PROGNOSTIC FACTORS IN BREAST-CONSERVING THERAPY
A PROSPECTIVE POPULATION-BASED COHORT STUDY

Jan J. Jobsen

Prognostic Factors
In
Breast-Conserving Therapy
A Prospective Population-Based Cohort Study

Jan J. Jobsen

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Voor mijn vader

Two roads diverged in a wood, and I --
I took the one less traveled by,
And that has made all the difference.

by Robert Frost

Contents

Chapter 1

Introduction

In The Netherlands breast cancer is diagnosed in approximately 12.000 women annually and is still increasing (IKCNET.nl). The probability of developing breast cancer in the lifespan of a woman is 12-13%. Breast cancer is the most frequent occurring type of cancer in the Netherlands.

Breast-conserving therapy (BCT) consists of surgery and radiotherapy. The surgical part involves radical removal of the tumour (e.g. lumpectomy) in combination with the achievement of an optimal cosmetic result and adequate axillary staging. The radiotherapy part, which follows the surgical part, involves the irradiation of the whole breast with or without a boost irradiation on the primary tumour area.

In the early eighties of the last century BCT was a relatively new type of treatment, whereas the modified radical mastectomy (MRM), also called Patey or Madden operation, was seen as the standard breast cancer treatment. BCT and MRM for early-stage breast cancer were compared in several randomized trials as to their efficacy, carried out during the 1970s and 1980s.[1-6] After 5 to 10 years of follow-up, none of these trials revealed a significant difference in overall survival or distant disease-free survival. Since BCT was not a common type of treatment for breast cancer patients worldwide in the eighties of the last century, it was neither in the Twente-Achterhoek region of the Netherlands in those days. I took the opportunity to build, from the very beginning in this region, a prospective cohort of breast cancer patients, all primarily treated with BCT. This provided the opportunity of assessing treatment efficacy in the Twente-Achterhoek region, and of evaluating the relevance of various predictive and prognostic factors for recurrent disease and survival.

STUDY DESIGNS

Cohort studies are the choice design for studying the course of a disease or for establishing risk factors associated with poor outcome, because they are longitudinal and follow a group of subjects over a period of time.[7-9] Generally speaking, causation cannot be proven in cohort studies because they are observational. However, because these studies follow a cohort of patients through time, they possess the correct time sequence for providing strong evidence as to possible causes and effects. In addition, in prospectively designed cohort studies -as opposed to historical cohort studies –, investigators can control many sources of bias related to patient selection and recorded measurements.

It is stated that randomized trials carry the highest level of evidence and observational studies are more prone to distortion (due to lack of randomization). Retrospective studies, like case-control studies, should, according to some, be looked at with caution. These statements are questionable. Undoubtedly, performing a randomized controlled trial is the best method for comparing the (relative) efficacy of various treatments and modalities and they play a central

role in the development of new therapeutic strategies. However, these studies have their own problems. The often rigid selection of patients creates questions related to the representativity of the obtained results and does, therefore, not provide a satisfactory answer for all future patients. Also, ethical aspects might be a problem in the design of randomised controlled studies, and interim analyses sometimes lead to an early closing of these studies. All these aspects lead to the conclusion that all types of studies have their own advantages and disadvantages. With respect to possible predictive and prognostic variables it is often difficult, or not even feasible to evaluate those variables adequately in the setting of a phase-III randomized study. Phase-III randomised controlled studies are sometimes used identify prognostic factors in sub-analyses, but one has to realize that those studies were not designed to look at those factors and also often included a selected group of patients. However, publications of these sub-analyses, receive a disproportionate amount of attention.

Prospective cohort studies that, generally, include more patients and have a longer follow-up period are pre-eminently better suited to study the relevance of prognostic variables. In a prospective cohort study the researcher, after identifying the research group, has the ability to follow this group for a long period of time and has the opportunity to select the collection of variables at baseline and during follow-up. These studies are usually confined to the determination and investigation of aetiological and predictive factors. They do not allocate patients to treatments, but observe treatment as given in clinical practice and monitor the well-being of individuals over time. The advantages of a cohort study are the identification of relevant items on an individual basis; the order in which the follow-up is performed follows the natural course of the disease, and no selection bias is present because the definition of the cohort population takes place before events occur. In oncology the disadvantage lies in the need for large numbers of patients that must be followed for a long period of time. When investigating prognosis, it is essential to have complete follow-up data.

The reproducibility of epidemiological cohort studies remains a problem. The main source of variation affecting precision is the chance variation. A larger cohort diminishes variation and so increases the level of reproducibility.

In 1988 I started my cohort for breast cancer patients treated with breast-conserving therapy. In the Twente-Achterhoek region all patients from the four regional hospitals refer their patients with breast cancer to the Radiotherapy department of Medisch Spectrum Twente Hospital at Enschede. All inhabitants of the Twente-Achterhoek region will visit one of these four hospitals, making this cohort unique. The cohort study included all breast cancer patients treated with BCT, lumpectomy with or without axillary dissection or sentinel node procedure followed by radiotherapy to the breast as the primary treatment. This treatment for breast cancer was initiated in the eighties of the last century in our region, and the first patient was treated and registered in 1983. Up till 1988 only 116 patients were treated this way, and they were

retrospectively entered in the cohort. From 1988 every new patient referred to our department was entered in the cohort and followed up for at least 15 years after entering. Since the start of the study we performed a continuous up-date with the registration of recurrences, family history, and mortality. At the end of every year all missing files were retrieved and the data updated. Unto the present day, over 3.800 patients with BCT have been included in the cohort.

STUDIES

The thus formed cohort of breast cancer patients treated with BCT, made it possible to investigate clinically relevant items like the influence of a positive family history for breast cancer on the prognosis of the patients. Since the early nineties of the last century it is possible to test for a BRCA 1 or BRCA 2 mutation. Particularly young patients with a positive FH have a high risk of a mutation. The problem is that, at the time of breast cancer diagnosis it is not known whether the patient bears a mutation in her genome. On the other hand, every patient is well informed on the presence or absence of breast cancer in her family, and in particular with her first-degree relatives. In **chapter 2** the impact of a positive family history in breast cancer as a prognostic factor is investigated.

Age has been an important issue in oncology. In breast cancer this is an important item in relation to local control and survival for both young women and older women. Due to our cohort we had the opportunity to look at different aspects in breast cancer treatment in relation to age. Margin status might have a relation to age in breast cancer. As mentioned later, we are interested in the relation of margin status and local control. Incorporating age might have an impact on local control and survival. In **chapter 3** we addressed this issue.

Another topic is the occurrence of bilateral breast cancer, synchronous or metachronous. Bilateral breast cancer and particularly synchronous bilateral breast cancer is rare, and for this reason alone it is no option to investigate possible treatments in phase III studies. Still, it is important to know the efficacy of BCT in those patients. It has long been the policy in some centres to perform bilateral mastectomy in synchronous bilateral breast cancer, although no literature considers this treatment to be the primary treatment in those patients. Also, it is important to evaluate the possible impact of bilateral synchronous breast cancer on recurrences and prognosis. This is presented in **chapter 4**.

Radiotherapy in BCT has always been radiation of the whole breast followed by a boost to the former tumour area or lumpectomy area. In this respect the whole breast is a well defined area in contrast to the boost area. No definitions exist on how large or how small the boost volume should be. Another item has been the accuracy we can achieve in the location of the boost in the

breast. Nowadays we have the possibility of CT-planning, but before CT-planning was possible, we were dependent on mammography, the scar, if possible preoperative examination, and, if present, surgical clips. In this respect it is interesting to look at the impact of the boost volume, particularly on local control. We addressed this in **chapter 5**.

Timing of treatment in breast cancer has become increasingly important, due to the proven impact of adjuvant chemotherapy on survival. Lumpectomy followed by radiotherapy to the breast, regarded as an integral part of the primary treatment, has become an essential item in this discussion. With respect to adjuvant chemotherapy it is important to know how long radiotherapy can be postponed without compromising local control and survival. This has been investigated by the study presented in **chapter 6**.

Margin status in BCT has always been an interesting subject, both for the clinician and the pathologist. When is the primary tumour removed radically? When the inked margin is not affected or when there is a tumour free margin of 1, 2 or more than 2 millimetres? What is the impact of focal non-free margins on local recurrence? Is there a difference in outcome for margin status of infiltrating carcinoma or carcinoma in situ, or both? These questions are addressed in many papers and are still important to evaluate in a large prospective cohort of patients with long-term follow-up. **Chapters 7**, **8**, and **9** address these issues.

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Chapter 2

Family history in breast cancer is not a prognostic factor?

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SUMMARY

The aim of this study is to determine if breast conservative treatment is justified for patients with a positive family history of breast cancer and to investigate whether they have a worse prognosis.

