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LOCAL RECURRENCE AFTER BREAST CONSERVING SURGERY IN BREAST CANCER

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ABSTRACT

The general aim of this thesis was to gain increased insight into the problem of local recurrences after breast conserving surgery for breast cancer.

In a population-based cohort of 4,694 women with invasive breast cancer, operated in 1981 to 1990 and followed through 1997, we studied how breast conserving surgery had been adopted into clinical practice. As adoption became more widespread, the indications for this type of surgery broadened. A simultaneous moderate impairment of the results was noted. Generally, the risk of local recurrence was higher than expected, but the estimated survival rates were gratifying. The overall risk of local recurrence was 9.2% at five years and 21.1% at ten years, and the breast cancer-specific survival was 93.3% and 85.2% at five and ten years, respectively. A large proportion of the women had non-protocol treatment; nearly 30% were not given radiotherapy.

Prognosis and prognostic factors after a local recurrence in the breast were studied in 391 women from a population-based cohort of 6,613 women. The prognosis differed notably between the different subgroups of breast recurrences, the subgroups being defined by time to and location of recurrence. Radiotherapy prevented or delayed the appearance of a local recurrence, but had little influence on the breast cancer-specific survival in women who experienced a local recurrence. The strongest independent prognostic factors for breast cancer-specific survival were time to local recurrence and Nottingham Prognostic Index.

In the cohort of 6,613 women, 92 women experienced a local recurrence in the axilla. The overall risk of axillary recurrence in the cohort was 1.0% at five years and 1.7% at ten years. The major risk factors for axillary recurrence were low age, large tumour size and minor or no axillary surgery, while radiotherapy to the breast reduced the risk of axillary recurrence. The breast cancer-specific survival after axillary recurrence was poor, 59.2% and 43.5% at five and ten years, respectively.

In an analysis of risk factors for local recurrence including 491 cases and 1,098 controls from a cohort of 7,502 women with invasive or non-invasive breast cancer, multivariate analysis showed low age, multicentricity and unclear/unknown surgical margins to be associated with an increased risk of local recurrence, while radiotherapy to the breast and adjuvant hormonal therapy were protective. Cancer in situ was not associated with a higher risk of local recurrence than invasive cancer. Nottingham Histologic Grade and Nottingham Prognostic Index were not helpful in determining the risk of local recurrence.

The time relation between local recurrences and distant metastases was studied in a cohort of 5,496 women with invasive breast cancers. Women who had experienced a local recurrence had a higher hazard rate of distant metastases than women with no local recurrence, and the hazard rate curve showed two peaks, at three and seven years after the primary operation. In women with early breast cancer who had experienced a local recurrence, the second peak represented approximately half of the documented distant metastases, and may be explained by dissemination from the local recurrences.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Fredriksson I, Liljegren G, Arnesson L-G, Emdin S O, Palm-Sjövall M, Fornander T, Frisell J, Holmberg L. Time trends in the results of breast conservation in 4,694 women. Eur J Ca 2001; 37: 1537-1544

II. Fredriksson I, Liljegren G, Arnesson L-G, Emdin S O, Palm-Sjövall M, Fornander T, Holmqvist M, Holmberg L, Frisell J. Local recurrence in the breast after conservative surgery – a study of 391 recurrences. Eur J Ca 2002; 38: 1860-1870 (in press)

III. Fredriksson I, Liljegren G, Arnesson L-G, Emdin S O, Palm-Sjövall M, Fornander T, Holmqvist M, Holmberg L, Frisell J. The consequences of axillary recurrence after conservative breast surgery. Br J Surg 2002; 89: 902-908.

IV. Fredriksson I, Liljegren G, Palm-Sjövall M, Arnesson L-G, Emdin S O, Fornander T, Lindgren A, Nordgren H, Idvall I, Holmqvist M, Holmberg L, Frisell J. Risk factors for local recurrence after breast conserving surgery. Submitted.

V. Fredriksson I, Blomqvist C, Holmqvist M, Frisell J, Holmberg L. Local recurrence in breast cancer – a cause of dissemination and death? In manuscript.

CONTENTS

LIST OF ABBREVIATIONS

AR	Local recurrence in the ipsilateral axilla
BR	Local recurrence in the ipsilateral breast
CAFt	Cyclophosphamide, Doxorubicin, Ftorafur
CI	Confidence interval
CMF	Cyclophosphamide, Methotrexate, 5-Fluorouracil
DCIS	Ductal carcinoma in situ
EIC	Extensive intraductal component
ER	Estrogen receptor
Gy	Gray
HR	Hazard rate
LCIS	Lobular carcinoma in situ
LR	Local recurrence
OR	Odds ratio
NHG	Nottingham Histologic Grade
NPI	Nottingham Prognostic Index
RH	Relative hazard
ROC	Receiver operating characteristic
RR	Relative risk
RT	Radiotherapy
SE	Standard error
SEM	Standard error of the mean

1 INTRODUCTION

Breast cancer is the most common cancer among women in the western world, with the life-time risk of developing breast cancer estimated to be 1 in 10. More than 6,300 new cases were diagnosed in Sweden in 2000 [1], after an average annual increase of 1.5 % during the previous decade. At around 1,500 breast cancer deaths per year [2], breast cancer mortality remained relatively stable, although with a downward trend, probably reflecting the combined benefits of early detection and better treatment.

During the 1980s, when large randomised clinical trials had shown that the results after breast conserving surgery and postoperative radiotherapy were very similar to those after mastectomy, breast conserving therapy became the treatment of choice for early breast cancer.

At a ten-year follow-up, a local recurrence in the ipsilateral breast or axilla, has occurred in 10-20% of those operated with breast conserving surgery for an invasive breast cancer. That incidence is of the same magnitude as the incidence of chest wall recurrences after mastectomy. A local recurrence often leads to loss of the breast, and is also known to be associated with an increased risk of distant metastasis and death from breast cancer.

The numerous questions regarding the results of breast conserving surgery when practised routinely, the prognosis associated with a local recurrence in breast or axilla, the risk factors for local recurrence and whether a local recurrence could be a source of distant dissemination led to the research effort presented in this thesis.

2 BACKGROUND

2.1 PRIMARY SURGERY FOR BREAST CANCER

The results of breast conserving therapy and mastectomy are similar in terms of distant disease-free and breast cancer-specific survival [3-7]. Breast conserving therapy, combining breast conserving surgery and postoperative radiotherapy, was introduced in Sweden in the late 1970s and became more widely used during the 1980s. It is now the treatment of choice in women when tumour size allows for radical removal with a good and cosmetic result.

The proportion of women who can be offered breast conserving surgery in a given population varies with the presence of mammography screening and the distance to a radiotherapy unit. In Sweden a notable regional variety in the usage of breast conserving surgery has been observed [8], the proportion ranging between 35% and 75% [9]. In 1991 the US National Institutes of Health consensus conference stated that breast conserving procedures could be recommended to at least 50% of all women with operable breast cancer [10].

Breast conserving surgery is not a uniform surgical procedure. In trials and studies of breast conserving treatment, the extent of breast surgery ranges from tumourectomy with a minimal surgical margin to quadrantectomy. The wider the excision, the lower the risk of local recurrence [11] but also the more difficult it is to achieve a good cosmetic result [12, 13]. To facilitate the interpretation and comparison of results from different studies, some investigators have tried to standardise the surgical procedure [14].

Mastectomy has traditionally been the gold standard in the treatment of early stage breast cancer. It remains an excellent choice for some patients, as a sole operation or combined with simultaneous or delayed reconstructive surgery, for example when wanting to avoid radiotherapy. Patients best treated with mastectomy include those with large tumours in small breasts, large central tumours, multifocal/multicentric disease, collagen vascular disease or a previous history of breast irradiation.

Axillary surgery has generally been indicated in all patients with an invasive breast cancer. Axillary dissection is primarily a staging procedure to determine prognosis and select appropriate adjuvant therapy, but does also lead to good loco-regional control and in it-self benefits survival [15, 16].

At axillary surgery, the number of retrieved nodes shows a linear relationship with the number of detected positive nodes until more than ten nodes have been retrieved [17, 18]. The fewer the nodes that are removed, the greater is the likelihood of understaging disease and of decreased survival [19]. Also, the fewer the nodes removed, the greater is the likelihood of leaving involved nodes in the axilla and the higher the incidence of axillary recurrence [19-22]. On the other hand, the greater the extent of the axillary dissection, the greater the risk of arm morbidity such as lymphedema [23, 24]. The reasonable compromise between the competing goals of accurate staging, regional control and avoiding postoperative complications has been suggested to be the removal of ten axillary lymph nodes [25, 26].

Axillary radiotherapy is an alternative to axillary dissection but does not provide the important prognostic information and is associated with somewhat poorer loco-regional control [27].

A more selective approach in axillary surgery, sentinel node biopsy [28-32], is currently under investigation. With this technique, the sentinel node - the first node that receives lymph drainage from the tumour area – is located and removed for histological examination, which indicates the status of the remaining nodes and the necessity of subsequent axillary dissection. The results are promising, but as the long-term risk of axillary recurrence is still uncertain, the method remains investigational.

2.2 POSTOPERATIVE ADJUVANT RADIOTHERAPY

Postoperative radiotherapy after breast conserving surgery reduces the risk of local recurrence in the operated breast [4, 11, 33-36], possibly by destroying residual tumour cells left in the surgical field and eliminating undetected multifocal lesions.

There is no world-wide uniformity in the radiation dose and fractionation that are used after breast conserving surgery. In Sweden, radiotherapy to the breast is generally delivered as two opposed tangential fields in 25 fractions of 2 Gray (Gy) up to a total dose of 50 Gy over 33 days. An additional boost to the initial tumour bed has not been used to any extent, due to lack of evidence of its necessity in patients with free margins and comparatively large resections. Recent data have shown that an additional booster dose of 16 Gy nearly halved the annual odds of local recurrence, with the greatest absolute benefit for the youngest women [37]. Radiotherapy to the regional lymph nodes, including the axillary, supraclavicular and infraclavicular nodes, has generally been offered women with node-positive disease.

The need for radiotherapy in all patients after breast conserving surgery is still a controversial issue. No subgroups of patients have been identified that do not benefit from radiotherapy. Thus, breast irradiation is still considered standard treatment for all patients with invasive cancers operated with breast conserving surgery.

Loco-regional radiotherapy after mastectomy reduces the risk of a chest wall recurrence in all patients [38]. However, postmastectomy radiotherapy has generally been offered only to patients at high risk of a chest wall recurrence, i.e. those with advanced tumours or four or more involved axillary nodes.

Whether the improved local control associated with radiotherapy after breast conserving surgery and mastectomy also leads to increased survival remains controversial, although results indicating that this is the case have been published recently [36, 39-41]. Some investigators have stated that large studies with a long-term follow-up would be needed to detect a difference in overall survival. In the meta-analysis published by the Early Breast Cancer Trialists' Group [36], the survival benefit from radiotherapy was overshadowed by an increased mortality in cardiovascular disease.

2.3 POSTOPERATIVE ADJUVANT SYSTEMIC TREATMENT

Adjuvant systemic treatment is well established and is now offered all women with node-positive disease and to a majority of women with node-negative disease. The randomised trials concerning the efficacy of systemic treatment have focused on its impact on distant metastasis and survival. For women with estrogen-receptor (ER) positive tumours, tamoxifen is significantly associated with a decreased risk of distant metastasis and an improved survival [42]. Polychemotherapy is associated with a decreased risk of distant metastasis and an improved survival in women with either node-negative or node-positive disease [43].

