---|
| **RT** | Yes | 0.378 (0.238-0.600) | <0.001 |
| **Age in years** | | 1.001 (0.982-1.020) | 0.925 |
| **Lymph node status** | 1–3 nodes | 2.225 (1.254-3.946) | 0.006 |
| | ≥4 nodes | 5.485 (2.729-11.026) | <0.001 |
| | No ALND | 0.925 (0.478-1.789) | 0.817 |
| **ER status** | Positive | 0.657 (0.350-1.235) | 0.192 |
| **PgR status** | Positive | 0.933 (0.551-1.579) | 0.797 |
| **Chemotherapy** | Yes | 0.571 (0.328-0.994) | 0.047 |
| **Endocrine treatment** | Yes | 0.463 (0.287-0.747) | 0.002 |
| **Radicality** | Yes | 0.343 (0.153-0.766) | 0.009 |
| | Not certain | 0.382 (0.107-1.358) | 0.137 |

*Adjusted for age, lymph node status, ER status, PgR status, chemotherapy, endocrine treatment and radicality. Out of 329 patients, 115 had a recurrence. Abbreviations: HR hazard ratio; RT radiotherapy; ALND axillary lymph node dissection; ER oestrogen receptor; PgR progesterone receptor.*

## Overall survival

The multivariable Cox regression model for death from any cause included 344 patients of whom 142 (41.3%) were confirmed to be deceased 15 years after diagnosis. Adjustment was made for age, ER status, PgR status, radicality, chemotherapy, endocrine treatment and lymph node metastases. Both RT and endocrine treatment approximately halved the risk of death (HR for RT 0.516; 95% CI 0.343-0.777; p=0.002; HR for endocrine treatment 0.463; 95% CI 0.298-0.721; p=0.001). Having ≥4 positive lymph nodes was associated with a more than five-fold increase in the risk of death, and not undergoing ALND was associated with a

doubled risk (HR for ≥4 nodes 5.669; 95% CI 3.014-10.660; p <0.001; HR for no ALND 2.059; 95% CI 1.254-3.380; p=0.004). ER status was not statistically significant (p=0.796). The risk of death for patients not treated with RT was 69.9%, and for RT-treated patients 42.6%, an absolute risk reduction of 27.3%.

Table 6. Multivariable Cox proportional hazards model with death within 15 years as outcome.

| Variable | Category | HR (95% CI) | P-value |
|---|---|---|---|
| **RT** | Yes | 0.516 (0.343-0.777) | 0.002 |
| **Age** | | 1.043 (1.023-1.063) | <0.001 |
| **Lymph node status** | 1–3 nodes | 1.935 (1.136-3.296) | 0.015 |
| | ≥4 nodes | 5.669 (3.014-10.660) | <0.001 |
| | No ALND | 2.059 (1.254-3.380) | 0.004 |
| **ER status** | Positive | 0.926 (0.519-1.653) | 0.796 |
| **PgR status** | Positive | 0.719 (0.456-1.134) | 0.156 |
| **Chemotherapy** | Yes | 0.706 (0.415-1.201) | 0.199 |
| **Endocrine treatment** | Yes | 0.463 (0.298-0.721) | 0.001 |
| **Radicality** | Yes | 0.774 (0.343-1.744) | 0.536 |
| | Not certain | 0.324 (0.080-1.303) | 0.112 |

*Adjusted for age, lymph node status, ER status, PgR status, chemotherapy, endocrine treatment and radicality. The model included 344 patients, of whom 142 (41%) had died after 15 years. Abbreviations: HR hazard ratio; RT radiotherapy; ALND axillary lymph node dissection; ER oestrogen receptor; PgR progesterone receptor.*