We performed a prospective cohort study of breast cancer patients, treated with breast conservative treatment with radiotherapy at the Radiotherapy Department of the Medisch Spectrum Twente. Between 1984 and 1996, 1204 patients with T1and T2 ≥3 cm were treated. Family history (FH) was recorded according to first degree relative (FDR). Treatment consisted of lumpectomy with axillary dissection followed by radiotherapy to the whole breast with a boost to the primary area. Adjuvant systemic therapy was given to patients with positive nodes.

A positive FH was noted in 243 (20.5%) patients, of whom 208 (17.6%) had one FDR, and 35 (3.0%) ≥2 FDRs. The local recurrence rate was 4.1%, with similar rates for all groups. In young patients, ≤40 years, a significant relation between local recurrence and FH was found. The distant metastasis rate was 15.5%, with the lowest rate (5.7%) among patients with ≥2 FDRs. Patients with a positive FH had significantly more contralateral tumours. The 5-year corrected survival was 91.3%. Among patients with a positive FH, a 5-year corrected survival of 91% was observed and the survival 100% among patients with one and ≥2 FDR.

Family history is not a contraindication for breast conservative treatment and is not associated with a worse prognosis. Family history is not a prognostic factor for local recurrence rate in patients older than 40 years.

INTRODUCTION

It has been estimated that 5–10% of breast cancer patients have a major inherited component.[1] The question has risen whether breast conservative treatment for patients with a family history (FH) of breast cancer is justified and if these patients have a worse prognosis. To address these questions we performed a prospective cohort study of breast cancer patients, treated with breast conservative treatment only, and radiotherapy at the Radiotherapy Department of the Medisch Spectrum Twente (MST). Our research question was, whether a positive FH of breast cancer is a risk factor for increased rates of contralateral breast cancer, local recurrence and distant metastasis, and a decreased 5-year survival in patients receiving breast conservative treatment.

MATERIALS AND METHODS

Between 1984 and 1996, 1204 patients with early breast cancer, T1 and T2 ≤3 cm, were treated with breast conservative treatment in the Twente-Achterhoek region. All patients have undergone close follow-up and details of family history, local recurrence, regional recurrence, distant metastasis and survival were available. To get the most reliable family history (FH) we only recorded the history of the first-degree relatives. The FH was recorded according to first degree relative (FDR): none, or one or more (≥1) FDRs. We also made a subdivision with a positive FH of one, or more than one (≥2) FDRs. Patients were divided into three age categories: 40 years or less, 41 to 50 years, and over 50 years. For the purpose of this study the cut-off for analysis was July 1999. Patients were followed-up for local and regional recurrence, distant metastasis, second breast tumour contralateral, time to local recurrence and distant metastasis, and for survival. Because local recurrence and new primaries in the treated breast are often difficult to differentiate, they were classified as local recurrences. Recurrences in the axilla, parasternal, or a combination were classified as regional recurrence. Clinical histological, demographic and follow-up information was regularly collected and entered in our data base on all breast cancer patients treated with breast conservative treatment. The specific features recorded for each patient include tumour size, presence and number of positive lymph nodes (subdivided by number of nodes), TNM classification, histologic subtype, presence of an intraductal component (CIS), presence of microscopically involved margin of the lumpectomy specimen, radiotherapy with or without regional or parasternal radiotherapy and treatment with systemic adjuvant therapy. These data are displayed in Table 1.

Table 1: Comparison of the distribution of clinical, histological and treatment features of patients with no family history (FH) to a positive FH, ≥1 FDR, and the subdivision of first degree relative (FDR).

	None (*n*=941) number (%)	**≥1 FDR** (*n*=243) number (%)	***P* value**	**one FDR** (*n*=208) number (%)	**>2 FDR** (*n*=35) number (%)	***P* value**
Age, mean	56	56.3	ns	56.3	56.3	ns
Age cat						
≤40	76 (8.1)	23 (9.5)		20 (9.6)	3 (8.6)	
41–50	251 (26.7)	59 (24.3)	ns	49 (23.6)	10 (28.6)	ns
>50	614 (65.3)	161 (66.3)		139 (66.8)	22 (62.9)	
TNMclass						
pT_1N_0	558 (59.3)	151 (62.1)		129 (62.1)	22 (62.9)	
pT_1N_1	182 (19.3)	46 (18.9)	ns	40 (19.2)	6 (17.1)	ns
pT_2N_0	95 (10.1)	24 (9.9)		18 (8.6)	6 (17.1)	
pT_2N_1	91 (9.7)	17 (7)		16 (7.7)	1 (2.9)	
Histology						
ductal carc	744 (79.1)	190 78.2)		163 (78.4)	27 (77.1)	
lobular carc	92 (9.8)	25 (10.3)		22 (10.6)	3 (8.6)	
tubular carc	53 (5.6)	14 (5.8)	ns	12 (5.8)	2 (5.7)	ns
medullary carc	24 (2.6)	6 (2.5)		3 (1.9)	2 (5.7)	
rest	28 (3)	8 (3.3)		7 (3.4)	1 (2.9)	
CIS						
none	648 (68.9)	165 (67.9)		142 (68.3)	23 (65.7)	
DCIS	239 (25.4)	58 (23.9)	ns	50 (24)	8 (22.9)	ns
lob.CIS	42 (4.5)	15 (6.2)		13 (6.3)	2 (5.7)	
NO. pos. lymph node						
None	653 (69.4)	178 (73.3)		150 (72.1)	28 (80)	
1–3	199 (21.2)	49 (20.2)	ns	45 (21.6)	4 (11.4)	ns
>3	78 (8.3)	14 (5.8)		11 (5.3)	3 (8.6)	
Margin lumpectomy						
Positive	84 (8.9)	28 (11.5)	ns	22 (10.6)	6 (17.5)	ns
Negative	854 (90.6)	214 (88.1)		185 (88.9)	29 (82.9)	
Radiotherapy						
Mamma	666 (70.8)	179 (73.7)		154 (74)	25 (71.4)	
Mamma+regional	155 (16.5)	37 (15.2)	ns	33 (15.9)	4 (11.4)	ns
Mamma+parast.	120 (12.8)	27 (11.1)		21 (10.1)	6 (17.1)	
Adjuvant syst.ther.						
none	688 (73.1)	193 (79.4)		164 (78.8)	29 (82.7)	
Horm or chemo	253 (26.9)	50 (20.6)	*P*=0.044	44 (21.6)	6 (17.1)	ns

CIS: carcinoma in situ, DCIS: ductal carcinoma in situ, lob.CIS: lobular carcinoma in situ.

Treatment

The standard treatment for breast conservative treatment consisted of lumpectomy with axillary dissection, clearance level I–III, followed by radiotherapy to the whole breast with a boost to the primary tumour area. Twelve patients did not have an axillary dissection. According to FDR 11 of those 12 patients had none and 1 patient had one FDR.

Radiotherapy consisted of 50 Gy to the whole breast delivered by tangential technique in 2 Gy fraction 5 times a week. This was followed by a boost to the primary tumour bed of 14 Gy in 2 Gy fraction 5 times a week delivered by external photon or electron beam therapy. In the early years a boost of 15 Gy, 2.5 Gy per fraction was delivered to 172 patients. Twenty-eight patients were treated by iridium implantation peroperatively with a dose of 15 Gy low dose rate.

Adjuvant therapy consisted of regional or parasternal radiotherapy and of hormonal and/or chemotherapy. The regional or parasternal radiotherapy was 50 Gy in 2 Gy fraction 5 times a week. The indication was the presence of and number of positive lymph nodes and/or extranodal (EN) disease.

For premenopausal patients chemotherapy was related to the number of positive lymph nodes in the early years of the treatment period. Nowadays all premenopausal patients with positive lymph nodes have chemotherapy.

For postmenopausal patients adjuvant hormonal therapy was given when positive lymph nodes were present.

Statistical methods

Time to recurrence and follow-up was calculated from the start of the treatment. To test between-group differences for categorical data, α^2-tests were used, while differences in continuous variables were analysed by Student-*t*-test. Survival statistics were calculated by the method of Kaplan and Meier. The overall survival, due to all causes and corrected survival, corrected for intercurrent death, were calculated. This means that data on patients who died of other causes were regarded as censored data. For comparing survival distributions we used the logrank test. Multivariate survival analysis was done with Cox regression, while for the categorical data logistic regression was used.

RESULTS

For 20 of the 1204 patients FH was unknown, leaving 1184 patients for analysis. A positive FH of carcinoma of the breast was noted in 243 (20.5%) patients, of which 208 (17.6% of total) had one FDR, and 35 (3% of total) ≥2 FDRs. The mean age was 56 years (range 20–89) and when separated according to FH there was no significant difference in age (Table 1). Comparisons in

terms of clinical, histological, and demographic characteristics, between patients without and with a positive FH, and among the groups with one FDR and ≥2 FDRs are presented in Table 1. The only significant difference between patients with and without positive FH was found regarding adjuvant systemic therapy. Patients with a positive FH more often did not receive adjuvant systemic therapy (*P*=0.042).

The distribution of adjuvant treatments is presented in Table 2.