Few investigators have studied the effect of adjuvant systemic therapy on the risk of local recurrence after breast conserving surgery. However, results regarding systemic treatment as a possible substitute for radiotherapy seem unequivocal. Compared with radiotherapy alone, chemotherapy and tamoxifen are both associated with a higher risk of local recurrence after breast conserving surgery [4, 35]. However, adjuvant systemic therapy given in conjunction with radiotherapy after breast conserving surgery does seem to be better than radiotherapy alone [4, 44-47]. Buchholz et al [47] found no difference in the local control between chemotherapy and tamoxifen. A combination of chemotherapy, hormonal therapy and radiotherapy after breast conserving surgery may have an even greater impact on the risk of local recurrence [48].

2.4 LOCAL RECURRENCES – DEFINITION AND INCIDENCE

Generally, local recurrence is defined as the appearance of any new breast tumour, invasive or in situ, in the ipsilateral residual breast, in the overlying skin or in the ipsilateral axilla. In recent studies, axillary recurrence is frequently recorded separately, and the term local recurrence is restricted to recurrences in the breast and in the overlying skin. Regional recurrence refers to a new appearance of tumour growth in the axilla, in the parasternal lymph nodes or in the infraclavicular lymph nodes. Loco-regional recurrence is a collective term used for recurrences appearing in any of the locations mentioned above. Supraclavicular recurrences are defined as distant metastases, according to the UICC classification [49]. Most often only the recurrences occurring before or at the same time as the diagnosis of a distant metastasis are included in the definition as local recurrences appearing after distant metastases may be less accurately recorded.

The risk of a local recurrence in the breast after breast conserving surgery is between 1% and 2% per year and is relatively constant over time, with an overall ten-year risk of 10-20%. However, the reported incidences do vary considerably between series, due to differences in patient selection, extent of surgery and usage of postoperative adjuvant radiotherapy and systemic treatment. Although the risk of local recurrence after mastectomy has generally been considered to be much lower than after breast conserving surgery, most of the randomised comparative have not demonstrated any significant difference in this respect [5, 11, 50-53].

According to a US study, approximately 5-10% of the women with a local recurrence after breast conserving surgery present with concurrent distant metastases and another 5-10% are inoperable because of advanced local disease [54].

The majority of local recurrences occur in the area of the previous excision [55-57] and are most likely due to incomplete removal of the primary tumour. As the time since the primary operation increases, so does the proportion of local recurrences in another quadrant [56-59]. Recurrences in another quadrant may originate from an unknown multicentric focus of the same monoclonal origin as the primary tumour, or may be a new, second primary tumour [56, 58, 60, 61]. There are difficulties in distinguishing "true" local recurrences from "new primary tumours", although some investigators have tried to do so by comparing location, histological type, Nottingham Histologic Grade (NHG) and DNA flow cytometry between primary tumours and local recurrences [61, 62]. A majority of the local recurrences have the same histological characteristics as the primary tumours [63, 64]. About 90% of the recurrences are invasive [55, 65]; the proportion of non-invasive recurrences rises with the duration of the follow-up [66].

Local recurrences after breast conserving surgery without postoperative radiotherapy are known to appear earlier than those with prior irradiation [67].

2.5 RISK FACTORS FOR LOCAL RECURRENCES IN THE BREAST

Many variables related to the patient, the tumour and the treatment have been considered as possible risk factors for local recurrence. The results have tended to conflict, possibly reflecting differences in patient selection, type of breast conserving surgery, postoperative treatment and length of follow-up. Many studies have included comparatively few patients, which limits the statistical power of this type of analysis. As many potential risk factors for local recurrence are also risk factors for distant metastases, the problem of competing risks may obscure an association with local recurrence (patients with distant metastases get censored in further life-table-analysis regarding local recurrence) [68, 69].

The most established risk factors - associated with a risk that is at least two- or three-fold greater than the average, or greater than the risk of a chest wall recurrence following mastectomy - are age, surgical margin, multicentricity and vascular invasion. Another important risk factor in subgroups of patients is an extensive intraductal component (EIC).

2.5.1 Age

Age is one of the most established risk factors for local recurrence after breast conserving surgery [53, 70-76]. The risk seems to be a continuous function of age, decreasing by 3% per year of increasing age [74]. Most of the attention regarding age has concentrated on very young women, for whom risk of recurrence is highest. The lack of a consistent definition of young age has contributed to the differences in the level of the increased risk associated with this variable. Nixon et al [71] reported a less than two-fold risk for women younger than 35 years compared to women aged 35 to 65, while Elkhuizen et al [75] found a four-fold risk for women under 45 years compared to women over 65 years.

Whether low age is also a risk factor for local recurrence after mastectomy is controversial, leading to difficulties when using age in decision-making between the two types of surgery [11, 53, 77, 78].

Younger patients are known to have a higher prevalence of high NHG, hormone receptor negativity, vascular invasion [71], and EIC [70, 79, 80], although this can only partially explain the higher risk of local recurrence. Low age has also been shown to be an independent predictor of breast cancer-specific survival and distant disease-free survival after breast conserving surgery [71, 72, 75, 76]. Fowble et al [72] found that the adverse effect on outcome was statistically significant only for node-negative patients.

2.5.2 Surgical Margin

Several investigators have reported a significantly increased rate of local recurrence in patients with positive surgical margins compared to those with negative margins [81-85]. Furthermore, focally positive margin is associated with a lower risk of local recurrence than a margin that is more extensively positive [81, 85, 86]. The risk does not seem to be affected by whether the tumour present at the resection edge is invasive or in situ [85].

While it is generally accepted that a positive margin is defined by the presence of tumour cells immediately at the resection edge, the definitions of negative and close margins differ among the published studies. Negative margin has been defined as the absence of cancer cells immediately at the resection edge or within a distance of 1 to 5 mm. In the studies that defined a negative margin as more than 3 mm, the risk of local recurrence was not found to be lower than in studies using less strict definitions [84].

A close margin has been defined as cancer cells within 1 to 5 mm from, but not involving, the resection edge. Series using strict definitions of close have not found any difference in the risk of local recurrence between close and negative margins, while in series using a definition of close margins as within 2 mm, the risk of local recurrence was comparable to that seen in patients with positive margins [84].

It is debatable whether higher doses of radiotherapy can fully compensate for the higher risk of local recurrence associated with positive margins [83, 84, 86, 87]. The effect of adjuvant systemic treatment on the risk associated with positive margins has also been studied [84, 85]. A re-excision of an initially positive margin that results in a negative final margin reduces the risk of local recurrence to that of an initially negative margin [84, 88].

Apart from the differences in definitions, there are also institutional differences in the methods and the extent of margin evaluation, making it difficult to compare the magnitude of the increased risk associated with margin involvement. But irrespective of the definition and the method used, the status of the surgical margin does provide an indication of the amount of residual cancer in the breast [89].

In a few series, margin involvement has also been found to be significantly associated with the risk of distant metastases [81, 83].

2.5.3 Multicentricity

Multifocality/multicentricity is defined as the presence of more than one cancer in the breast; the distinction between the two is based on whether or not the multiple foci are located in the same quadrant. Multicentricity, used here as a collective term for both

multifocality and multicentricity, is most often seen in invasive ductal tumours; in view of histological and immunohistochemical similarities between the foci, it has been suggested to result from a monoclonal proliferation [90].

Even when the detected multiple foci are totally resected, patients with multicentricity are, at an increased risk of local recurrence after breast conserving surgery [76, 91, 92]. Multicentricity within the sample is generally considered to be an indicator of foci in the rest of the breast, making breast conserving surgery unsuitable. The higher the number of multicentric foci, the greater the risk of local recurrence [92].

The prevalence of multicentricity varies greatly between series, probably due to differences in definitions and methods for detection. Kurtz et al [92] reported a trend for multicentricity diagnosed clinically or mammographically to have a closer association with local recurrence than multicentricity diagnosed by histopathology alone. Studying multicentricity in mastectomy specimens, Holland et al [93] found multicentric foci, in situ or invasive, beyond the index tumour in 63% of patients; 90% of the foci were located within the same quadrant. Conversely, Vaidya et al [94] found that nearly 80% of their patients had a multicentric foci beyond the index quadrant, widely scattered throughout the breast. Vaidya et al described an increasing incidence of multicentricity with increasing tumour size, while Holland et al found no such association.

Women with multicentricity are reported to have a higher prevalence of EIC as well as a greater frequency of positive surgical margins [91, 92].

Multicentricity has also been shown to be a risk factor for distant metastases after breast conserving surgery [53] but is not associated with any adverse outcome after mastectomy [95].

2.5.4 Vascular Invasion/Lymphovascular Invasion

Invasion of cancer cells into blood vessels and/or lymphatic vessels, analysed together or separately, has been shown to be associated with an increased risk of local recurrence [53, 73, 76, 96-99] and distant metastases [53, 98, 99] after breast conserving surgery. Here, too, the definitions vary between investigators, leading to a wide range in the reported frequency of the variable, from 5% to 70% of the patients. Questions have been raised about the variable's reproducibility. Clemente et al [98] found that the frequency of patients with vascular invasion at review rose from 7% to 20% compared to the initial histopathology reports, while the predictive value regarding outcome decreased.

Vascular and lymphovascular invasion are also associated with an increased risk of local recurrence after mastectomy and should therefore not be used for decision-making between conservative surgery and mastectomy [53].

2.5.5 Extensive Intraductal Component

EIC is the risk factor that has been analysed most extensively. EIC was initially defined as the simultaneous presence of cancer in situ within the primary tumour, comprising 25% or more of the tumour mass, <u>and</u> cancer in situ clearly extending beyond the infiltrating margin of the tumour or present in grossly normal adjacent breast tissue [100]. Alternative

definitions have been proposed, most often based on presence of cancer in situ adjacent to the primary tumour [53].

The prevalence of EIC varies greatly between series, with a higher reported prevalence in younger women [70, 79, 80]. EIC is known to be related to high NHG, multicentricity and positive surgical margins [79, 99]. Presence of EIC accordingly correlates with the quantity of residual disease, particularly intraductal disease, remaining in the breast after conservative surgery, and is also associated with residual disease at a distance from the primary tumour [81, 101]. The higher the degree of EIC, the higher the risk of local recurrence [79]. In cases with large resections and negative margins, EIC is seemingly of little prognostic value [73, 81, 82]. Jacquemeir et al [79] also noted EIC to be of limited importance as a risk factor in postmenopausal women. Moreover, they found EIC to be a risk factor only for local recurrences appearing in the same quadrant as the primary tumour. Boyages et al [102] noted that of the local recurrences after an EIC-positive tumour, 88% were located in the region of the primary tumour, while the figure for EIC-negative tumours was 55%.

EIC has not been reported to be a risk factor for either local recurrence after mastectomy [53] or for distant metastases [53, 99, 103].

2.5.6 Other Risk Factors

Nottingham Histologic Grade (NHG) is an important predictor of distant metastases and breast cancer-specific survival in breast cancer [53, 104, 105]. Whether NHG is also a risk factor for local recurrence is controversial. Some investigators report that the risk of local recurrence increases with an increasing NHG [80, 99, 104, 106], while others have found no such association [53, 76, 105].

Tumour size is another important predictor of distant metastases, but does not, in most studies, appear to influence the risk of local recurrence. The lack of importance for the risk of local recurrence has been suggested to be a consequence of the use of adjuvant chemotherapy in women with large tumours which are often node-positive, and the use of postoperative radiotherapy. Fisher et al [107] reported tumour size to be the only significant risk factor for local recurrence after lumpectomy in the ten year follow-up of the NSABP B-06 randomised trial.