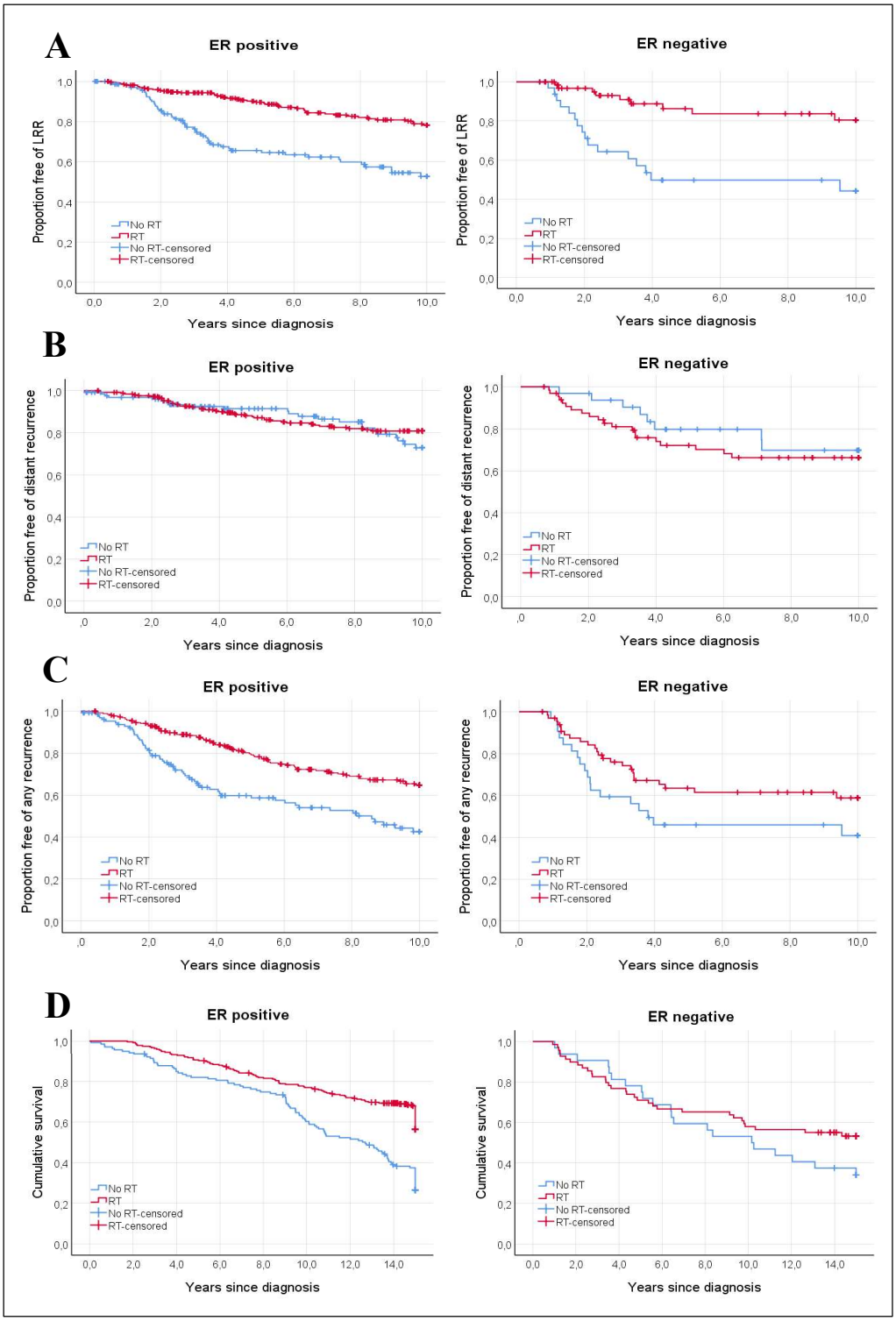


*Figure 2. Kaplan-Meier curves of cumulative survival, for A) LRR, B) distant recurrence, C) any recurrence and D) death. Separate curves are displayed for ER positive and ER negative patients. Abbreviations: ER oestrogen receptor, LRR locoregional recurrence.*

**The effect of ER status on response to RT**

Interaction terms between ER status and RT were included in separate Cox regression models for all outcomes (LRR, distant recurrence, any recurrence and death from any cause), in both unadjusted analysis and with adjustment for confounders. This is shown in *table 7*. The variables adjusted for are described under each outcome section. The interaction term was not significant for any outcome, meaning that the effect of RT did not statistically differ between ER positive and ER negative patients. For death, the interaction was nearly significant in an adjusted model (HR for interaction 0.384; 95% CI 0.147-1.003; p=0.051).