The follow-up ranged from 2 to 175 months, with a median of 65 months and a mean of 70 months.

Table 2: Distribution of the adjuvant treatment of systemic and radiotherapy with 1184 patients.

Radiotherapy	Hormonal	Chemother.	Horm.+chemo	Trial	None	Unknown
Breast only (71.4%)	54 (4.6%)	33 (2.8%)		1	756 (63.9%)	1
Breast + regional node (16.2%)	100 (8.5%)	47 (4%)	2 (0.2%)	7 (0.6%)	36 (3%)	
Breast + parasternal node (12.4%)	28 (2.4%)	31 (2.6%)			86 (7.3%)	2
Total (100%)	182 (15.4%)	111 (9.4%)	2 (0.2%)	8 (0.7%)	878 (74.2%)	3 (0.2%)

Recurrence rates (Table 3)

The local recurrence rate was 4.1%, with similar rates and localisations of the recurrence for all groups. The relationship between local recurrence and FH was significant (*P*=0.005) for patients of ≤40 years (Table 4). In 11 (1%) patients a regional recurrence was observed, of which 7 were in the axilla, 2 parasternal and 2 both together.

Univariate analysis showed a significant relationship between regional recurrence and a positive FH (*P*=0.04). Distant metastases were found in 183 patients (15.5%), with the lowest rate (5.7%) among the patients with ≥2 FDRs. No significant relation between metastasis and FH for the three different age categories was found. Contralateral carcinoma of the breast was diagnosed in 69 (7.4%) of the 935 patients without a positive FH, and in 32 (13.2%) of those with a positive FH (*P*=0.004).

In a multivariate logistic regression we analysed the relative risk of getting local and regional recurrence, distant metastasis and contralateral tumour in relation to FH. A significant increased risk was seen for regional recurrence (OR=4.8; 95% Confidence Interval 1.4−16.7; *P*=0.014) and contralateral carcinoma of the breast (OR=2.0; 95% Confidence Interval 1.3−3.1; *P*=0.003) for patients with a FH.

The 5-year overall survival was 88% with a corrected survival of 91.3% and it was similar for patients with or without a positive FH. Also stratified for the different age categories there was no significance difference. Among the 243 patients with a positive FH, a 5-year survival of

91% and 100% was observed among patients with one and ≥2 FDR, respectively (Figure 1). In a multivariate Cox regression, with FH and other clinical and histological factors family history was not a significant factor.

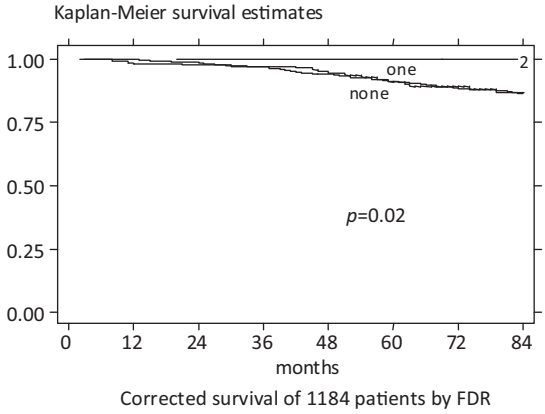

Figure 1: Corrected survival of 1184 patients by FDR.

Table 3: Univariate analysis of results in breast conservative treatment for 1184 patients with a family history according to first degree relative (FDR).

	None 941 pat. (%)	**≥1 243 pat. (%)**	***P* value**	**One 208 pat. (%)**	**≥2 35 pat. (%)**	***P* value**
Contralat. tumour						
yes	69 (7.4)	32 (13.2)	*P*=0.004	29 (14)	3 (8.6)	*P*=0.009
no	866	210		178	32	
Local recur.						
yes	39 (4.2)	10 (4.1)	ns	9 (4.3)	1 (2.9)	ns
no	901	233		199	34	
Regional rec.						
yes	6 (0.6)	5 (2.1)	*P*=0.040	4 (1.9)	1 (2.9)	ns
no	935	238		204	34	
Metastasis						
yes	152 (16.2)	31 (12.8)	ns	29 (13.9)	2 (5.7)	ns
no	789	212		179	33	

Table 4: Univariate analysis of the relation of family history and local recurrence according to age category.

Age category	Family history	Local recurrence		*P* value
≤40 Years		Positive	Negative	
n=99	≥1 FDR	7 (30.4%)	16 (69.6%)	*P*=0.005
	None	6 (7.9%)	70 (92.1%)	
41–50 years				
n=310	≥1 FDR	1 (1.7)	58 (98.3%)	ns
	none	15 (6%)	236 (94%)	
>50 years				
n=774	≥1 FDR	2 (1.2%)	159 (98.8%)	ns
	none	18 (2.9%)	595 (97.1%)	

DISCUSSION

One of the main reasons to look at the influence of family history, is the fact that women with a FH and a tumour in the breast were and still are often advised not to have a breast conservative treatment in our region. This is because of the so-called high rate of local recurrence and in consequence a less good prognosis. Except for retrospective and case control sutdies, no prospective randomised trial is known to us, that could scientifically confirm this hypothesis.

In order to obtain a reliable family history from every patient we chose to ask only for first degree relatives. We are aware of the fact that by doing so we might miss patients with positive second-degree relatives. Despite that, it is our opinion that in this way we have obtained a reliable family history. Data from the literature with regard to local recurrence are not consistent.[6-11] Chabner et al. and others did not find a higher rate of local recurrence after breast conservative treatment, this in contrast to Ravaioli et al. and others who did find a higher local recurrence rate. In our large study we did not find a higher rate of local recurrence for patients with a FH.

Looking at the local recurrence rate in relation to FH in different age categories we found a very high rate for patients of ≤40 years (Table 4). In the multivariate logistic analysis we did not find a significant relation between age category and FH. Also the multivariate survival analysis did not show any significance in this respect. This indicates that FH might not be the dominant factor in the relation to local recurrence for patients ≤40 years.

While for all patients a positive FH did not result in a higher local recurrence rate and as a consequence FH is not a contra indication for breast conservative treatment, it might be contraindicated for young patients, ≤40 years, and a positive FH. On the other hand we do not know if mastectomy will give better results in this respect.

In our analysis we found a significant relation between the incidence of regional recurrence and FH. When analysing the relevance of this in relation to other clinical, histological and demographic factors we find could not an significant relation. This makes the importance of the significance questionable, which is supported by the wide 95% confidence interval in the multivariate analysis.

Also the prognosis for patients with a FH is not consistent.[15-17]

Looking at the incidence of metastasis for the different groups, a positive FH of breast cancer did not have any influence in the incidence of distant metastasis on univariate analysis. Also in the multivariate logistic regression metastasis did not have a significant relation with FH. This is not consistent with Marcus et al. who found a lower rate, but is consistent with data of Israeli and of Chabner.[4,6,7] It suggests that the prognosis is not influenced by a positive FH according to FDR. Marcus et al. found in hereditary breast cancer patients a lower recurrence rate.[4] We could not confirm his results with our small series of 35 patient with ≥2 FDRs and who possibly had hereditary breast cancer.

Looking at the survival our results are consistent with the literature.[2,3,5,7,8,14,15] There is no survival difference between patients with or without a FH. Only if we look in particular to the small group of patients with ≥2 FDRs (Figure 1) we see a 100% survival, which is supported by data of Marcus et al. and Malone et al.[4,12,16] We must be aware that this group of 35 patients with possibly hereditary breast canceris rather small, which means that we have to interpret this with caution. The results with regard to the incidence of contralateral tumour are consistent with other data.[6,7,16] However, in those 35 patients with ≥2 FDRs we observed a similar rate as in patients with no FH.

In conclusion, patients with a positive family history have no worse prognosis. A positive family history is no contraindication for breast conservative treatment for patients older than 40 years. A positive family history and an age of ≤40 years might be a contra indication to breast conservative treatment. Larger prospective cohort studies are necessary to evaluate further the influence of a positive FH on the treatment results and prognosis of women with breast carcinoma.

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Chapter 3

The impact of age on local control in women with pT1 breast cancer treated with conservative surgery and radiation therapy

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ABSTRACT

The aim of the study was to evaluate the importance of young age with regard to local control in a prospective cohort of 1085 women with pathological T1 tumours treated with breast conservative treatment (BCT). Patients were divided into two age groups: 40 years or younger, 7.8%, and older than 40 years, 92.2%. With a median follow-up of 71 months, the local recurrence rate was 10.6% in women ≤40 years, and 3.7% in older women. The local recurrence-free survival (LRFS) was significantly different for the two age groups, respectively 89%, ≤40 years, and 97.6%, >40 years (*P*=0.0046). A separate analysis showed a significantly decreased LRFS for young women with a positive family history, 75.4% versus 98.4% 5-year LRFS for older women. A worse LRFS for young women with a negative lymph node status was also observed, respectively 84% versus 98% 5-year LRFS (both *P*<0.001). In a multivariate analysis, taking into account the pre-treatment and treatment factors, age ≤40 years, was the only significant predictor of a decreased LRFS. Thus, young age is an important factor in relation to local control. In a subset analysis, this significant adverse effect of young age on outcome appears to be limited to the node-negative patients and those with a positive family history. To date, there is no evidence that young women with pT1 breast cancer, treated by mastectomy have an improved outcome when compared with those treated with conservative surgery and radiotherapy. Taking into account results from a subset analysis suggests that giving systemic therapy to a subgroup of women who are ≤40 years, node-negative and/or have a positive family history might give a better local control.