Lobular tumours are associated with a higher risk of chest wall recurrence after mastectomy [53], whereas an increased risk has usually not been seen after breast conserving surgery [53, 73, 76]. Suggested reasons for this difference has been the routine use of radiotherapy after conservative surgery but not after mastectomy, and that lobular tumours may be more sensitive to radiotherapy than ductal tumours. In the Swedish randomised trial of sector resection with or without radiotherapy, both lobular and comedo cancers showed an increased risk of local recurrence [74].

Nodal status does not appear to be associated with an increased risk of local recurrence after either breast conserving surgery or mastectomy, but here too the results from different series are contradictory [53, 63, 76, 97, 108, 109]. Some investigators have

suggested that the lack of an association may be due to the almost universal use of radiotherapy and adjuvant therapy in node-positive patients [108, 110].

Among other variables discussed as potential risk factors are pausality [64, 76, 83, 111], hormone receptor status [73, 76, 108], mononuclear cell reaction [80], BRCA-1 and -2-mutations [112-114] and over-expression of growth factors [115].

2.6 THE PROGNOSTIC IMPACT OF A LOCAL RECURRENCE

Local recurrence is associated with an increased risk of distant metastases [59, 63, 64, 67, 76, 107, 116, 117] and death from breast cancer [60, 67, 117]. Estimates of the magnitude of the increased risk of distant metastases range from two- [67] to ten-fold [64], and the increased mortality from two- to four-fold [67, 117]. The risk decreases significantly with increasing time from primary operation to local recurrence [56, 59, 63, 64, 107, 118]. Whelan et al [67] found that the increased relative risk of distant metastasis was higher for women with local recurrences appearing after radiotherapy than for non-irradiated women with a local recurrence, although the difference was not statistically significant.

Many other factors have also been analysed for their ability to predict survival after a breast recurrence. The suggested prognostic factors are related both to the recurrence and to the primary tumour. The extent and type of local recurrence consistently seem to be of prognostic importance. A large local recurrence is unfavourable [65, 119], while a pure intraductal local recurrence is favourable [59, 65, 117, 118, 120]. Tumour size, NHG and nodal status at primary surgery have been reported to be significant prognostic factors [57, 65, 117, 118].

The prognosis after a chest wall recurrence following mastectomy has generally been considered to be worse than after a local recurrence following breast conserving surgery. Recently, van Tienhoven et al [52] showed in a randomised series that survival after salvage treatment for local recurrence was as poor after breast conserving surgery as after mastectomy.

A highly controversial issue is whether the local recurrence by itself can cause dissemination of tumour cells, leading to distant metastases, or if it is simply a marker for a more aggressive disease. According to the Halstedian hypothesis, breast cancer is a localised disease at inception, spreading sequentially, infiltrating the lymph nodes, and finally causing distant disease through hematogenous dissemination. According to this hypothesis, the chances of cure are related to the extent of surgery, and a local recurrence can cause distant metastases.

An alternative hypothesis, formulated by Fisher [107], is that breast cancer is a systemic disease from the beginning. The extent of surgery may influence the risk of local recurrence but not survival. A local recurrence is admittedly associated with poorer survival but is simply an indicator of poor prognosis, that is, of the risk of distant disease that was present at the time of the primary operation. According to this hypothesis, a local recurrence does not cause distant dissemination.

Until recently, Fisher's hypothesis was generally accepted but it is now being questioned on several grounds. Early treatment of screening-detected breast cancers has led to a lower breast cancer mortality [121], axillary dissection provides good loco-regional control and entails in it self a survival benefit [15, 16], and loco-regional postoperative radiotherapy may improve survival in patients at high risk of a recurrence [39-41].

A suggested intermediate concept between the Halstedian and the Fisherian hypotheses [122] is that breast cancer is a heterogeneous disease, ranging from one that remains local throughout its course to one that is systemic when first detectable. According to this intermediate hypothesis, persistent disease, locally or regionally, may give rise to distant metastases. For women with tumours that are not systemic at primary operation, and for women in whom adjuvant chemotherapy obliterates existing micrometastases, radical surgery and postoperative adjuvant treatment seem to be of major importance for survival. In patients in whom micrometastases are present at the time of the primary operation, residual disease leading to a local recurrence is of minor prognostic importance.

2.7 AXILLARY RECURRENCE – DEFINITION AND INCIDENCE

An axillary recurrence is defined as the detection of new tumour growth in the ipsilateral axilla before or simultaneously with the diagnosis of a local breast recurrence or distant metastases. Most axillary recurrences are suggested to arise from lymph node metastases left behind at primary surgery [123].

Axillary recurrence is rare after breast conserving surgery with a level I and II axillary dissection [21, 27, 111, 124-127], occurring in 0.5-2.5% of the patients at ten years. A much higher risk has been found when no or only minor axillary surgery has been performed, although axillary irradiation has been shown to reduce the risk of axillary recurrence significantly after inadequate axillary dissection [27]. No differences in the risk of axillary recurrence after axillary dissection have been demonstrated between breast conserving surgery and mastectomy [4, 21].

2.8 RISK FACTORS FOR LOCAL RECURRENCES IN THE AXILLA

The numbers of retrieved and involved nodes are risk factors for axillary recurrence [21, 27, 123, 126-128]. Vicini et al [126] found the five-year risk of axillary recurrence to be 8% in women with five or fewer retrieved nodes, and 0.3% in those with more than five retrieved nodes.

Age [125, 127, 129, 130], histological grade [125], tumour size [127, 130, 131], presence of extracapsular extension of tumour [21, 126] and location of the primary tumour [123] have also been implicated as possible risk factors. Voogd et al [123] found that patients with negative axillary lymph nodes had a 73% lower risk of axillary recurrence if the primary tumour was located medially compared to laterally. This is in accordance with the notion that axillary involvement is less frequent with medial compared to lateral tumours [132, 133].

2.9 THE PROGNOSTIC IMPACT OF AN AXILLARY RECURRENCE

Axillary recurrence may evolve into painful intractable growth into the brachial plexus and is also associated with an increased risk of distant metastasis and death [111, 125, 127, 131]. The prognosis in patients with an axillary recurrence is poor, but due to the small numbers of patients, survival estimates in most series lack precision. Baxter et al [131] found that the breast cancer-specific survival at ten years was 52% for those with an axillary recurrence versus 88% for those without. According to de Boer et al [127] the distant disease-free survival estimate was 35% at five years after an axillary recurrence.

As for local recurrences in the breast, some investigators have claimed an axillary recurrence to be only an indicator of more aggressive disease [18, 127], while others regard it as a possible source of distant dissemination [134].

3 AIMS OF THE THESIS

The general aim of the present thesis was to gain increased insight into the problem of local recurrences after breast conserving surgery for breast cancer. More specifically the aim was to:

- assess how breast conserving therapy was adopted into clinical practice from its introduction up to its general use, with particular reference to the results over time as regards the risk of local recurrence and death from breast cancer

- study the prognosis and prognostic factors in women with local recurrences in the breast

- study the incidence of axillary recurrences, their risk factors and the prognosis for women with axillary recurrences after breast conserving surgery

- define risk factors for local recurrence in the breast with a special interest in factors related to surgical management

- investigate whether a local recurrence is only a marker for, or also a source of, distant metastases.

4 PATIENTS AND METHODS

4.1 PATIENTS

Sweden has unique facilities for epidemiologic studies thanks to personal social security numbers, the Swedish Cancer Registry, the Causes of Death Registry and a comprehensive public health care system. The social security numbers make it possible to identify every person living in Sweden. To the Swedish Cancer Registry, all physicians in hospitals and other medical establishments under public administration are required to submit reports on every diagnosis of malignant disease made on clinical and histopathological grounds. As the involved clinician and the pathologist are each required to report a malignant diagnosis, the proportion of underreported cases is estimated to be only about 2% [135]. The Causes of Death Registry is likewise a nation-wide report registry covering Swedish residents. The physician signing the death certificate is required, within three weeks after a death, to establish and report the cause of death to the Causes of Death Registry. This registry is linked to the population statistics. If a cause-of-death certificate is missing, a request for it is sent to the medical establishment handling the patient at the time of death. The drop-out rate is reported to be 0.36% of all deaths.

For the purpose of this thesis, all women with invasive or in situ breast cancer from five of Sweden's six health care regions, operated with breast conserving surgery between 1981 and 1990, were studied and followed through 1997. All women reported to have undergone breast conserving surgery aimed at radical excision of the breast tumour were eligible. Women with a previous cancer, distant metastases at the time of diagnosis, or undergoing preoperative adjuvant treatment were excluded. Women reoperated with a mastectomy due to involved margins or node-positive disease were also excluded.

In three health care regions, data were collected from regional breast cancer registers containing information about stage of disease, types of treatment and recurrences. In the two regions that did not have regional breast cancer registers at that time, the medical records of all patients, recorded as having undergone any type of breast conserving operations, were retrieved and read. This population-based cohort of 7,502 women was used fully or partly in all the analyses included in the present thesis (Figure 1).

In paper I, the cohort study, 4,694 women with invasive breast cancers operated in four of the five regions were included. In the fifth region, the number of person-years was incorrect and the data from this region were therefore excluded from this analysis. Thus, 4,694 women were studied and followed through to 1997.

In paper II, the 391 women who had experienced a local recurrence in the ipsilateral breast, out of the 6,613 with invasive breast cancer, were included. Patient characteristics, data on the primary tumour and the local recurrence, follow-up data concerning distant disease, death and date of each woman's latest clinical examination were collected from the medical records.

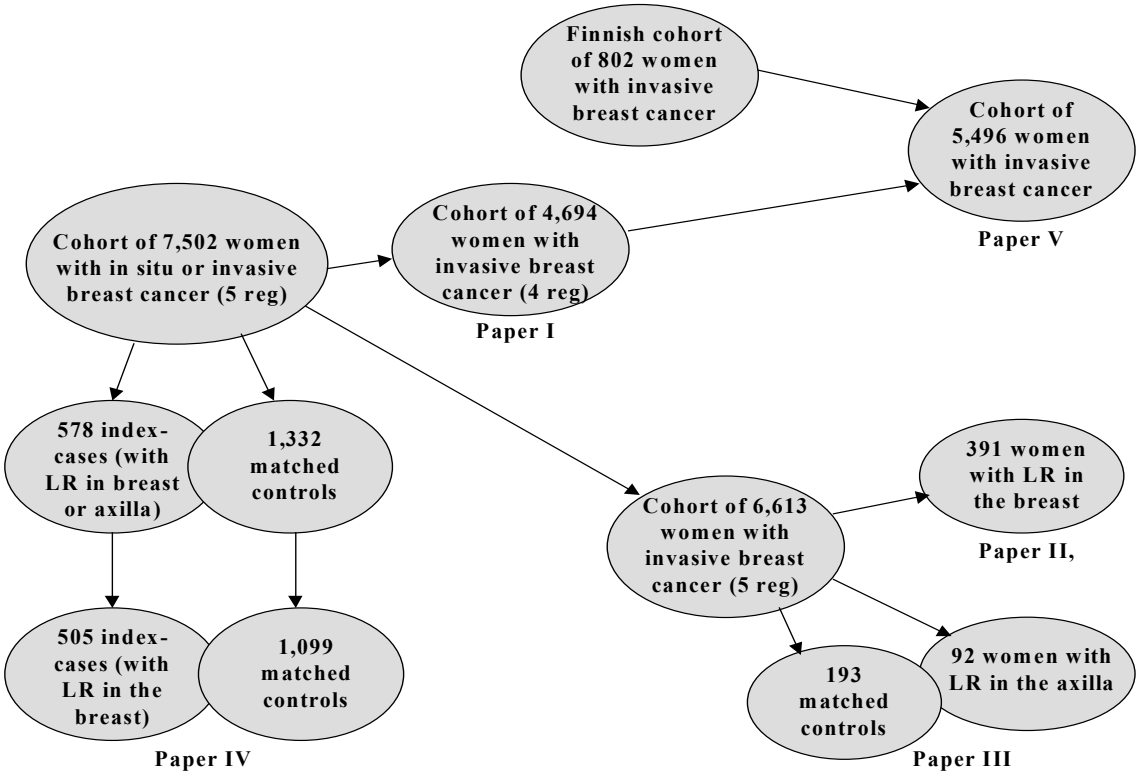

Figure 1. The patients included in papers I-V.