*Figure 2* depicts Kaplan-Meier curves for the different endpoints, separately for ER positive and ER negative patients. Separate curves are displayed for RT treated and non-RT treated in each graph. Upon visual inspection, ER positive patients treated with RT seem to have a slightly better prognosis concerning distant recurrence, any recurrence and survival. Furthermore, the difference in proportions free from distant and any recurrence, between RT and non-RT treated patients, is marginally bigger among ER positive than ER negative patients. The same can be seen for survival, while the opposite seems to be true for LRR.

Table 7. Hazard ratios and p-values for the interaction term between ER status and RT.

| Event | | HR for interaction ER*RT | P-value |
|---|---|---|---|
| **LRR** | Adjusted | 1.87 | 0.287 |
| | Unadjusted | 1.516 | 0.370 |
| **Distant recurrence** | Adjusted | 0.358 | 0.127 |
| | Unadjusted | 0.625 | 0.339 |
| **Any recurrence** | Adjusted | 0.672 | 0.415 |
| | Unadjusted | 0.867 | 0.688 |
| **Death** | Adjusted | 0.384 | 0.051 |
| | Unadjusted | 0.707 | 0.269 |

*Hazard ratios and p-values calculated with Cox regression models, in unadjusted analysis and adjusted for confounding factors (age, ER status, PgR status, endocrine treatment, chemotherapy, lymph node status, and, for LRR and any recurrence, radicality). Abbreviations: LRR locoregional recurrence, HR hazard ratio, ER oestrogen receptor, RT radiotherapy.*

**Identifying patient groups that may be spared RT or endocrine treatment**

Patients with low-risk factors in different combinations were grouped together, and their absolute recurrence risk calculated. Among patients not treated with RT, a group of 8 patients was identified where none of the patients had a LRR, these were >50 years at diagnosis, had a tumour of less than 15 mm, and had received endocrine treatment. Among 10 patients with the same characteristics who had received RT, one (10.0%) had a LRR. *Figure 3* compares these groups. The lowest recurrence rate in a somewhat larger group was 11.8%, among 17 patients aged >50 years at diagnosis, with an ER positive tumour of <18 mm, treated with endocrine therapy. Of these patients, 2 had a LRR within 10 years.

Patients not treated with endocrine therapy had a lower recurrence risk in general. Two distinct groups could be identified where the rate of LRR was <10% in 10 years. The first group included 36 patients with a tumour <25 mm who had received both RT and chemotherapy, these had a recurrence rate of 8.3%. 6 patients had the same characteristics but had not received RT, among these 1 (16.7%) experienced a LRR. *Figure 4* shows the effect of RT in this presumed low-risk group. The second group were >50 years old at diagnosis, had a radical surgery, < 3 lymph node metastases, an ER positive tumour and were treated with RT. This was true for 27 patients among whom two had a LRR within 10 years, resulting in a recurrence rate of 7.4%. There were 17 patients with the same characteristics who had not received RT, among these 5 had suffered a LRR (29.4%). As can be seen in *figure 5*, the prognosis for these patients was substantially worse than for those treated with RT.