INTRODUCTION

Nowadays, breast conservative treatment (BCT) is the standard treatment for small breast tumours, stage I and II. Large randomised trials such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-06, the European Organization for Research and Treatment of Cancer (EORTC) trial 10801, and other data showed equal results for lumpectomy with irradiation, compared with mastectomy.[1-4]

Women with T1 tumours are an excellent group for BCT. In addition, from a psychological and social point of view, BCT offers women a better treatment compared with mastectomy. In this respect, young women are an important group. Many studies report a higher local recurrence rate in young women, ranging from 8 to 31% in women younger than 45 years of age.[5-14,29]

The identification of patients at an increased risk of local recurrence after BCT continues to generate controversy. Many factors have been identified. Unfortunately, direct comparison of published data is limited because of differences in surgical and radiation techniques, histological evaluations and the use of adjuvant systemic therapy.

In the EORTC trial, investigating the value of the boost dose, which included 5569 patients, young age (<40 years) was again one of the major prognostic factors for worse local control.

This raises the question of whether BCT is the right primary treatment for young women or whether other factors should be considered. To evaluate the importance of young age as a prognostic factor for local recurrence, we analysed a prospective cohort study of breast cancer patients with T1 tumours, all treated with BCT, and all treated with radiotherapy at the Radiotherapy department of the Medisch Spectrum Twente (MST).

PATIENTS AND METHODS

Between 1984 and 1997, 1085 patients with a pathological T1 breast cancer (pT1), were treated with BCT in the Twente-Achterhoek region, and all had the radiotherapy at the Radiotherapy Department of the MST.

The standard treatment for BCT consisted of lumpectomy with axillary dissection, clearance level I–III, followed by radiotherapy of the whole breast with a boost to the primary tumour area.

The radiotherapy was 50 Gy to the whole breast delivered by tangential technique in 2 Gy fractions, five times a week. This was followed by a boost to the primary tumour bed of 14 Gy in 2 Gy fractions five times a week, delivered by external photon or electron beam therapy. In the early years, a boost of 15 Gy, 2.5 Gy fractions, four times a week was delivered to 143 patients (13%). 27 patients were treated by an iridium implantation peroperatively with a dose of 15 Gy at a low dose rate.

The adjuvant therapy consisted of regional or parasternal radiotherapy, and of hormonal and/or chemotherapy. 50 Gy was given for regional or parasternal radiotherapy in 2 Gy fractions five times a week. Regional radiotherapy, including axilla, supraclavicular and parasternal, was indicated for patients with more than three positive lymph nodes and/or extranodal disease (EN). Parasternal radiotherapy was indicated for those with less then four positive lymph nodes without EN. Giving parasternal radiotherapy depended also on the medial implantation of the breast, because priority was given to radiotherapy of the breast as part of the primary treatment. This may have led to patients with an indication for parasternal radiotherapy not receiving it.

Until 1992, premenopausal women received chemotherapy when the number of positive lymph nodes was more than three. Nowadays, all premenopausal patients with positive lymph nodes have chemotherapy. Generally, the chemotherapy was administered post-radiotherapy.

For postmenopausal patients, adjuvant hormonal therapy was given when positive lymph nodes were present. All patients underwent a close follow-up every 3 months for the first 3 years and twice a year thereafter. The follow-up included family history, local recurrence, regional recurrence, distant metastasis and survival. For the purpose of this study the cut-off for analysis was July 2000.

As local recurrence and new primaries in the treated breast are often difficult to differentiate, they were all classiffied as local recurrences. Recurrences in the axilla, parasternal or a combination were classiffied as regional recurrence. Patients were divided into two groups according to age; either 40 years or younger or older than 40 years of age. The comparability of the two age groups was assessed in terms of clinical factors (localisation of the primary, family history), histopathological factors (histology, presence of carcinoma in situ (CIS), involvement margins in the lumpectomy, presence and number of positive lymph nodes, incidence of extra-nodal disease and oestrogen receptor status, and treatment-related factors (type of radiotherapy and incidence of adjuvant systemic therapy). We defined the presence of CIS by having CIS in the lumpectomy specimen. No distinction was made for an extensive intraductal component. Involvement of the margin in the lumpectomy specimen was defined as having microscopical involvement of infiltrating carcinoma in the margin.

Statistical methods

Time to recurrence and follow-up was calculated from the start of the treatment. To test between-group differences for categorical data, Chi-square tests were used, while differences in continuous variables were analysed by the *t*-test, when normal distributions were present. Survival statistics were calculated by the method of Kaplan and Meier. The disease-specific survival, corrected for intercurrent death, was calculated. This means that data on patients who died of other causes were regarded as censored data. The disease-free survival (DFS) is defined by survival without any recurrence. The local recurrence-free survival (LRFS) is defined by survival without local

recurrence. For comparing survival distributions we used the logrank test. Multivariate survival analysis was done using Cox regression, while for categorical data, logistic regression was used.

RESULTS

Of the 1085 women with a pT1 tumour, only 7.8% (85/1085) were 40 years or younger at the time of the primary treatment. The follow-up ranged from 3 to 194 months with a median of 71 months and a mean of 78 months.

Table 1 shows a comparison in terms of clinical, histological and treatment characteristics between the two age groups. The two groups of women defined by age were homogeneous in terms of family history, pN classification, number of positive lymph nodes, margins in the lumpectomy specimen, and carcinoma in situ (CIS). An imbalance was observed for histology ($P<0.001$), oestrogen receptor status ($P<0.001$), and systemic adjuvant therapy ($P=0.002$). Young women had predominantly ductal carcinoma and virtually no tubular or lobular carcinoma. In addition, young women showed more often a negative receptor, although this result must be treated with caution due to the large number of women with unknown receptor status. Young women also had significantly more adjuvant systemic therapy, although again the numbers in the subgroups were small.

Table 1: Clinical, histopathological and treatment characteristics of 1085 pT1 breast cancer patients according to age.

	≤40 years n=85 (%)	>40 years n=1000 (%)	*P* value
Family history			
≥1 FDR	15 (17.6)	224 (22.4)	
None	68 (80)	761 (76.1)	ns
Unknown	2 (2.4)	15 (1.5)	
Histology			
Ductal carcinoma	79 (92.9)	758 (75.8)	
Lobular carcinoma	1 (1.2)	117 (11.7)	
Tubular carcinoma	0	79 (7.9)	*P*<0.001
Medullar carcinoma	4 (4.7)	17 (1.7)	
Other	1 (1.2)	29 (2.9)	
pN classification			
pN0	60 (70.6)	750 (75)	
pN1	25 (29.4)	236 (23.6)	ns
Unknown		14 (1.4)	
Number of positive lymph nodes			
None	60 (70.6)	749 (74.9)	
1–3	19 (22.4)	189 (18.9)	ns
>3	6 (7.1)	48 (4.8)	
Unknown		14 (1.4)	
Margin in lumpectomy			
Positive	7 (8.2)	85 (8.5)	
Negative	77 (90.6)	906 (90.6)	ns
Unknown	1 (1.2)	5 (0.5)	
Carcinoma in situ			
None	58 (68.2)	688 (68.8)	
DCIS	25 (29.4)	254 (25.4)	ns
LCIS	2 (2.4)	58 (5.8)	
Oestrogen receptor			
Positive	19 (55.9)	293 (80.1)	
Negative	15 (44.1)	62 (16.9)	*P*<0.001
Unknown		11 (3)	
Missing *n*=685			
Adjuvant radiotherapy			
None	57 (67.1)	761 (76.1)	ns
Treated	28 (32.9)	239 (23.9)	
Adjuvant systemic therapy			
None	54 (63.5)	780 (78)	*P*=0.002
Treated	31 (36.5)	220 (22)	

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; FDR, first-degree relative; ns, non-significant.

Table 2: Local recurrence related to clinical, histopathological and treatment factors, and differences in local recurrence-free survival (compared by log rank test).