In paper III, 92 women with a local recurrence in the axilla and 193 women without local or axillary recurrence up to the same interval at risk were selected as cases and controls, respectively, from the cohort of 6,613 women with invasive breast cancer. The cases and the controls were matched for year of primary operation and health care region of residence. Patient characteristics, data on the primary tumour and the local recurrence, follow-up data concerning distant disease, death and date of each woman's latest clinical examination were collected from the medical records. In the analysis of the incidence of axillary recurrence, 107 women with axillary recurrence diagnosed before 1997, from the 4,694 women in paper I, were included.

In paper IV, 491 women with a local recurrence in the breast before 1994, and 1,098 women without local or axillary recurrence up to the same interval at risk, were selected from the cohort of 7,502 women with invasive or in situ breast cancer. Cases and controls were matched for year of primary operation and health care region of residence. When analysing variables applicable only to women with invasive breast cancer, the study base was restricted by including cases and matched controls with invasive tumours only (382 cases and 784 controls). All data such as patient characteristics, data on the primary tumour and the local recurrence, data about primary treatment and treatment at local recurrence, follow-up data concerning distant disease, death, and dates of each woman's latest clinical control, were collected from the medical records. Histopathological specimen from the primary breast tumour were reviewed for 460 cases and 529 matched controls to attain valid and uniformly evaluated tumour characteristics. Data about tumour size, nodal metastases, surgical margin and multicentricity were, however, taken from the original histopathological reports as these variables could not be evaluated with validity at review.

In paper V the 4,694 women included in paper I were combined with a Finnish cohort of 802 women with invasive breast cancers, in order to get a cohort that included both early and more advanced stages of breast cancer. The Finnish cohort was gathered in connection with five treatment studies at the Department of Oncology, Helsinki University Central Hospital, between 1981 and 1994 [136-140]. The Finnish cohort data about patient characteristics and therapy were prospectively registered for the different treatment studies. Follow-up data concerning loco-regional recurrence, contralateral cancer, distant disease, death and date of each woman's latest clinical examination were collected and updated from the medical records for the purpose of this study.

4.2 SURGICAL PROCEDURES

In Sweden, breast conserving surgery has been performed as a sector resection aiming at local radicality [14] so that the tumour-bearing portion of the breast was removed by dissection of the breast parenchyma in the plane of Scarpa's fascia down to the pectoral muscle. Excision of the pectoral fascia has been recommended as part of the procedure. The skin incisions and the excision of overlying skin have varied.

The indications for breast conserving surgery changed during the study period. In the early 1980s breast conserving surgery was offered mainly to T1N0M0 patients. Successively from 1985, conservative surgery became generally accepted also for node-positive patients with tumours up to 30 mm in size.

Routine axillary dissection included dissection of level I and II [141] through a separate incision unless the primary breast tumour was situated high up in the axillary tail. During the 1980s, the regional treatment protocols recommended axillary dissection for all patients with invasive breast cancer. At a few of the participating centres, patients had axillary sampling rather than an axillary dissection.

A majority of the Finnish women included in paper V were operated with mastectomy, performed as a modified radical mastectomy with resection of the whole breast, including the mamilla, the pectoralis fascia and the axillary nodes at levels I and II, with sampling of nodes at level III [142].

4.3 RADIOTHERAPY

Radiotherapy to the breast up to a total dose of 50-58 Gy was recommended as standard treatment after breast conserving surgery for invasive breast tumours during the whole study period. For in situ tumours, radiotherapy to the breast was not recommended, but was given to a few women on special indications. Boost has generally not been used in Sweden.

Regional radiotherapy of 46-50 Gy was given to selected patients with invasive breast tumours not operated in the axilla, who were node-positive or deemed to have undergone inadequate axillary surgery.

The Finnish women included in paper V were, with a few exceptions (52 women randomised not to receive radiotherapy and five women with T3N0-disease), given radiotherapy targeting chest wall and regional nodes in axilla, fossa supraclavicularis and parasternal nodes. The radiotherapy was given either in 3 Gy-fractions up to a total dose of 45 Gy, or in 2 Gy-fractions up to a total dose of 50 Gy.

4.4 ADJUVANT SYSTEMIC TREATMENT

Adjuvant systemic therapy was seldom used before 1985. After 1985, the larger central hospitals began to use postoperative adjuvant CMF in nine courses for premenopausal women with node-positive disease. For postmenopausal women with stage II disease, adjuvant tamoxifen therapy of 20-40 mg daily was used from 1985 and at full scale from about 1987. During these initial years of tamoxifen use, estrogen receptor status did not generally guide treatment recommendations. The standard treatment period was two years, but some women were treated for up to five years within a randomised trial [143]. Of the invasive controls selected from the cohort of 7,502 women, 15.1% were treated with hormonal treatment and 2.5% with adjuvant chemotherapy.

The Finnish women included in paper V were all participating in different treatment studies. In the Finnish cohort, 33.4% of the patients received adjuvant hormonal therapy and 73.2% adjuvant chemotherapy.

4.5 HISTOPATHOLOGICAL RE-EVALUATION

For paper IV, and also for use in paper II, a histopathological re-evaluation of specimens from the primary tumour was performed for index cases and at least one control each. The three pathologists taking part in the review used standardised forms and well-defined criteria for classification [144]. Case-control status was unknown to the reviewing pathologists.

At review, the histopathological type of tumour was classified into: ductal cancer in situ (DCIS), lobular cancer in situ (LCIS), ductal invasive, lobular invasive (including tubulolobular invasive), tubular invasive, tubular mixed invasive, medullar invasive and special type ductal (including apocrine, mucinous, papillary, adenocystic and cribriform invasive). According to the van Nuys classification, DCIS was classified as grades 1-3 with or without necrosis [145]. An obvious vascular invasion or an invasive tumour with an intraductal component of more than 25% was specially noted. Presence of cancer in situ outside an invasive primary tumour was also noted.

For invasive tumours, Nottingham Histologic Grade was analysed according to Elston [146]. The Nottingham Prognostic Index [147] was calculated for each invasive case and control.

4.6 STATISTICAL ANALYSIS

To estimate the local recurrence-free survival, distant disease-free survival, overall survival and breast cancer-specific survival (papers I-III), the life-table method [148] was used. The life-table estimates at five and ten years are given together with their standard errors. The differences between survival curves were tested with a log rank test [149]. In paper I the term corrected survival was used instead of breast cancer-specific survival.

For paper II a Receiver Operating Characteristic (ROC) curve [150] was constructed to choose the optimal time, with regard to prognosis, for separating early from late recurrences. Different cut-off points were compared for analysing time between primary operation and the recurrence as a marker of risk of breast cancer death.

Multivariate Cox proportional hazards analyses [151] were computed for papers I-III to evaluate the prognostic factors for local recurrence and breast cancer-specific survival. The relative hazards are presented with their 95% confidence intervals. In paper II, potential explanatory variables were studied by stepwise regression backwards to evaluate whether they contributed to the model fit or if the parameter estimates of the main variables of the study changed when they were removed [152].

Uni- and multi-variate conditional logistic regression analyses [153] were used in paper III and IV to analyse possible risk factors for local recurrence in breast or axilla. The estimates were given as odds ratios with their 95% confidence intervals.

Since some variables analysed in paper III and IV were closely related to each other, in the multivariate analyses they were introduced one at a time to determine which gave the best model fit as judged by model chi square analysis.

For paper V, graphs of yearly hazards of distant metastases were constructed for women who had or had not experienced a local recurrence. The hazard rates*100 at different times of follow up were presented with their 95% confidence intervals (95% CI). To standardise for different tumour growth rates, the time from primary operation to distant metastases was divided by the time from primary operation to local recurrence for each patient with a local recurrence. The standardised hazard of distant metastases over time is presented graphically.

5 RESULTS

5.1 PAPER I

Studying time trends in the population-based cohort of 4,694 women with an aggregate follow-up period of more than 30,000 person-years, we found that the use of breast conserving surgery increased successively (Figure 2), and in all age groups. The proportions of women aged under 50 and over 70 were higher in the earlier years.

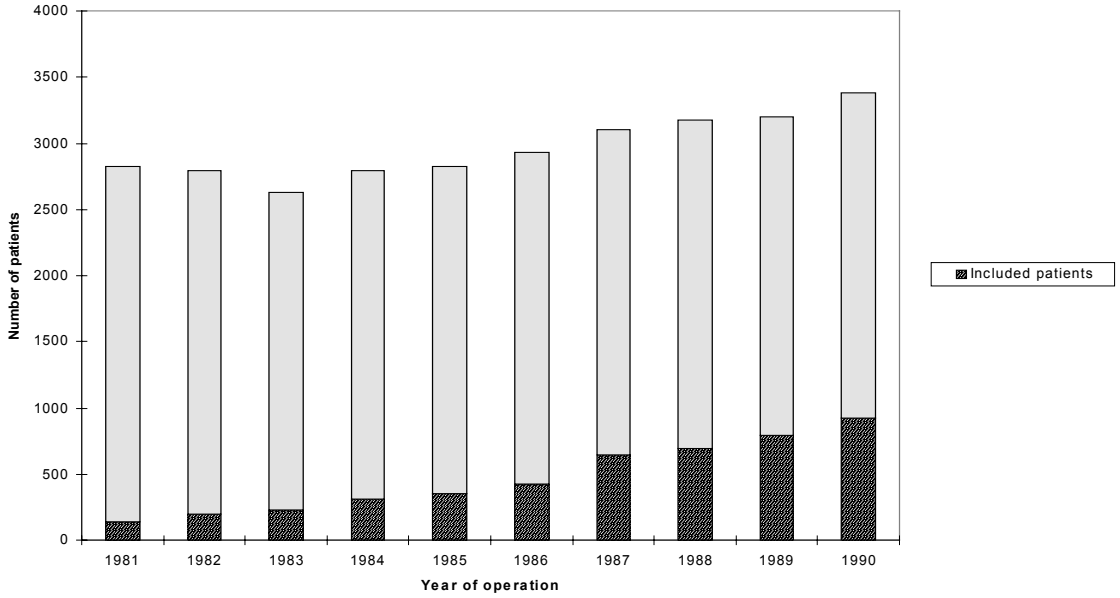

Figure 2. Number of women included in study I (operated with breast conserving surgery) in relation to number of all women diagnosed with breast cancer in four of Sweden's six health care regions, by year.

The indications for breast conserving surgery became slightly broader during the studied period, including successively larger tumours and a larger proportion of node-positive patients. The broadest criteria for breast conserving surgery were noted for the youngest women. The proportion of patients not operated in the axilla decreased over time from about 15% to 8%. Axillary dissection was avoided most often in patients over 70 years of age. Postoperative radiotherapy was given to 70.2%, but its use did increase over time. The women who did not receive radiotherapy were mostly elderly, but even among those aged less than 70 years, 20.4% did not receive irradiation. Thus, non-protocol treatment (defined here as omission of radiotherapy or axillary dissection or a tumour size larger than 30 mm) was given to almost one third of the patients.