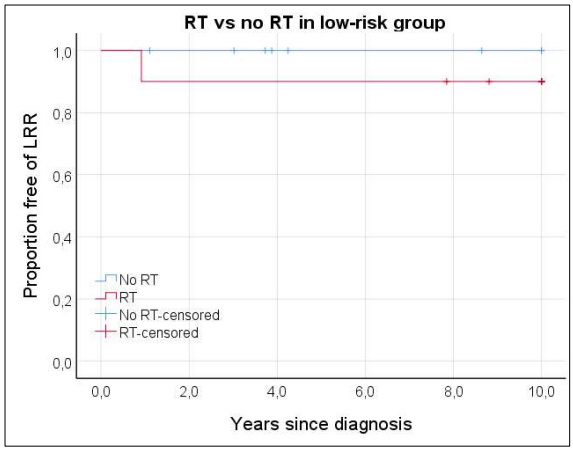


*Figure 3. Kaplan-Meier curve of proportion free of LRR for the first 10 years after diagnosis in a presumed low-risk group. 18 patients were included, aged >50 years with tumours <15 mm in size, and all had received endocrine treatment. Separate lines displayed for patients that had received RT (N=10) and patients who had not (N=8).*

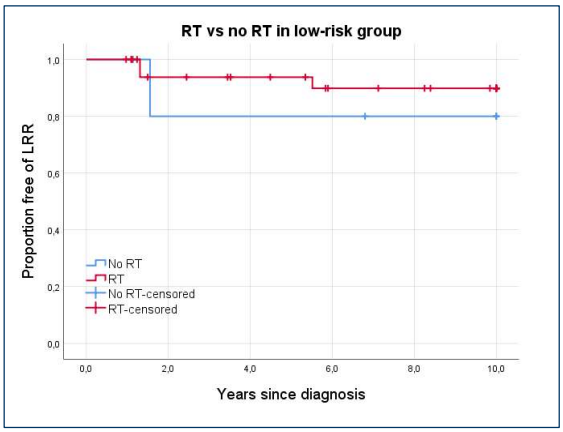


*Figure 4. Kaplan-Meier curve of proportion free of LRR for the first 10 years after diagnosis in a presumed low-risk group not treated with endocrine therapy. 42 patients were included, with tumours <25 mm in size, and all had received adjuvant chemotherapy. Separate lines displayed for patients that had received RT (N=36) and patients who had not (N=6).*

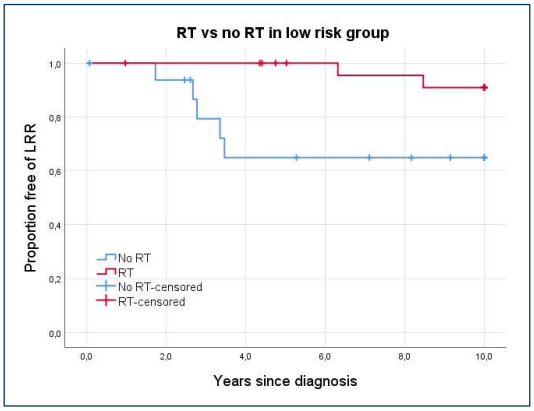


*Figure 5. Kaplan-Meier curve of proportion free of LRR the first 10 years after diagnosis, in a presumed low-risk group of 44 patients who had not received endocrine treatment. The patients were >50 years at diagnosis, had a radical surgery, < 3 positive lymph nodes, and an ER positive tumour. Separate lines displayed for patients treated with RT (N=27) and not treated with RT (N=17).*

# Discussion

The aims of this thesis were to describe the benefit of RT after BCS on the risks of recurrence and death, and to investigate the influence that ER status has on the RT effect, in a population-based cohort. We found that RT, in an adjusted model, reduced the risk of LRR within 10 years by 73%, the risk of any recurrence within 10 years by 62% and the risk of death from any cause within 15 years by 48%, while it had no statistically significant effect on the risk of distant recurrence. ER status was not associated with recurrence or death, and no difference in RT effect depending on ER status could be confirmed.