	Local recurrence (2 unknown)		*P* value
	Present *n*=46 (%)	**None *n*=1037 (%)**	
Age (years)			
≤40	9 (10.6)	76 (89.4)	
>40	37 (3.7)	961 (96.7)	*P*=0.0046
Family history			
≥1 FDR	8 (3.4)	231 (96.6)	
None	37 (4.5)	791 (95.5)	
Unknown	1	15	ns
Histology			
Ductal carcinoma	37 (4.4)	798 (95.7)	
Lobular carcinoma	4 (3.4)	114 (96.6)	
Medullar carcinoma	4 (19)	17 (80)	
Tubular carcinoma	1 (1.3)	78 (98.7)	
Rest	0	30	*P*=0.0032
pN-stage			
pN0	33 (4.1)	777 (956.13)	
pN1	13 (4.6)	246 (95.4)	
Unknown	0	14	ns
Number of positive lymph nodes			
1–3	8 (3.9)	200 (96.1)	
>3	5 (9.3)	48 (90.7)	
None	33 (4.1)	776 (95.9)	
Unknown	0	14	ns
Margin in lumpectomy			
Positive	6 (6.5)	86 (93.5)	
Negative	40 (4)	945 (96)	
Unknown	0	6	ns
Carcinoma in situ			
DCIS	15 (5.4)	263 (94.6)	
LCIS	2 (3.4)	58 (96.6)	
None	29 (3.9)	716 (96.1)	ns
Adjuvant radiotherapy			
Treated	16 (6)	250 (94)	
None	30 (3.7)	787 (96.3)	ns
Adjuvant systemic therapy			
Treated	10 (4)	240 (96)	
None	36 (4.3)	797 (95.7)	ns

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; FDR, first degree relative; ns, non-significant.

Local recurrences

The local recurrence rate of all 1085 women was 4.2% (46/1085), and according to age group 10.6% (9/85) in women ≤40 years, and 3.7% (37/998) in women >40 years of age. The time to local recurrence ranged from 9 to 127 months, with a mean of 45 months. According to the age group, the mean was 43 months for women ≤40 years and 58 months for older women. The log rank test did not show a signifficance difference.

In univariate analysis, we analysed the clinical, histopathological and treatment factors for local recurrence-free survival (LRFS) (Table 2). Young women showed a significantly reduced LRFS (*P*=0.0046), respectively 89% versus 97.4% 5-year LRFS, as well as those with medullar carcinoma (*P*=0.0032).

In a separate analysis, young women were compared with older women for pretreatment factors in relation to LRFS (Table 3). Young women with a positive family history had a significantly reduced LRFS, 75.4% at 5-years, than women >40 years, 98.4%. This was also the case for young women with a negative lymph node status, 84% versus 98% 5-year LRFS, respectively (both *P*<0.001). There was also a reduced LRFS for young women without the presence of CIS and for young women with a negative lumpectomy margin, both relative to the older women. The separate analysis for treatment factors showed a reduced LRFS for young women not treated with adjuvant radiotherapy or systemic therapy (Table 4). The separate analysis for the two age categories in relation to adjuvant treatment showed no significant relationship with LRFS (Table 5).

In a multivariate logistic regression for local recurrence, we took into account the pretreatment and treatment factors. A borderline significantly increased risk was seen for women ≤40 years (OR=2.3; 95% confidence interval (CI): 1.0–5.3; *P*=0.057) and significant for medullar carcinoma (OR=6.1; 95% CI: 1.8–20.6; *P*=0.004). In the same analysis, adjuvant systemic therapy showed a trend of having a protective effect with respect to local recurrence (OR=0.3; 95% CI 0.1–1.2; *P*=0.083).

In a multivariate Cox regression, taking into account the pretreatment and treatment factors from the separate analysis, age ≤40 years, was the only significant risk factor for a reduced LRFS (OR=2.4; 95% CI: 1.1–5.3; *P*=0.027).

The distant metastasis rate was 13.5% for all women; 29.4% (25/85) in women ≤40 years and 12.2% (122/ 999) in women >40 years, which was highly significant (*P*<0.001).

Table 3: Local recurrence-free survival analysis (log rank test) of the relationship of age and local recurrence according to the pretreatment factors.

	Age category	Local recurrence		*P* value (log rank)	Relative hazard
		Positive n (%)	Negative n (%)		
Family history					
None					
n=828	≤40 years	5 (7.4)	63 (92.6)	ns	
	>40 years	32 (4.2)	728 (95.8)		
Positive					
n=239	≤40 years	3 (20)	12 (80)	*P*<0.001	8.1
	>40 years	5 (2.2)	219(97.8)		0.9
Lymph node status					
Negative					
n=810	≤40 years	8 (13.3)	52 (86.7)	*P*<0.001	3.8
	>40 years	25 (3.3)	725 (96.7)		0.9
Positive					
n=259	≤40 years	1 (4)	24 (96)	ns	
	>40 years	11 (4.7) 2	23 (95.3)		
Margin in lumpectomy					
Negative					
n=985	≤40 years	8 (10.4)	69(89.6)	*P*=0.008	2.5
	>40 years	32 (3.5)	876 (96.5)		0.9
Positive					
n=92	<40 years	1 (14.3)	6 (85.7)	ns	
	>40 years	5 (5.9)	80 (94.1)		
In situ carcinoma					
None					
n=745	≤40 years	6 (10)	52 (86.7)	*P*=0.02 2.5	
	>40 years	23 (3.3)	664 (96.7)		0.9
DCIS					
n=278	≤40 years	3 (12)	22 (88)	ns	
	>40 years	12 (4.7)	241 (95.3)		
LCIS					
n=60	≤40 years	0	2	ns	
	>40 years	2 (3.4)	56 (96.6)		

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ns, non-significant.

Table 4: Local recurrence-free survival analysis of the relationship of age and local recurrence according to the treatment factors.

	Age category	Local recurrence (2 unknown)		*P* value (log rank)	Relative hazard
		Positive *n* (%)	**Negative** *n* (%)		
Adjuvant radiotherapy					
None					
n=817	≤40 years	6 (10.5)	51 (89.5)	*P*=0.0036	3.2
	>40 years	24 (3.2)	736 (96.8)		0.9
Treated					
n=266	≤40 years	3 (10.7)	25 (89.3)	ns	
	>40 years	13 (5.5)	225 (94.5)		
Adjuvant systemic therapy					
None					
n=833	≤40 years	8 (14.8)	46 (85.2)	*P*<0.001	3.7
	>40 years	28 (3.6)	751 (96.4)		0.9
Treated					
n=250	≤40 years	1 (3.2)	30 (96.8)	ns	
	>40 years	9 (4.1)	210 (95.9)		

ns, non-significant.

Survival

The 5-and 10-year disease-specific survival, corrected for intercurrent death, was 84.4 and 66% for women ≤40 years, respectively, and 93.7 and 87% for older women (log rank test, *P*<0.001). The 5-year disease-free survival (survival without any recurrence) was 71.2% for women ≤40 years and 88.8% for the older women (*P*<0.001) (Figure 1). The local recurrence-free survival (survival without local recurrence) was significantly different for the two age groups, 89%, for women ≤40 years, and 97.6% for those >40 years (*P*=0.0046) (Figure 2). In a separate analysis, young women were compared with older women for family history, lymph node status, margin in the lumpectomy specimen, in situ carcinoma, adjuvant radiotherapy and adjuvant systemic therapy pretreatment and treatment factors in relation to disease-specific survival (Table 6).

In a multivariate Cox regression analysis, taking into account age, family history, histology, lymph node status, CIS, contra-lateral breast cancer, adjuvant radiotherapy and adjuvant systemic therapy, a significantly higher risk for a reduced disease-specific survival was seen for young women, ≤40 years of age, (Hazard Ratio (HR)=2.0; 95% CI: 1.2–3.4; *P*=0.007) and a significantly lower risk was observed for lobular carcinoma compared with ductal carcinoma (HR=0.1; 95% CI: 0.0–0.9; *P*=0.04).

Table 5: Local recurrence-free survival analysis of the relationship of treatment factors and local recurrence according to age category.

Age category	Adjuvant therapy	Local recurrence (2 unknown)		*P* value (log rank)	Relative hazard
		Positive *n* (%)	Negative n *(%)*		
≤40 years	Radiotherapy			ns	
n=85	Treated	3 (10.7)	25 (89.3)		
	None	6 (10.5)	51 (89.5)		
	Systemic therapy				
	Treated	1 (3.2)	30 (96.8)	*P*=0.072	0.4
	None	8 (14.8)	46 (85.2)		1.8
>40 years	Radiotherapy			ns	
n=998	Treated	13 (5.5)	225 (94.5)		
	None	24 (3.2)	736 (96.8)	ns	
	Systemic therapy				
	Treated	9 (4.1)	210 (95.9)		
	None	28 (3.6)	751 (96.4)		

ns, non-significant.

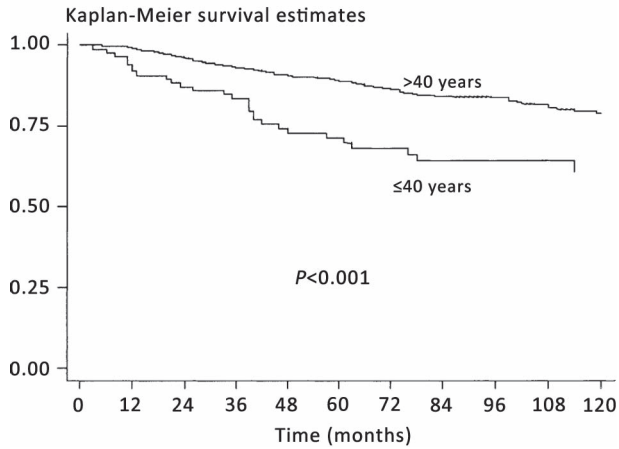

Figure 1: The disease-free survival rate of 1085 pT1 breast cancer patients according to age.