The overall risk of local recurrence was 9.2% (SE 0.4) at five years and 21.1% (SE 0.9) at ten years. For women receiving radiotherapy as part of the primary treatment, the risk of local recurrence was 7.6% (SE 0.5) and 17.8% (SE 1.2) at five and ten years, respectively. Without radiotherapy, more than 30% had experienced a local recurrence at ten years.

The breast cancer-specific survival was 93.3% (SE 0.4) and 85.2% (SE 0.8) at five and ten years, respectively. The probability of death from breast cancer was markedly higher

in women who experienced a local recurrence, 24.6% (SE 2.4) at ten years compared to 12.8% (SE 0.8) for those without a local recurrence. The corresponding probability of distant metastatic disease was 31.3% (SE 2.6) at ten years for women with a previous local recurrence, and 15.7% (SE =0.8) for those without.

In a multivariate Cox analysis, taking tumour size, nodal status, age at primary operation and radiotherapy into account, there was a trend for the risk of local recurrence to be higher in the later time period, RH 1.5 (1.0-2.1). This time trend also applied to breast cancer-specific survival.

5.2 PAPER II

In the population-based cohort of 6,613 women with invasive breast cancer, 391 recurrences in the ipsilateral breast were identified. A tenth of the local recurrences presented with concurrent distant metastases, and another 4% were inoperable due to advanced local disease.

Subgroups of local breast recurrences were defined by time to recurrence, location of recurrence and previous radiotherapy. Irradiated women had a lower cumulative probability of a local recurrence in the breast throughout the observed period compared to women without radiotherapy. The recurrences that occurred despite radiotherapy did so later. The risk of local breast recurrence did not level out for either group during the ten years of follow-up (Figure 3).

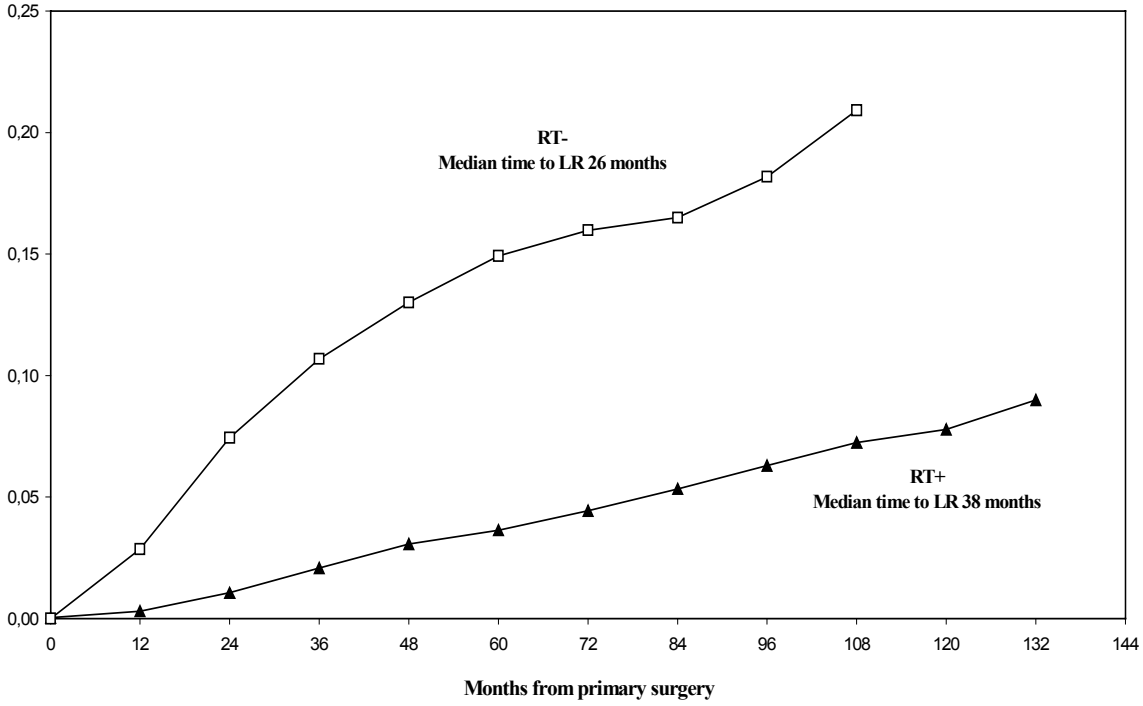

Figure 3. Cumulative probability of local breast recurrence with or without prior radiotherapy (n=123 and n=152, respectively) in a cohort of 4,383 women operated upon with breast conserving surgery from 1981 to 1990 for an invasive breast cancer. *Data based on women from four health care region; information about RT was lacking in 311 women.*

According to a Receiver Operating Characteristic (ROC) curve, the best trade-off between sensitivity and specificity to mark risk of death was at 2.3 years after the primary operation; the previously suggested cut-off point at 2 years was therefore used (Figure 4).

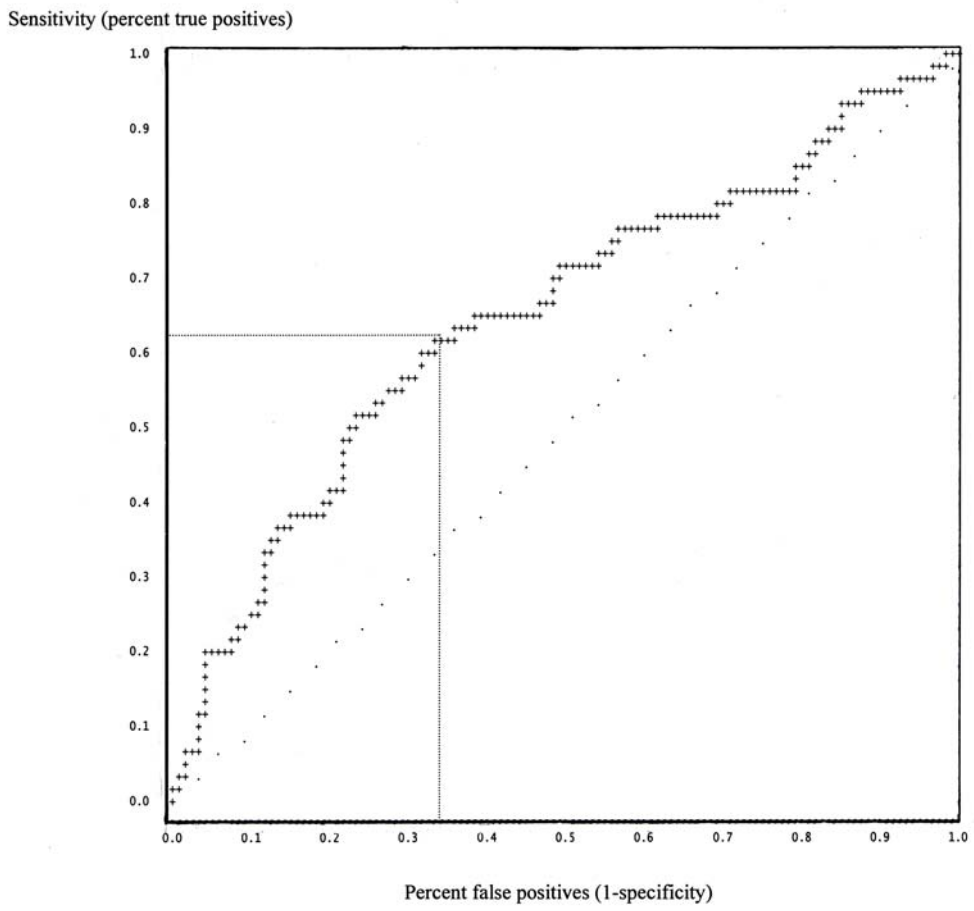

Figure 4. ROC curve illustrating analysis of optimal time, with regard to prognosis, for separating early from late recurrences.

The life-table estimates for breast cancer-specific survival in women with local breast recurrences were 84.5% (SE 1.8) at five years and 70.9% (SE 2.7) at ten years. The risk of breast cancer death was highest among women who had an early (≤2 years) recurrence in the same quadrant as the primary tumour, with a breast cancer-specific survival of 56.0% (SE 5.9) at ten years, while late (>2 years) recurrences were associated with a probability of breast cancer death of approximately 20% at ten years. Stratification of the life-table analyses for time of local recurrence and Nottingham Prognostic Index (NPI) gave an even wider separation of the estimates (Figure 5).

The probability of breast cancer-specific survival as measured from the recurrence showed a statistically significant difference between women who did or did not receive radiotherapy (for the non-irradiated women 68.4% (SE 4.5) at ten years compared to 54.3% (SE 6.3) for the irradiated women). When measured from primary treatment, however, the difference was not significant (for the non-irradiated women 72.5% (SE 3.6)

at ten years compared to 69.8% (SE 3.9) for irradiated women), indicating that the difference in prognosis could be due to a lead-time bias.

In the multivariate Cox analyses of prognostic factors for breast cancer-specific survival in women experiencing a local breast recurrence, neither tumour size nor axillary node status showed statistical significance. NPI was, however, an important prognostic factor in all subgroups of local recurrences in the breast. Time to local recurrence had a strong prognostic impact, while location of local recurrence had a somewhat weaker association with prognosis. Multicentricity was associated with a worse prognosis in several models.

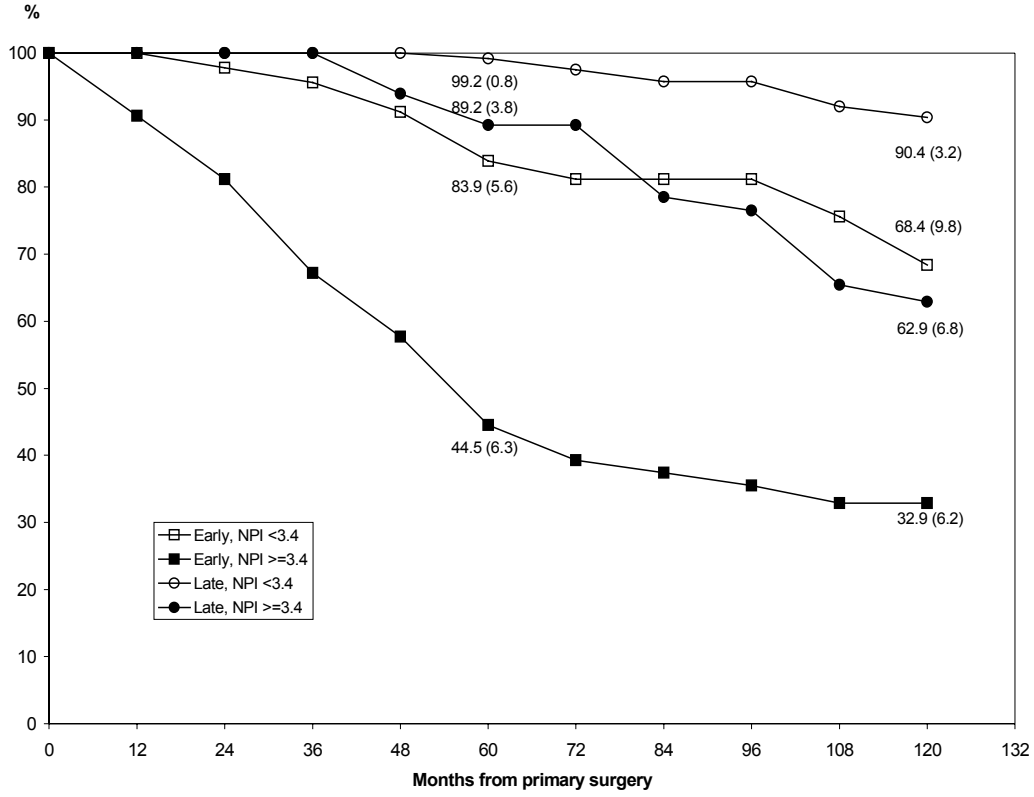

Figure 5. Life-table curves showing estimated probabilities of breast cancer-specific survival as measured from the primary operation, in 391 women with local recurrence after breast conserving surgery from 1981 to 1990 for an invasive breast cancer.*
**Due to missing data, these analyses are based on only 309 women.*

5.3 PAPER III

In the cohort of 6,613 women with invasive breast cancer, 92 recurrences in the ipsilateral axilla were identified. The overall risk of axillary recurrence was 1.0% (SE 0.1) at five years and 1.7% (SE 0.2) at ten years; moreover, in all of the studied subgroups it was less than 4% at ten years.