A further aim of the study was to identify, if possible, any patient groups within the cohort that had a sufficiently small recurrence risk without RT, and without endocrine treatment, that omission of the examined treatment could be considered. Among patients not treated with RT, one small group of eight patients could be identified of whom none had a LRR. Two distinct groups were identified where the risk of LRR in 10 years without endocrine treatment was 8.3% and 7.4%, respectively. In summary, based on the results from this cohort, there seem to be patients that may be spared endocrine treatment, if a risk of LRR of up to 8.3% in 10 years is considered acceptable.

**The effect of RT and other factors on recurrence and death**

RT was associated with a substantial decrease in the risk of LRR, any recurrence and death from any cause, while no effect was observed on the risk of distant recurrence. The largest effect was seen on LRR within 10 years, where RT reduced the risk by 72.5% (HR 0.275), and the absolute risk from 39.5% to 16.7%. The risk of any recurrence within 10 years in this study was 47.9% without RT and 31.5% with RT. RT reduced the risk by 62% (HR 0.378). In

addition, the median time to LRR and any recurrence was significantly longer in the RT group. The finding that the RT effect is largest on LRR is in line with previous studies (17), and corresponds well with the biological effect of RT as a means of eliminating any tumour cells remaining in the tissue after BCS, thus executing its largest effect on local disease control. In the EBCTCG meta-analysis (17), the 10-year risk of any first recurrence was 35.0% without RT and 19.3% with RT, a much lower rate than was observed in this study. RT halved the rate of any recurrence; hence, the effect of RT was bigger in our cohort.

The risk of death within 15 years was lowered by 48% with RT (HR 0.516), in absolute terms the risk was reduced from 69.9% to 42.6% (an absolute risk reduction of 27.3%). The EBCTCG meta-analysis (17) reported a 15-year absolute reduction in all-cause mortality of 3.0% with RT, corresponding to a relative reduction of 1/6. The considerable benefit of RT on survival in our cohort is therefore somewhat surprising. Patients that did not receive RT were older in general, however, age was adjusted for in the multivariable analysis. In light of this, it is probable that there is some other confounding factor in the analysis that has not been adjusted for, that partially explains the beneficial prognosis of RT-treated patients.

Surprisingly, we did not find an association between age and the risk of recurrence. This finding is contrary to previous studies which have suggested that young age is a strong risk factor for breast cancer recurrence (13-15). In general, patients in the RT group in this study were younger than in the no RT group. Since younger patients were more aggressively treated, the age difference could be a confounding factor, which could explain why age was not significantly associated with recurrence risk. Moreover, many studies have found that subtype is predictive of recurrence risk, with luminal A type generally having the best prognosis (14, 15, 18, 32), however, no such association was observed in this study.

**The effect of ER status on recurrence and RT effect**

Previous studies have described an association between ER-positivity and a lowered risk of recurrence (13, 31). Moreover, older women more often have ER positive tumours with a generally less aggressive biology, contributing to a low recurrence risk (31). This study did not, however, find an association between ER status and the risk of recurrence, although the proportions of RT treated patients free from distant and any recurrence at 10 years were slightly higher (though not significantly so) among ER positive patients.

No significant effect of ER status on the benefit of RT was confirmed. Nevertheless, the difference between RT treated and non-RT treated patients, regarding the proportion free of distant and any recurrence, is marginally larger in ER positive than in ER negative patients (although not significant). The interaction between ER status and RT was nearly significant for death ($p = 0.051$). However, since it was not significant for distant recurrence (and we assume that breast cancer death is mostly due to distant metastases), the effect seen on survival is most likely not a true effect but a result of selection to RT treatment. There is currently no consensus in the literature of whether ER status influences the response to RT. The EBCTCG meta-analysis (17) reported that RT was less effective among ER poor patients, Kyndi et al (36) found that RT was more effective among ER positive HER2 negative patients (after mastectomy), and Sjöström et al (35) found a larger, but not significantly different, effect of RT in ER positive patients. No definite conclusions can be drawn from the present study, although the results accord somewhat with those of Sjöström et al.