Table 6: Disease-specific survival analysis for the relationship of age according to the pretreatment and treatment factors

	Age category	*P* value (log rank)	Relative hazard
Family history			
None			
n=829	≤40 years	*P*=0.0085	2.1
	>40 years		0.9
Positive			
n=239	≤40 years	*P*=0.03 3.7	
	>40 years		0.9
Lymph node status			
Negative			
n=810	≤40 years	*P*<0.001	3.5
	>40 years		0.9
Positive			
n=261	≤40 years	ns	
	>40 years		
Margin in lumpectomy			
Negative			
n=987	≤40 years	*P*<0.001	2.4
	>40 years		0.9
Positive			
n=92	≤40 years		ns
	>40 years		
In situ carcinoma			
None			
n=745	≤40 years	*P*=0.0034	2.2
	>40 years		0.9
DCIS			
n=278	≤40 years	*P*=0.0054	2.6
	>40 years		0.9
LCIS			
n=60	≤40 years	ns	
	>40 years		
Adjuvant radiotherapy			
None			
n=818	≤40 years	*P*<0.001	3.5
	>40 years		0.9
Treated			
n=267	≤40 years	ns	
	>40 years		
Adjuvant systemic therapy			
None			
n=833	≤40 years	*P*=0.0003	3.1
	>40 years		0.9
Treated			
n=250	≤40 years	ns	
	>40 years		

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; ns, non-significant.

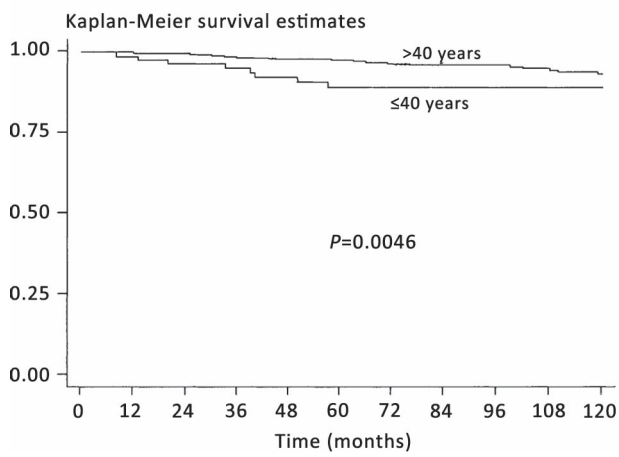

Figure 2: The local recurrence – free survival of 1083 pT1 breast cancer patients according to age.

DISCUSSION

In our analysis, young age was demonstrated to be an important prognostic factor in a failure of local control. In addition, age was a major prognostic factor for survival.

The clinical factors, such as the localisation of the primary in the breast and the family history with respect to first-degree relatives, showed no differences with respect to local recurrence rate, which is in accordance with the literature.[6,14-16,27] In contrast to the overall analysis, a separate analysis showed that women with a positive family history and aged ≤40 years had a significant higher local recurrence rate. This might indicate that the suggested negative effect of a positive family history is limited to young women.[27] Fourquet and Touboul showed that local control was also impaired by premenopausal status.[13,17]

Histopathological prognostic factors for local recurrence in breast cancer following BCT vary in the literature. Medullar carcinoma was a prognostic factor for local failure in our analysis. Nevertheless, this result should be viewed with caution because of the small number of patients with a medullar carcinoma and further analysis with a larger cohort of medullar carcinoma should be done to confirm this data.

The multivariate survival analysis showed a 10 times better survival of those patients with lobular carcinoma. Because of the small number with a known grade of differentiation, only 21%, we did use this information in our analysis. This means we cannot compare our results with those of Kollias, who explained the worse prognosis they observed for young patients as being due to the higher proportion of poorly differentiated tumours in this age group.[28]

Despite the small number of women with a known oestrogen receptor status (400/1085), we found significantly more oestrogen-negative receptors in young women ($P<0.001$), a finding also noted by Kurtz and colleagues.[6] However, de la Rochefordiere and colleagues[22] noted no significant difference in the oestrogen receptor status for young women. However, because of the small number of patients with a known oestrogen receptor status, this factor was excluded in the multivariate analysis.

Recht and colleagues[5] showed the presence of an extensive intraductal component (EIC) to be an important prognostic factor. Young women had a higher incidence of EIC, but even in the absence of EIC the local recurrence rate was still higher for young women. In addition, Boyages and colleagues, Veronesi and colleagues, and others showed EIC to be an important factor.[9,13,17-19] In the present study, we noted that the presence of CIS in the lumpectomy specimen was not related to a significantly higher incidence rate of local recurrence. In our separate analysis, young women had a significantly reduced LRFS in the absence of DCIS or LCIS. Both with and without CIS, a high rate of local recurrence was found in young women. Probably because of the low numbers, this did not reach statistical significance. The data from the literature suggest the presence of an EIC may be related to a higher local recurrence rate.

Inadequate or positive margins are seen in many studies as an important risk factor for local recurrence.[10,13,19,20,25] Solin and colleagues, unlike many other reports did not note a higher incidence rate but in agreement with our results, associated with positive margins.[23] In the separate analysis, for young versus older women, both positive and negative margins were associated with a higher rate of local recurrence in young women, although this was not statistically significant for the positive margins, possibly because of the small number of patients. The differing reports in the literature could be explained by the difficulties encountered in comparing these kinds of data due to the lack of uniformly accepted definitions of positive and negative margins. We defined positive margins as having infltrating carcinoma present at an inked surface of the specimen. Close to the surface was considered as negative. In contrast with other data, the presence of CIS was not taken into account with respect to the margin status.[25]

The presence of positive lymph nodes was an independent predictor for local recurrence in a study by Dalberg and colleagues, a result we did not confirm.[21] In our study, we noted that the adverse effect of young age was limited to the node-negative patients, which is in accordance with other data.[12,26] The same was seen in the separate disease-specific survival analysis.

In the univariate analysis, adjuvant treatment whether with radiotherapy or with systemic therapy, did not show a relationship to local recurrence. In the separate analysis, the reduced LRFS for young women was limited to the patients not treated with adjuvant therapy. Whether adjuvant treatment might reduce the LRFS in young women was examined in a separate analysis (Table 5). Only a trend was seen in the group of patients treated with adjuvant systemic therapy in contrast to the group of adjuvant radiotherapy, in which both treated and untreated young

women, had a high LRFS. From the adjuvant systemic therapy data, it looks as if giving young node-negative patients adjuvant systemic therapy might reduce the local recurrence rate. However, due to the small number of young women in the subgroups, we have to interpret this data with caution.

In a multivariate logistic regression analysis for local recurrence in relation to pre-treatment and treatment factors, young age was a borderline significant risk factor with an OR of 2.3 (95% CI: 1.0–5.3). In the same analysis, adjuvant systemic therapy showed a clear trend of having a protective effect with respect to local recurrence, which supports the conclusion by Elkhuizen.[26] However, the Cox regression analysis for disease-specific survival and local recurrence-free survival could not confirm the benefit of adjuvant systemic therapy, but showed young age to be a clear significant risk factor. This data is in accordance with results by Fourquet and Locker, who also found young age to be an independent significant factor.[13,29]

The high local recurrence rate in young women was accompanied by an even higher rate of distant metastases; 29.4% for young women compared with 12.2% for older women (P<0.001). This increased incidence has been noted in several other studies,[8,11,12,14,18,22] which supports the idea of giving adjuvant systemic therapy to young women.

Finally, the high recurrence rate in young women was clearly shown in the reduced disease-specific survival. To conclude, young women with pT1 breast cancer, undergoing conservative surgery and radiotherapy, fare significantly worse compared with older women, in terms of local control, distant metastases and survival. In a subset analysis, this significant adverse effect of young age on outcome appears to be limited to the node-negative patients and patients with a positive FH. To date, there is no evidence that young women with pT1 breast cancer, treated by mastectomy have an improved outcome when compared with those treated with conservative surgery and radiotherapy.

Young age is generally accepted as a prognostic factor. Nevertheless, it is not regarded as a factor in determining certain adjuvant treatment. Whether young age should be regarded as a treatment-related prognostic factor is doubtful. Future and ongoing treatment with more adjuvant systemic therapy might provide answers.

Prospective randomised studies for this category of women are therefore necessary, and might provide new prognostic and predictive factors, as stated by Hayes.[24] However, young women, ≤40 years of age, with breast cancer are a small group. In this respect, prospective cohort studies might be important in answering these questions.