The risk of axillary recurrence increased with tumour size (p=0.033) and was highest in young women (OR 3.9 for women under 40 years compared to women aged 50-59 years). An axillary dissection with retrieval of more than ten nodes tended to diminish the risk of recurrence in the axilla compared to axillary sampling or no axillary surgery.

Radiotherapy to the breast reduced the risk of axillary recurrence significantly (OR 0.1 (0.1-0.4)).

The breast cancer-specific survival rates after axillary recurrence as measured from primary treatment were 78.0% (SE 4.4) at five years and 52.3% (SE 6.0) at ten years (Figure 6).

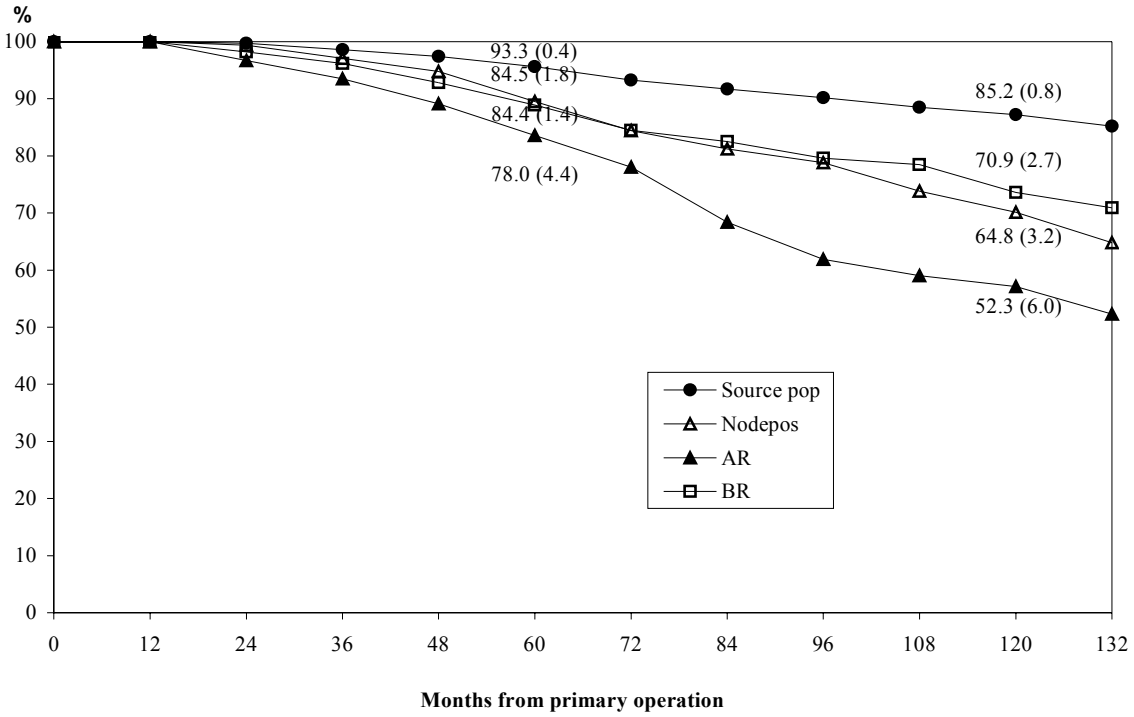

Figure 6. Life-table curves showing estimated probabilities of breast cancer-specific survival as measured from the primary operation, in 92 women with a local recurrence in the ipsilateral axilla. Curves for the source population (4,694 women studied in paper I), node-positive women (729 studied in paper I), and women with a local recurrence in the ipsilateral breast (391 women studied in paper II) are shown for comparison.

Results from the Cox multivariate analysis of prognostic factors for breast cancer-specific survival showed tumour size to have a statistically significant effect on death in breast cancer (RH 2.0 (1.0-4.4)). The same was true for nodal status (RH 4.0 (1.1-14.4)).

5.4 PAPER IV

In the case-control study nested within the cohort of 7,502 women with invasive or non-invasive breast cancer, a local recurrence in the breast was experienced by 505 women. In the full multivariate analysis, 491 cases and 1,098 controls were included.

Multivariate analysis showed a statistically significant trend for the risk of local recurrence to decrease with increasing age (p=0.0005). The trends towards an increasing risk of local recurrence with increasing tumour size, with increasing histologic grade and with increasing NPI were not statistically significant (p= 0.14, p= 0.37 and p=0.24, respectively). Histopathological subtypes other than ductal invasive were all associated

with a statistically significantly increased risk of local recurrence. An in situ tumour moderately increased the risk (OR 2.0 (1.6-2.5)) compared to a ductal invasive tumour. However, compared with all types of invasive tumours grouped together, cancer in situ carried no increased risk of local recurrence (OR 1.0 (0.8-1.3)). A multicentric appearance of the primary tumour modestly increased the risk of local recurrence, both for all women (OR 1.6 (1.2-1.9)) and for those with invasive tumours only (OR 1.5 (1.1-1.9)).

In the analysis of risk factors related to quality of surgical management, the variables standardised breast operation, breast re-operation, surgical margin, type of axillary surgery and number of retrieved nodes were evaluated. With the exception of surgical margin, these variables did not predict the risk of local recurrence. A positive, a doubtful and an unknown surgical margin were all associated with a higher risk of local recurrence compared to a negative margin, both for all women and for those with invasive tumours (for positive margins OR 1.8 (1.1-2.8) and OR 1.7 (1.0-2.9) respectively).

Radiotherapy to the breast statistically significantly reduced the risk of local recurrence, with similar estimates for all women and for only those with invasive tumours (OR 0.4 (0.4-0.5) and OR 0.4 (0.3-0.5)). Adjuvant hormonal therapy also reduced the risk significantly (OR 0.6 (0.4-0.9) for the whole case-control set and OR 0.5 (0.3-0.8) for the women with invasive tumours).

5.5 PAPER V

In the cohort of 5,496 Swedish and Finnish women, 5,324 women were without a history of contralateral cancer. Of these 5,324 eligible women, 912 experienced distant metastatic disease and 579 a local recurrence. Distant metastatic disease after a prior local recurrence was found in 213 women. Women without a previous local recurrence had a fairly constant hazard of distant metastases over time, while the hazard curve for those with a previous local recurrence showed two peaks, at three and seven years after the primary operation (Figure 7).

The hazard of distant metastases at three and seven years, respectively, was 0.75 (0.43-1.07) and 0.94 (0.43-1.45) for those that experienced a local recurrence, compared to 0.23 (0.17-0.29) and 0.12 (0.05-0.19) for those that did not. The differences in hazard of distant metastases were statistically significant. Women with early disease accounted for most of the second peak.

Also after standardisation for different tumour growth rates, two clusters in the hazard of distant metastases-curve were noted. The second cluster in the hazard represented half of the documented distant metastases, which may be explained by dissemination from the local recurrence (Figure 8).

The standardised time was closely related to the time from local recurrences to distant metastases. Approximately 90% of the women with a short standardised time, i.e. a short time between the primary operation and the local recurrence, had a short time between the diagnosis of local recurrence and the diagnosis of distant disease. Three quarters of the

women with a long standardised time had their diagnosis of distant metastases more than two years after the local recurrence.

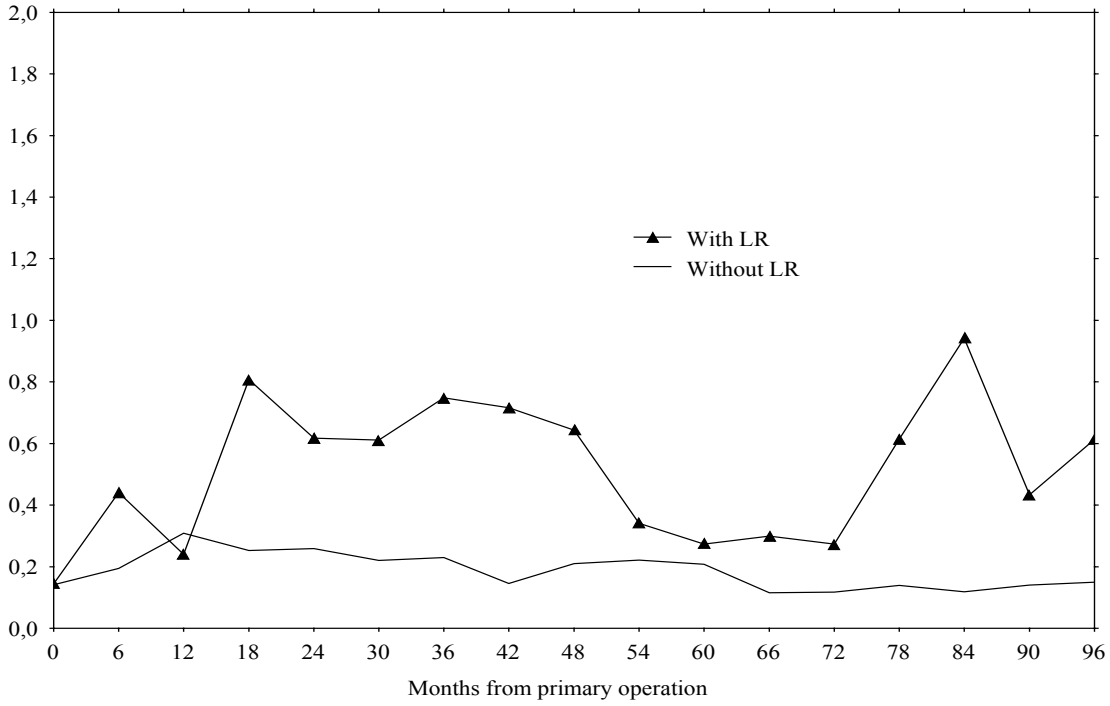

Figure 7. The hazard of distant metastases over time in the cohort of 5,324 Swedish and Finnish women with invasive breast cancer. The figure shows curves for patients with (n=579) and without (n=4,745) a previous local recurrence.