**Groups that may be spared RT or endocrine treatment**

Among patients not treated with RT, one group of eight patients was identified among whom none had a LRR within 10 years. These patients were characterized by an age >50 years at

diagnosis, tumour size <15 mm, and treatment with endocrine therapy. There were 10 patients with the same characteristics who had received RT, among these 1 (10.0%) had a LRR. Several studies have suggested the possibility to omit RT in patients with a favourable prognosis (30, 31, 34), while some have stated that the recurrence risk without RT is still relatively high in a low-risk group and that all patients benefit from RT (33, 35). In our study there was a low-risk group where none of the patients had experienced a LRR without RT, but since it only contained eight patients, this result is difficult to interpret.

Two distinct groups were identified that had a risk of LRR of <10% in 10 years without endocrine treatment – one group of 36 patients among whom 8.3% had a LRR, and one group of 27 patients among whom 7.4% had a LRR. The first group included patients with a tumour size <25 mm and had received both chemotherapy and RT, while the second group were >50 years at diagnosis, ER positive, had a radical surgery, < 3 positive lymph nodes, and had received RT. This finding suggests that for patients with similar criteria, omission of endocrine treatment could lead to a 10-year risk of LRR of up to 8.3%. Similar to the results by Sjöström et al (35), this points towards endocrine treatment being less of a necessity than RT for the prognosis of low-risk breast cancer patients.

**Aspects that may have affected the results**

Apart from the inclusion criteria described in the Methods section of this paper, there was no intentional selection of patients. However, there were 122 patients for whom we were not able to find any follow-up information. This may have created an unintended selection, since patients who had been deceased for many years were subsequently erased from the medical records system Melior. The question arises of whether these patients differed in any way from those included in the study. The frequency of RT treatment did not differ significantly

between the groups (p=0.513), neither did the median age (0.764). Nevertheless, it is possible that there were more recurrences in the excluded group, which caused an earlier death.

Patient data was sampled from three different sources for different patients (printed medical records from hospital archives, digital medical records in Melior, or register data), and the information provided might have varied between them. Review of patient data in digital and printed records provided essentially the same information, although pathology reports were not available as frequently in the digital records. A comparison was made between reviewed and non-reviewed (register data) patients. The main differences were the follow-up time which was considerably longer for reviewed patients, and the percentages of missing values for grade and lymph node status that were substantially higher in the register data group.

There are some factors that may have influenced the results of this study. Firstly, as there were two persons reviewing and summarizing patient data, it cannot be excluded that in some cases variables were interpreted differently, although we did take care to discuss all variables, definitions and criteria on numerous occasions and with an experienced clinician. Secondly, the patients were treated at different hospitals around the VGR, and since the study was retrospective, it is possible that clinical practice differed slightly between different clinicians and hospitals. Thirdly, the length of follow-up ranged from less than a month to over 30 years, in extreme cases, although the interquartile range was 4.1 years to 16.1 years. For patients that were reviewed, the last follow-up was noted as the last visit to the Department of Surgery or Oncology where breasts and lymph nodes were palpated, or otherwise if recurrence status was clearly stated. However, the length of follow-up for register data could not be controlled. Additionally, most patients' clinical follow-up was terminated after five to ten years, and only those that had a recurrence were followed up anew (for breast cancer,

some patients were followed up for other diseases). Therefore, it is probable that patients who did not experience a recurrence had a shorter follow-up in general in this study.

Additional analyses with Kaplan-Meier curves were conducted to check if the distribution of competing events for the different outcomes (events described in detail in the Methods section of this report) differed between the RT and no RT groups (data not shown). For distant recurrence, the frequency of competing events was significantly higher in the no RT group (15% compared to 7.7% in the RT group, p=0.01). Among non-RT treated patients, 14 patients (8.4%) had died within 6 months and 11 patients (6.6%) had been diagnosed with contralateral breast cancer, and among RT treated patients 8 patients (2.4%) had died within 6 months and 18 (5.3%) been diagnosed with contralateral breast cancer.