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Chapter 4

Synchronous, bilateral breast cancer: prognostic value and incidence

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SUMMARY

The purpose of this study was to address the question whether patients with bilateral breast cancer (BBC) have a worse prognosis in terms of recurrence and survival than patients with primarily unilateral breast cancer (UBC) following breast-conserving treatment (BCT). From 1983 to 2000, a total of 1760 BCT were registered in the Radiotherapy Department of the Medisch Spectrum Twente. We defined synchronous BBC as cancer diagnosed in both breasts at the same time or within a period of 3 months of diagnosis of the first tumor. One thousand seven hundred and sixty BCT were performed on 1705 patients, 26 of whom presented with BBC. Of these 26 patients, 18 had BCT for both breasts. A higher proportion of patients with BBC showed more tubular carcinoma (P=0.029) and medially located tumors (P=0.076) than those with UBC did. The 5-and 10-year local recurrence rates (LRRs) were 4.5% and 9.1%, respectively, in BBC patients, as against 3.3% and 7.6% for UBC after BCT. The 5-and 10-year distant metastasis rates were 26.9% and 50.7%, respectively, for BBC as against 13.4% and 21.1% for UBC after BCT (P=0.065 and P=0.014, respectively). The 5-and 10-year disease-specific survival (DSS) rates for the 1705 patients were 82.1% and 41%, respectively, after BBC, and 91.4% and 84% after UBC (P=0.086 and P=0.0045, respectively). Patients with BBC have a higher rate of distant metastasis and a worse DSS than those with UBC. As the LRR is similar for BBC and UBC, BCT is not contraindicated in BBC. The incidence of BBC is low, at 1.5% which makes it difficult to reach any more definitive conclusions on outcome and treatment.

INTRODUCTION

Bilateral synchronous breast cancer is uncommon. In the literature 'bilateral' and 'contralateral' breast cancer are most often associated with synchronous and metachronous breast cancer, respectively, and the two terms are used indiscriminately. No clear distinction is made, and the definitions of synchronous bilateral and metachronous contralateral breast cancer (CBC) in the existing literature are ambiguous. The timespans quoted as defining breast cancer as synchronous and bilateral range from 1 month to 2 years, which makes a meaningful interpretation difficult.[1-6] The incidence rates cited range from 0.8% to 3%, this difference is due partly to the different definitions used for bilateral synchronous breast cancer.

The best management of patients with bilateral breast cancer (BBC) is still not known. Patients are often treated with bilateral mastectomy rather than breast-conserving treatment (BCT) and the prognosis is also regarded as worse than in the case of unilateral breast cancer (UBC). In large part, this is due to the small number of patients concerned and the limited data available on recurrence rate and disease-free survival (DFS) in this group of patients.

In this paper, we specifically address the question of whether patients with BBC have a worse prognosis in terms of recurrence and survival than patients with primarily UBC treated with BTC.

PATIENTS AND METHODS

From the start of the study in 1983, all patients treated with BCT in the Twente-Achterhoek region received radiotherapy as part of the primary treatment in the Radiotherapy Department of the Medisch Spectrum Twente. From 1983 to 2000, a total of 1760 BCT were registered. Pathological examination of all the lumpectomy specimens was done in the Pathology Laboratory of Oost Nederland.

We defined synchronous BBC as cancer diagnosed in both breasts simultaneously or within a period of 3 months of diagnosis of the first tumor and regard this as true BBC.[7] Metachronous CBC was defined as breast cancer occurring in the contralateral breast more than 3 months after the diagnosis of the tumor in the first breast affected. Some patients with BBC or CBC had BCT on one side and mastectomy on the other, while others had BCT on both sides.

Involvement of the margins of the lumpectomy specimen was defined as the presence of microscopic involvement of invasive carcinoma in the inked margin. Carcinoma in situ (CIS) was recorded when present in the lumpectomy specimen. Any extensive intraductal component was not recorded separately.

Although the grade of differentiation was recorded when known, it was not routinely reported along with the histology; and there were too few patients with known grade for this particular factor to be analyzed.

To obtain the most reliable family history (FH), the breast cancer history of first-degree relatives (FDRs) only was recorded, as zero, or one or more (≥1).

BCT consisted of lumpectomy with axillary clearance of levels I–III, followed by radiotherapy to the whole breast with a boost to the primary tumor area. In patients with BBC, radiotherapy to both breasts was given at the same time. The radiotherapy consisted in 50 Gy to the whole breast, delivered in 2-Gy fractions five times a week by a tangential technique. This was followed by a boost of 14 Gy to the primary tumour bed, in 2-Gy fractions five times a week, as external photon or electron beam therapy. In the early years, a boost of 15 Gy in 2.5-Gy fractions four times a week was delivered to 183 patients (10.4%). Thirty-seven patients were treated by iridium implantation peroperatively, with a dose of 15 Gy at a low dosage rate. The boost dose given was the same in all patients, regardless of margin status.

Adjuvant therapy consisted of radiotherapy to the regional lymph nodes, or to the internal mammary chain only, and hormonal and/or chemotherapy. The radiotherapy dose was 50 Gy in 2-Gy fractions five times a week. Regional radiotherapy, which included the axilla and the supraclavicular, and internal mammary chains, was indicated for patients with four or more positive lymph nodes and/or extranodal disease (EN). Radiotherapy of the internal mammary chain only was indicated for those with fewer than four positive lymph nodes and no EN. In the case of medial implantation of the tumor in the breast, the use of a separate anterior field for irradiation of the internal mammary chain was omitted to permit optimal irradiation of the breast.

Until about 1992, premenopausal women received chemotherapy when four or more lymph nodes were positive. Since 1992, all premenopausal patients with positive lymph nodes have received chemotherapy. For postmenopausal patients, adjuvant hormonal therapy was given when positive lymph nodes were present. Since 1999, whether or not adjuvant systemic therapy is given has depended not only on the lymph node status, but also, in the case of a negative lymph node status, on whether the mitotic activity index >10.[5]

All patients were seen every 3 months for the first 2–3 years and twice a year thereafter. During follow-up, FH, local recurrence, regional recurrence, distant metastasis, and survival were noted. None of the BBC patients was lost to follow-up. In the UBC group, 0.2% were lost to follow-up after a few years because they had left the area. For the purposes of this study, the cut-off for analysis was January 2002.

As it is often difficult to differentiate between a local recurrence and a new primary one in the treated breast, all tumours found in the same breast during follow-up were classified as local

recurrences. Recurrences in the axilla, or the internal mammary chain, or in both were classified as regional recurrences.

Statistical methods

Time to recurrence and length of follow-up were calculated from the start of the treatment. To test between-group differences for categorical data, Chi-square tests were used, and these analyses with regard to local recurrences were performed in relation to the number of BCT. The local recurrence-free survival (LRFS) is defined as survival without local recurrence.

Survival statistics were performed in relation to the number of patients and calculated by the method of Kaplan and Meier. The disease-specific survival (DSS), corrected for intercurrent death, was also calculated in relation to the number of patients. This means that data on patients who died of other causes were regarded as censored data. The DFS is defined as survival without any recurrence.

For comparison of survival distributions, the log rank test was used. Multivariate survival analysis was done using Cox regression, while for categorical data, logistic regression was used. Hazard ratios (HRs), relative hazard (RH), and 95% confidence intervals (95% CI) are presented.

RESULTS

From 1983 to 2000, 1760 BCTs were administered to 1705 patients. Both these numbers were used in the analysis. Fifty-five patients had a second BCT with BBC or CBC. The 1705 patients included 26 (1.5%) who presented with BBC, and 18 of the 26 had BCT for both breasts. Twenty six patients with BBC had 44 courses of BCT.

The length of follow-up ranged from 3 to 218 months, with a median of 71 and a mean of 77 months.

Table 1 shows a comparison of clinical and treatment characteristics of the patients with UBC and those with BBC. The two groups were homogeneous in terms of age, FH, and adjuvant radiotherapy. An imbalance was observed for adjuvant systemic therapy (P=0.016).

Table 1: Clinical and treatment features of 1706 breast cancer patients, by bilaterality/unilaterality of their breast cancer.

	Bilateral (*N*=26)		Unilateral (*N*=1679)		*P* value
	N (%)	N (%)	N (%)	N (%)	
Age category (years)					
≤40	3	(11.5)	135	(8)	ns
>40	23	(88.5)	1544	(92)	
Family history					
≥1FDR	7	(26.9)	358	(21.3)	ns
None	19	(73.1)	1305	(77.7)	
Unknown	0		16	(1)	
Adjuvant radiotherapy					
None	20	(76.9)	1257	(74.9)	ns
Treated	6	(23.1)	422	(25.1)	
Adjuvant systemictherarpy					
None	13	(50)	1200	(71.5)	
Treated	13	(50)	479	(28.5)	0.016

FDR= first-degree relative.