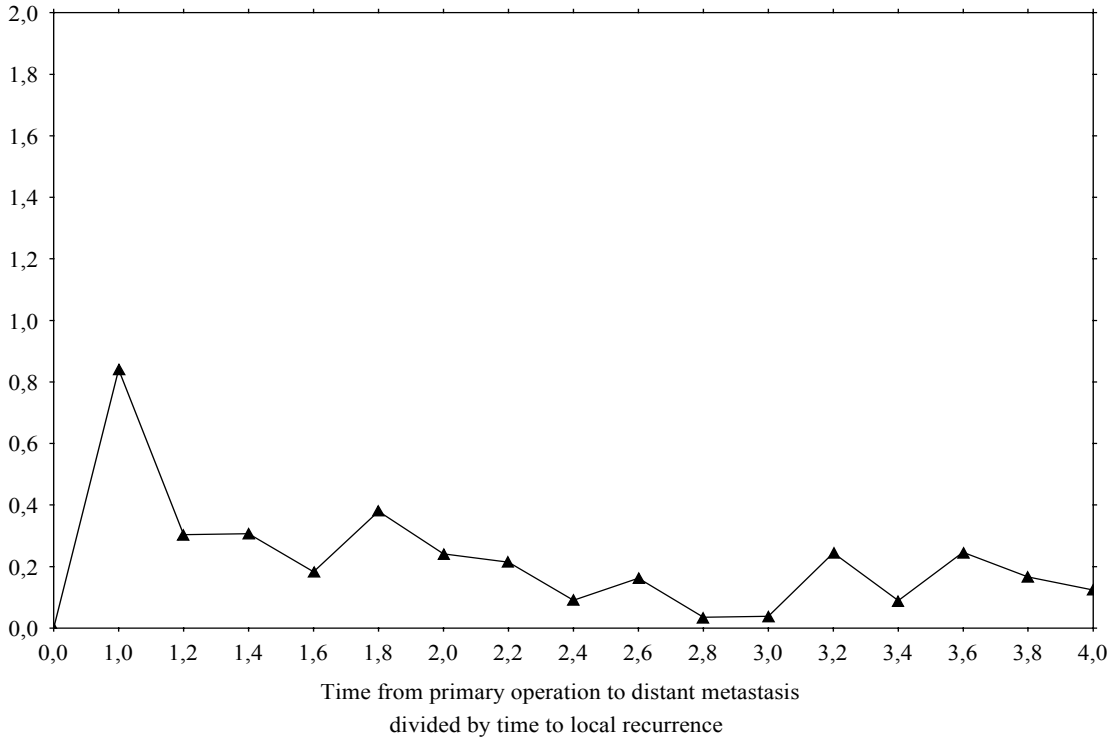

Figure 8. The standardised hazard of distant metastases over time in 579 women with a previous local recurrence.

6 DISCUSSION

6.1 PAPER I

During the 1980s the usage of breast conserving surgery in Sweden increased successively. The wider adoption of the technique involved a broadening of the indications for this type of surgery. A simultaneous moderate impairment of the results was noted, as regards the risk of local recurrence and death from breast cancer. Generally, the risk of local recurrence was higher than expected, but the survival estimates were gratifying. A surprising finding was the large proportion of women with non-protocol treatment; nearly 30% were not given radiotherapy.

It is remarkable that so many of the patients had not been given the postoperative adjuvant radiotherapy that was recommended in this period for all patients after breast conserving surgery. The non-irradiated patients in a randomised study [34] made up only approximately one-sixth of this group. The women not given radiotherapy were mostly elderly. The selection cannot be said to have targeted a group with a low risk of local recurrence as more than 30% had experienced a local recurrence at ten years.

Older age has also been identified by others as a major reason for not using radiotherapy after breast conserving surgery; the proportion given radiotherapy declined markedly with age, irrespective of the stage of disease [154, 155] and comorbidity [155]. Even among women with no comorbidity (84% of women aged 65 or more), the proportion treated with radiotherapy declined from 77% to 24% between the ages of 65-69 years and 80 years or older [155]. Older women also get operated less often in the axilla, less often have re-excisions to obtain negative surgical margins and seldom receive postoperative adjuvant chemotherapy or axillary radiotherapy [156]. Less aggressive treatment in older women may be based on the belief that older women are less likely to tolerate or benefit from this treatment. In fact, the incidence and severity of toxicity associated with radiotherapy are not higher for women over 70 [157]. The risk of local recurrence may be lower in older women compared to younger, but there is still an advantage in receiving radiotherapy compared to not receiving it [4, 11, 33-35].

While the side-effects of radiotherapy should not be underestimated, it may be asked whether radiotherapy might have saved many of the non-irradiated patients from local recurrences without involving substantial side-effects. A recently published study on the appropriateness of primary therapy for early-stage breast cancer, based on data from the US National Cancer Institute, showed a drop in appropriate treatment associated with the increased use of breast conservation surgery [158]. Omission of radiotherapy, axillary dissection or both, increased from 10% in 1989 to 19% at the end of 1995. Our study shows non-protocol treatment of 32% during the observed period, but in contrast to the US study, a successively increasing adherence to treatment protocols.

In spite of the increasing adherence to treatment protocols, the results tended to worsen as breast conserving surgery became more widespread. Given that the baseline risk of local recurrence was 7% at five years in 1981-1983, a relative hazard of 1.5 implies an excess risk of about 3.5%. This excess risk is clinically relevant. As a variable, time period otherwise reflects a complex underlying pattern of changing indications for surgery and

adjuvant therapy, increasing sub-specialisation in surgery, the introduction of screening, increased quality of clinical mammography and the successive introduction of breast clinics with a multidisciplinary approach to breast cancer treatment, ensuring that more and more patients receive proper management, factors that all aim to improve results. Thus, we postulate that wider indications and omission of radiotherapy seem to outweigh the possible benefit of other changes in management over time.

One might expect that some inappropriate treatment may be due to actual disagreement with treatment protocols. Controversy exists as to whether radiotherapy is necessary for older women and whether an axillary dissection can be omitted in patients with small tumours. The basis for the discussion regarding axillary dissection has been the low risk of axillary lymph node involvement associated with small tumours, and the assumption that adjuvant chemotherapy is often given irrespective of the result of the axillary dissection [159-162].

During the study period the issues concerning the necessity of axillary dissection and radiotherapy were not yet widely discussed. Nattinger et al [158] found inappropriate treatment in all subgroups, irrespective of age and tumour size, not just in older women and in women with small tumours. Most older women who do not receive axillary dissection also do not receive either radiotherapy or adjuvant chemotherapy [163]. Positive axillary nodes will be found on axillary dissection in approximately 20-50% of women with an early stage breast cancer. Even with very small tumours, the proportion that are node-positive will be around 10%, which means that an appreciable number of older women receive no treatment for their axillary spread. In the study by Du et al [163], the women who received neither axillary dissection nor radiotherapy had a significantly poorer survival than those who received either axillary dissection or radiotherapy or both. A direct survival advantage associated with axillary dissection has also been found by other investigators [15, 16]. Breast cancer survival has improved steadily world-wide over the past 25 years, except for older women [164]. A possible explanation for this could be the high proportion of inappropriately treated women in this group. Several studies have indicated that survival rates are comparable among older and younger women who have received comparable treatment [165-168].

It was discouraging to discover that even when radiotherapy had been used, the estimated ten-year risk of local recurrences was 17.8%. A risk of less than 1% per year has been stipulated as an important quality criterion [169]. In the study by Liljegren et al [34], in which the selection criteria were stricter (i.e. women with unifocal tumours visible on mammography operated with a standardised sector resection, level I-II axillary dissection and perioperative X-ray of the specimen), the risk of local recurrence was lower.

We reanalysed the data from the cohort study to investigate whether it was the inappropriately treated patients who accounted for the high overall risk of local recurrence (Table 1).

Table 1. Reanalysis of data from the cohort study. Life-table estimates with standard errors (SE) showing risk of local recurrence in a cohort of 4,694 women operated with breast conserving surgery for an invasive breast cancer between 1981 and 1990.

	Number	5 years		10 years	
		%	SE	%	SE
All women	4,694	9.2	0.4	21.1	0.9
All women treated with radiotherapy	3,89	7.6	0.5	17.8	1.2
Women with tumours 20 mm or smaller, operated in the axilla, treated with radiotherapy	2,277	7.4	0.6	17.8	1.3
Node-negative women with tumours 20 mm or smaller, operated in the axilla, treated with radiotherapy	1,899	7.3	0.6	17.4	1.3
Node-negative women aged 50 years or older, with tumours 20 mm or smaller, operated in the axilla, treated with RT	1,344	5.7	0.7	13.9	1.5

The risk of local recurrence overall was 9.2% (SE 0.4) at five years and 21.1% (SE 0.9) at ten years. For irradiated women the risk of local recurrence was 7.6% (SE 0.5) and 17.8% (SE 1.2) at five and ten years, respectively. The risk of local recurrence for appropriately treated women (women with tumours 20 mm or smaller, operated in the axilla and given radiotherapy) was almost the same, 7.4% (SE 0.6) and 17.8% (SE 1.3) at five and ten years. The quality expected from randomised trials was not achieved. Reasons for this discrepancy need to be further studied, since the underlying factors may include characteristics of the decision and management process, which can be influenced.

Both Iscoe et al [170] and Marubini et al [171] showed that ipsilateral breast recurrences are more common in routine treatment compared with trial series; our results underline this.

6.2 PAPER II

In the study of prognosis after local breast recurrence, the first main finding was that radiotherapy does save a substantial proportion of the women from a local recurrence and may delay a recurrence for others, but has little influence on breast cancer-specific survival in women who have had a local recurrence. The hitherto reported poorer survival after local recurrences despite radiotherapy, as measured from time of recurrence [67], may be partly due to a lead-time bias. Secondly, time since the primary operation had a very clear prognostic impact, stronger than that of the location of the recurrence. Further, Nottingham Prognostic Index of the primary tumour heavily influenced the prognosis in the different subgroups of women with local recurrence in the breast, defined by time to local recurrence.

Following the results of Whelan et al [67], we expected a poorer prognosis in women with local recurrence after radiotherapy than in non-irradiated women. Our multivariate models showed only a tendency in this direction. However, since those not irradiated were a selected group concerning co-morbidity and risk of dying, the findings concerning survival in relation to radiotherapy should be interpreted cautiously. Still, the decision not to irradiate did not select a group with a low risk of local recurrence. Thus, our findings, which indicate a substantial reduction of local recurrences after radiotherapy in absolute terms, a delay of local recurrences due to radiotherapy for some women, and a risk of local recurrence and/or new ipsilateral primary tumours that does not level off during ten years of observation, should be generalisable. Also, the selection mechanisms should not confound the comparison of survival analyses as measured from primary operation with those as measured from the local recurrence.

In accordance with the notion that a large proportion of these recurrences may be new tumours, we found that late recurrences and recurrences located in another quadrant than the primary tumour were associated with a better prognosis. The survival estimates after late local recurrences were similar to those expected after a contralateral cancer [172, 173], and also very similar to the estimates observed in the cohort study after a contralateral cancer (breast cancer-specific survival 89.3% and 76.8% at five and ten years, respectively).

The addition of NPI to the survival analyses stratified on time to local recurrence further separated two groups of breast recurrences with a clinically highly relevant difference in prognosis in absolute terms: a good prognosis group with low NPIs and late recurrences, and a bad prognosis group with high NPIs and early recurrences. There were no clear indications that the effect of NPI varied quantitatively in the different strata according to time or location of the recurrence. This pattern is in accordance with the fact that the behaviour of the metastases is associated with the characteristics of the primary tumour, as well as with the observation that the characteristics of both the first tumour and the second tumour – and the time interval between them - influence the prognosis in bilateral breast cancer [172].

From our data we cannot reliably tell which recurrences are “true” recurrences and which are new primary tumours. However, from a clinical standpoint we can conclude that time to recurrence, NPI and location of the tumour (especially information on multicentricity) can help us to distinguish groups of women for whom the prognosis resembles either that of a more aggressive recurring disease or that after metachronous bilateral disease.