The multivariable analyses were adjusted for confounders such as age, adjuvant treatment, hormone receptor status, lymph node status and radicality of surgery. Still, there may be confounding factors in the analyses, particularly for survival where the effect of RT was unexpectedly large. The analyses were not adjusted for malignancy grade, due to the fact that 43% of the values were missing. Similarly, s phase was not adjusted for because 67% of the values were missing. Thus, this study lacks a proper measurement of grade and proliferation marker, that could be confounding factors. Patients not treated with RT are likely to have more comorbidity, and be less healthy overall, something that would affect the rate of survival. It is possible that there are other confounding factors that may have influenced the results of this study as well.

The studied cohort has been referred to as “population-based”. It is of value to discuss this term, as the exact ways in which this cohort relates to the underlying breast cancer population

have not yet been studied. The patients that form this cohort were gathered from the bio bank of frozen tumour material, from patients treated with BCS in the VGR between 1989 and 1999, who were <80 years at diagnosis and had no distant metastases. Apart from this there are some other factors that may have led to a patient not being included in the biobank, most importantly the size of the tumour. This is because the tumour material in the bio bank was extracted and frozen in order to analyse the hormone receptor expression of the tumour, and to enable this analysis the tumour material had to be of a certain size. Thus, for very small tumours (a few millimetres in diameter), this procedure was often not done at all because no result was likely to come from the analysis, and no tumour material was stored in the bio bank. Therefore, there is a selection in the cohort, with a low proportion of small tumours and a high proportion of larger tumours.

**Strengths and limitations**

A strength of this study is that the cohort is population based and therefore reflects the underlying breast cancer population and clinical practise of the studied time period in the VGR. A limitation is that the study was retrospective and non-randomised, which in itself creates some bias. Patients treated with RT were generally younger, had more positive lymph nodes, and were presumably more healthy and less burdened by other diseases than those who were not treated with RT. Many previous studies have been prospective and randomised, which reduces confounding factors and thus provides more reliable results (13, 16, 30, 31). Nonetheless, we have attempted to take into consideration and adjust for any confounding factors. Another limitation is the relatively small size of this cohort compared to some other studies in the field (13, 15, 31). In spite of this, the number of recurrences observed in this cohort was high, increasing the power of the study. There was a high percentage of missing

data for some variables, i.e., malignancy grade, lymph node status, and s phase, limiting the capacity to test these clinical markers. We did not always have access to pathology reports, and even when we did the definitions and methods used may have differed between pathologists and hospitals. Some previous studies have used centralised pathology, as a way to ensure that the pathological assessments were consistent (35). As opposed to some previous studies with little to no use of systemic treatment, many patients in this cohort were given adjuvant systemic treatment (53.6% of ER-positive patients received endocrine treatment, and 27.2% of all patients received chemotherapy), which is more similar to current clinical practise. Lastly, a limitation is that HER2 status was not measured on these patients and none were given the anti-HER2 drug trastuzumab, as this was not clinical practise at the time.

# Conclusions and Implications

The purpose of this study was threefold; firstly, to describe the effect of RT after BCS; secondly, to examine the effect of ER status on RT effect; and thirdly, to identify any potential groups within the cohort that had a sufficiently low recurrence risk that they may be spared RT or endocrine treatment. We found that, in this population-based cohort of 530 patients, RT reduced the risk of LRR and any first recurrence substantially within the first 10 years after diagnosis, and greatly increased overall survival the first 15 years. We could not confirm any influence of ER status on the benefit of RT, although the results pointed towards there being some effect. One small group was identified, where none of the patients had experienced a LRR without RT. Two distinct groups were found where the risk of recurrence without endocrine treatment was 8.3% and 7.4%, respectively. Although these particular results need to be interpreted with some caution due to the low numbers of patients, this suggests that depending on the value placed on LRR, omission of endocrine treatment would be a reasonable option for patients with these characteristics. In addition, our results further demonstrate the invaluable advantage that RT provides after BCS. In the future, a more detailed subtyping or genetic profiling might enable a nuanced understanding of the cellular processes that affect RT effect, as well as aid the development of individualized breast cancer treatments.