In the analysis of prognostic factors in women experiencing a local recurrence in the breast, time to recurrence was more closely associated with prognosis than was the location of the recurrence. Multicentricity was associated with a worse prognosis in several models. Also in other recently published studies, time from primary operation to local recurrence has been found to be the most important prognostic factor after local recurrence [64, 118].

6.3 PAPER III

In the study regarding local recurrences in the axilla we found the overall risk of axillary recurrence to be low, 1.0% and 1.7% at five and ten years, respectively. The major risk factors for axillary recurrence were low age, large tumour size, minor or no axillary surgery and no radiotherapy to the breast. We found the prognosis after an axillary recurrence to be poor.

In this comparatively large case-series, the results can be discussed in at least two interesting clinical perspectives. First, the risk of axillary recurrence was less than 2% overall and less than 4% in any of the studied subgroups at ten years. This implies that even a marked difference in the odds ratios in the risk factor analysis amounts to a low absolute risk difference, mostly around 2% to 3%. Thus, more aggressive treatments specifically directed at reducing axillary recurrence would have to be weighed carefully in terms of benefits and risks, since the numbers needed to treat would be large.

Second, although the risk is low, an axillary recurrence causes significant suffering and presents a therapeutic dilemma. Since less extensive surgery, large tumour size and omitted radiotherapy are risk factors, the hypothesis emerges that most axillary recurrences in the present series were overlooked primary lymph node metastases. The finding that the traditional risk factors for death (nodal status, tumour size) also apply to a patient with axillary recurrence is also compatible with this theory.

It could be speculated that in untrained hands, axillary dissection through a separate incision in the axilla might fail to explore the lowest part of the axilla, where the first lymph node that drains the breast tumour (the sentinel node) is usually situated [30, 31]. In some women, the sentinel node may be sterilised by radiotherapy to the breast; as this treatment often includes the axillary tail and lower axilla [174]. In the multivariate analysis, radiotherapy to the breast was clearly protective against axillary recurrence. In a study by Liljegren et al [34] that compared the results of breast conserving surgery in women who did or did not receive postoperative radiotherapy to the breast, regional and distant recurrence was more frequent in the group that did not receive radiotherapy. The difference between the groups was explained entirely by additional axillary recurrence in the non-irradiated group of women. If the sentinel node biopsy technique has the potential to reduce the frequency of overlooked primary lymph node metastases, the incidence of axillary recurrence should be lowered.

Axillary radiotherapy has been notified to at least partially make up for omission of axillary surgery. In the present study, radiotherapy to the axilla was not standard treatment and was given only on special indications, which greatly influences the estimates. The findings concerning axillary radiotherapy should thus be interpreted cautiously.

6.4 PAPER IV

In the study of risk factors for local recurrence in the breast we found, as expected, low age, multicentricity and unclear/unknown surgical margins to be associated with an increased risk of local recurrence. Also in accordance with other's results, we found radiotherapy and adjuvant hormonal therapy to be protective. The association between in

situ tumours and an increased risk of local recurrence when compared to invasive ductal tumours but not to all invasive tumours grouped together, has not, to our knowledge, been shown previously. In this study, NHG and NPI were not helpful in determining the risk of local recurrence. With the exception of surgical margin, variables that we hypothesised to be related to quality of surgical management did not predict the risk of local recurrence.

Age below 40 was confirmed as a risk factor for local recurrence [53, 70, 72-76], with a trend for the risk of local recurrence to decrease with increasing age. Younger patients are known to have a higher prevalence of high NHG, hormone receptor negativity, vascular invasion [71] and EIC [70, 79, 80], though in this study these variables were not found to be significantly associated with risk of local recurrence.

When analysing tumour-related variables with multivariate technique, we found no effect of histopathological subtype on the risk of local recurrence in women with invasive tumours, as was reported in a previous randomised study from Sweden [74]. Neither could we substantiate an association between presence of cancer in situ outside the primary tumour and local recurrence, which may be due to the comparatively large resections performed and that re-excision was strongly recommended in the event of positive margins. This finding is in line with the notion that an extensive intraductal component is of little prognostic value if negative margins can be obtained [73, 81, 82]. The striving for large resections and free margins may also explain why multicentricity was not as strongly related to risk of local recurrence in this study as in others [76, 91, 92]. Furthermore, a preoperatively suspected multicentricity was a contraindication for breast conserving surgery during the studied period.

We found no association between vascular invasion and risk of local recurrence. Vascular invasion was considered positive only in those cases in which it was unequivocal, which is a stricter definition than in other studies. This definition entailed a low number of women notified to have vascular invasion, and thus a low statistical power in the analysis of this variable.

Nottingham Histologic Grade has been of importance as a risk factor for local recurrence in some studies but not in others. In our study, NHG was not a statistically significant risk factor and neither was NPI. Both variables are known to be prognostic factors of distant metastases and death in breast cancer. The competing risk of developing distant metastases, where women with distant metastases get censored from follow-up regarding local recurrence, may potentially obscure an association between the two variables and local recurrence.

We had hoped to find an association between variables indicating quality of surgical management and risk of local recurrence, as these variables could be targets for audit and corrective action. One clear finding was the previously known association between involved surgical margins and an increased risk of local recurrence. There may be several reasons for our otherwise negative findings. The other variables we recorded as being indicative of quality of surgical management - breast reoperation and type of axillary surgery - may have little relation to the risk of local recurrence in the breast. During the study period the variation in the surgical management may have been slight, leading to a small range of exposure to these particular risk factors. During the introductory years of

breast conserving treatment in Sweden, comparatively few surgeons were responsible for this type of surgery. As data for this study was collected retrospectively, some variables may be non-differentially misclassified, which drives risk estimates towards null. For example the extent of surgery was re-evaluated as either a standardised sector resection or a less wide excision in the light of often scantily worded operation theatre reports in the medical records. Low surgical quality may mainly influence the local recurrences that appear during the first years of follow-up, and we did not stratify our analyses by time to local recurrence.

There is a close relationship between the two variables breast reoperation and surgical margin. As the main reason for a breast reoperation is to achieve tumour-free surgical margins and lower the risk of local recurrence to the same level as in tumours with negative surgical margins, a breast reoperation is, despite our findings, important as a measurement of the quality of surgical management.

Radiotherapy reduced the risk of local recurrence by a similar magnitude for women with in situ and invasive tumours analysed together and for those with invasive cancers only. In view of earlier studies indicating that in situ tumours are less sensitive to radiotherapy [175], we would rather have expected a dilution of the effect including all women. Due to possible selection bias, the magnitude of the protective effect of radiotherapy is better estimated in the randomised studies of radiotherapy [4, 11, 33-35].

Selection bias may also have influenced the estimates of the effect of adjuvant hormonal therapy. In this cohort, very few women received adjuvant systemic treatment, which weakens the statistical power.

6.5 PAPER V

The main findings in paper V are the higher hazard rate of distant metastases seen in women with local recurrences, the presence of two peaks in the hazard curve that are not present in the corresponding curve for women with no previous local recurrence, and the notion that distant metastases occur later in women with a previous local recurrence. We suggest that the second peak in the hazard curve seen in women with a previous local recurrence may result from a dissemination of cancer cells emanating from the local recurrence.

The time-relation between local recurrences and distant metastases was studied in a very large cohort of breast cancer patients treated in many different centres, and with an almost complete long-term follow-up. The validity of the background information was well controlled since large parts of the cohort data were collected through direct studies of original medical records.

Starting from the pre-formed hypothesis that local recurrences do have a potential to cause distant dissemination, and that this may be of importance for the prognosis in women with early stage breast cancer without micrometastases present at time of the primary operation, we predicted that the distant metastases which are due to dissemination from a local recurrence would appear at a time interval after the local recurrence that

approximately equals the time from the primary operation to the local recurrence. Thus, we assumed both that the growth rate is constant throughout the natural history of a tumour, and that local recurrences and distant metastases are detected at about the same size and number of cancer cells. It can be argued that especially the latter part of this assumption is an over-simplification and does not fit our knowledge about the presentation of symptoms of metastases. If, however, it is the growth rate of an indeed multiple seed of micrometastases we observe, the theory may be realistic.

Local recurrence is associated with an increased risk of distant metastasis [59, 63, 107, 176] and death in breast cancer [60, 67, 117]. Although no direct evidence of dissemination from local recurrences has been presented, indirect indications are accumulating [40, 41, 117, 176, 177].

According to the findings in paper I, the women with a local recurrence have been shown to have more aggressive tumours than those who have not had a local recurrence. The hazard of distant metastases in paper V was also, as expected, higher in women experiencing a local recurrence. If a local recurrence is just a marker of aggressive disease, one would expect distant metastases to appear earlier in women with a previous local recurrence than in women with no local recurrence. We found, on the contrary, that the median time to distant metastases was longer in women with a previous local recurrence.

Our finding that a short interval between the primary operation and the local recurrence is associated with early distant metastases was not surprising. The results from paper II clearly showed that early local recurrence implies a bad prognosis. However, the relation between standardised time and time from local recurrence to distant metastases was more striking than we anticipated. It is mainly after late local recurrences that the risk of secondary dissemination is high, and at least partly this risk may be explained by the late local recurrences behaving rather as new primaries.

Regrettably, there is no generally accepted and sensitive way to formally test whether or not the two peaks in the curve illustrating hazard of distant metastases in women with a previous local recurrence constitute a recurring pattern reflecting an underlying biological mechanism rather than just being random variations. However, the contrast between women with and without a local recurrence was striking. Also Fortin et al [117] found a similar pattern with two peaks in the hazard curve of distant metastases in women with a previous local recurrence.

In the present study, the Finnish cohort of women with more advanced breast cancers contributed only negligibly to the second peak in the hazard of distant metastasis, indicating that the proportion of distant metastases originating from local recurrences may decrease with increasing stage of breast cancer disease. According to a graphical estimation of the two peaks in figure 2, approximately 50% of the distant metastases occurring after a local recurrence in women with early stage breast cancer (the Swedish cohort) have their origin in dissemination from the local recurrence.

To conclude, local recurrences may be a substantial source of distant metastases in a cohort of women with early stage breast cancer. Clinical implications are that adequate

attention and treatment are necessary when a local recurrence is detected. Furthermore, and even more important, a substantial part of the distant metastases notified in women with small early cancers may be preventable by combined surgical and oncological efforts to treat the primary tumour radically.

7 CONCLUSIONS

- With the wider adoption of breast conserving surgery, the indications for this type of surgery broadened. This was accompanied by a moderate impairment of the results regarding risk of local recurrence and death from breast cancer. The risk of local recurrence was higher than expected but the survival estimates were gratifying.

- There was a marked difference in prognosis between different subgroups of local recurrences in the breast, defined by time to recurrence, location of recurrence, Nottingham Prognostic Index and previous radiotherapy. Time to local recurrence and NPI were the strongest independent prognostic factors for breast cancer-specific survival.

- The overall risk of an axillary recurrence was low. Low age, large tumour size, minor or no axillary surgery and no radiotherapy to the breast were determinants of the risk of axillary recurrence. The prognosis after an axillary recurrence was poor, with tumour size and axillary node status as the major prognostic indicators.

- The most important determinants of local recurrence in the breast were age, multicentricity, surgical margin status, radiotherapy to the breast and adjuvant hormonal therapy.

- The time distribution of distant metastases differs between women with or without a previous local recurrence. Our results indicate that local recurrences may be a substantial source of distant metastases in early stage breast cancer.

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