# Populärvetenskaplig sammanfattning

Examensarbete på Läkarprogrammet, Göteborgs Universitet 2021

Filippa Sjölin

*Behandlingsalternativ vid bröstcancer och betydelsen av tumörens hormonkänslighet för effekten av strålbehandling*

Operation, strålbehandling, cellgifter, antihormonell behandling… Efter det omskakande bröstcancerbeskedet kommer för många patienter nästa smäll, den tuffa behandlingen. Behandlingen innebär för många patienter besvärliga biverkningar, och det är inte alla som gynnas av att få flera olika typer av behandling. Den här studien undersökte effekten av strålbehandling och hur nyttan varierar med bröstcancerns egenskaper, och försökte identifiera patienter där det gör mer skada än nytta att kombinera olika behandlingar.

Behandlingen av bröstcancer inkluderar nästan alltid kirurgi, som ofta följs av strålbehandling, cellgifter eller antihormonell behandling. Antihormonell behandling kan ges vid hormonkänslig tumör, det vill säga en tumör som har en tillväxteffekt av kvinnligt könshormon. Dessa behandlingar syftar till att eliminera eventuella kvarvarande tumörrester i kroppen efter operationen, och minskar risken för canceråterfall. Tyvärr medför behandlingen ofta biverkningar. Strålbehandling kan till exempel ge hudbiverkningar och i värsta fall påverka hjärtat och lungorna, och antihormonell behandling ger ofta symptom som liknar klimakteriebesvär.

Studien tittade på effekten av strålbehandling och hur den skiljde sig mellan olika patienter. Det finns tidigare studier som pekar mot att hormonkänsliga tumörer kan ha bättre effekt av

strålbehandling än andra, detta samband ville man undersöka. Man försökte även identifiera egenskaper hos patienter som hade en mycket låg risk för återfall trots att de inte hade fått strålbehandling respektive antihormonell behandling. För patienter med liknande egenskaper skulle man i framtiden kunna överväga att helt avstå från antingen det ena eller det andra, för att bespara patienten besvär med biverkningar. I studien granskades patientjournaler från 530 kvinnor i Västra Götaland som fick bröstcancer under 90-talet. Patienternas egenskaper noterades, och man jämförde andelen av de strålbehandlade och de icke strålbehandlade patienterna som fick ett återfall inom tio år efter operationen.

Resultaten visade att 35 procent av patienterna hade fått ett återfall inom 10 år. Strålbehandling ökade överlevnaden och minskade risken för återfall med mer än hälften, men tumörens hormonkänslighet påverkade inte effekten av strålbehandlingen. Bland patienter som inte fått antihormonell behandling fanns en grupp av patienter där endast åtta procent fått återfall inom tio år, dessa patienter hade en liten tumör och hade fått både cellgifter och strålbehandling. I en annan grupp fick sju procent återfall, där var patienterna över 50 år vid diagnos, de hade en hormonkänslig tumör utan spridning, som opererats bort med goda marginaler runtom, och de hade fått strålbehandling. Det var däremot få patienter som hade en låg återfallsrisk utan strålbehandling, som verkade gynna de allra flesta.

Sammanfattningsvis bekräftade den här studien att strålbehandling är en viktig del i behandlingen av bröstcancer. Effekten var utmärkt för alla patientgrupper och påverkades inte av tumörens hormonkänslighet. Två patientgrupper identifierades, där återfallsrisken utan antihormonell behandling var så låg att man för liknande patienter i framtiden kan tänka sig att avstå från denna behandling. Detta skulle möjliggöra riktade insatser hos patienter som verkligen behöver det och bespara andra patienter onödiga biverkningar.

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