Table 2 shows a comparison of histopathological characteristics between UBC and BBC for the 1760 BCT. Higher proportions of patients with BBC had tubular carcinoma (*P*=0.029) and medially located tumours (*P*=0.076). Analysis of the histopathological factors in the 26 BBC patients, showed that in 16 of the 26 patients the histology was the same in tumors from the left and right breast, while three patients had a lobular-ductal combination and three had a tubular-ductal combination. The other four had other combinations. The estrogen and progesterone receptor status was the same in both breasts in 20 of the 26, and the CIS, in 15.

Separate consideration of the localization of the primaries (lateral or medial) revealed that the incidence of medial tumors was significantly higher in patients with BBC, 47.7% (21/44) vs. 28.7% (493/1716) (*P*=0.021).

Local recurrences

Analysis for local recurrences was done according to the number of BCTs. The incidence rates of local recurrence after the 1760 courses of BCT was 6.8% (3/44) for patients with BBC and 4.3% (73/1716) for UBC. The 5-and 10-year local recurrence rates (LRRs) were 4.5% and 9.1%, respectively, for BBC as against 3.3% and 7.6% for UBC (*P*=0.43 and *P*=0.3, respectively).

Table 2: Pathohistological features of 1760 courses of BCT by bilaterality/unilaterality of the breast cancer in the 1706 patients.

	Bilateral (*N*=44)		Unilateral (*N*=1716)		*P* value
	N (%)	N (%)	N (%)	N (%)	
Localization					
LUQ	18	(40.9)	931	(54.2)	
LLQ	4	(9.1)	206	(12)	
MUQ	13	(29.5)	341	(19.9)	0.076
MLQ	8	(18.2)	152	(8.9)	
Central	1	(2.3)	86	(5)	
Histology					
Ductal ca	28	(63.6)	1328	(77.4)	
Lobular ca	4	(9.1)	189	(11)	
Tubular ca	7	(15.9)	112	(6.5)	0.029
Medullar ca	3	(6.8)	40	(2.3)	
Rest	2	(4.6)	47	(2.7)	
Margins of lumpectomy					
Positive	7	(15.9)	185	(10.8)	
Negative	37	(84.1)	1524	(88.8)	ns
Unknown	0		7	(0.4)	
Carcinoma in situ					
DCIS	9	(20.4)	438	(25.5)	
LCIS	5	(11.4)	98	(5.7)	ns
None	30	(68.2)	1176	(68.5)	
Unknown			4		
Estrogen receptors					
Positive	29	(65.9)	1125	(65.6)	
Negative	8	(18.8)	283	(16.5)	ns
Unknown	7	(15.9)	308	(17.9)	
Progesterone receptors					
Positive	27	(61.4)	940	(54.8)	
Negative	10	(22.7)	448	(26.1)	ns
Unknown	7	(15.9)	328	(19.1)	
pT classification					
pT1	37	(84.1)	1342	(78.2)	
pT2	7	(15.9)	361	(21)	ns
Rest	0		13	(0.8)	
pN classification					
pN0	31	(70.4)	1223	(71.3)	
pN1	11	(25)	472	(27.5)	ns
Unknown	2	(4.6)	21	(1.2)	

DCIS=ductal carcinoma in situ; LCIS=lobular carcinoma in situ; BCT=breast conservative treatment; LUQ=lateral upper quadrant; LLQ=lateral lower quadrant; MUQ=medial upper quadrant; MLQ=medial lower quadrant.

Distant metastasis

Analyses for distant metastasis and survival were referred to the number of patients. The incidence of distant metastasis for the 1705 patients was 30.8%(8/26) for BBC vs. 15.1% (254/1678) for UBC (*P*=0.028). In one case, no information about distant metastasis was available. The 5-and 10-year distant metastasis rates were 26.9% and 50.7%, respectively, for BBC as against 13.4% and 21.1% for UBC (RH 2.1; *P*=0.065, and RH 2.3; *P*=0.014, respectively) (Figure 1). In univariate analyses, we found an inverse relationship between distant metastasis-free survival on the one hand and BBC (*P*=0.015), younger age (*P*<0.001), histology (*P*<0.001), larger tumor size (*P*<0.001), CIS (*P*=0.02), positive margin of lumpectomy (*P*=0.04), positive lymph nodes (*P*<0.001), negative estrogen receptor status (*P*=0.003), negative progesterone receptor status (P=0.007), adjuvant systemictherapy (*P*<0.001), and adjuvant radiotherapy (*P*<0.001) on the other. In a multivariate Cox regression analysis including the above variables, BBC was not found to be significant. Young age, positive lymph nodes, large tumors, lobular carcinoma, and adjuvant systemic therapy were significant.

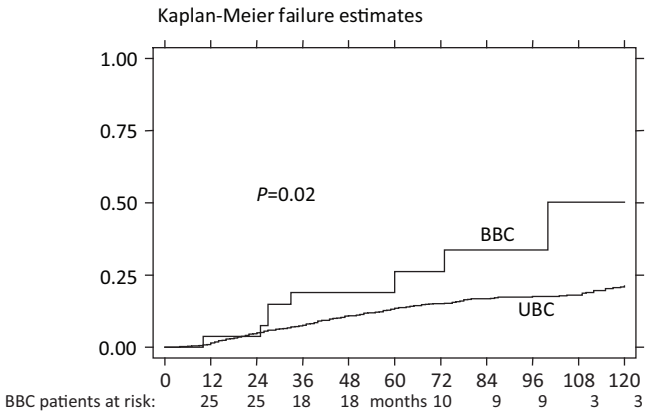

Figure 1: Rate of distant metastasis from synchronous BBC compared with UBC in 1705 breast cancer patients treated with BCT.

Disease-free survival

The 5-and 10-year DFS rates for the 1705 patients were 73.1% and 49.3%, respectively, for BBC patients, and 85.3% and 74.6% for those with UBC (RH 1.9; *P*=0.11, and RH 2.0; *P*=0.04, respectively).

Disease-specific survival

The 5-and 10-year DSS rates for the 1705 patients were 82.1% and 41%, respectively, for patients with BBC, and 91.42% and 84% for those with UBC (RH 2.3; *P*=0.086, and RH 2.8; *P*=0.0045, respectively) (Figure 2). In univariate analyses, we demonstrated a relationship between DSS on the one hand and BBC (*P*=0.0058), young age (*P*<0.001), histology (*P*<0.001), large tumor size (*P*<0.001), CIS (*P*=0.026), positive lymph nodes (*P*<0.001), estrogen receptor status (*P*<0.001), progesterone receptor status (*P*<0.001), adjuvant systemic therapy (*P*<0.001), and adjuvant radiotherapy (*P*<0.001) on the other. In a multivariate Cox regression analysis including the above variables, BBC was not found to be significant (HR 2.2; 95% CI 0.7–7.2; *P*=0.18). Young age, positive lymph nodes, large tumors, lobular carcinoma, negativity for estrogen receptor, and adjuvant systemic therapy were significant.

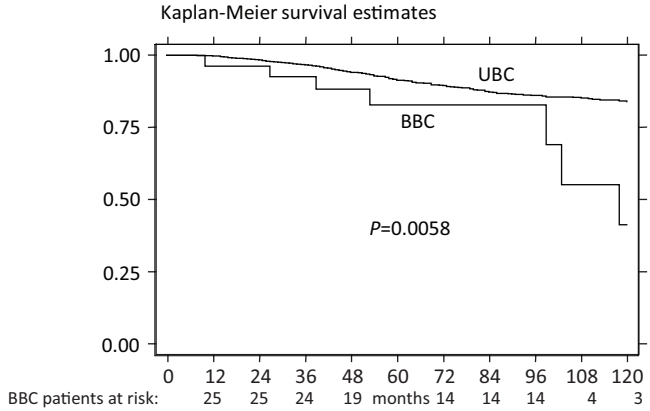

Figure 2: DSS after synchronous BBC and after UBC in 1705 breast cancer patients treated with BCT.

DISCUSSION

The incidence of BBC of 1.5% in our cohort of 1705 patients is in accordance with the literature, where the incidence ranges between 0.8% and3%.[1,3,4,6,8-10] As our institution is the only radiotherapy facility in this region, all patients with BCT are automatically referred to us and registered.

Our study showed a significantly higher rate of metastasis from BBC than from UBC, resulting in a significantly worse DSS for patients with BBC. This was especially evident after longer follow-up periods.

It is difficult to compare our results with those in the literature, because the literature reports are not all based on the same definition of BBC. Our definition of cancer diagnosed in both breasts simultaneously or within 3 months of diagnosis of the first tumour is in accordance with that used by the Radiation Oncology Advisory Group – a joint group of the National Breast Cancer Center and the Royal Australian and New Zealand College of Radiologist Faculty of Radiation Oncology, and other bodies.[7] In our opinion, this is the most accurate definition of bilateralism.

There are few papers on synchronous BBC in the literature, and they often refer to both synchronous and metachronous, CBC.

We looked for any clinical or histopathological risk factors for BBC. No significant relation identifying any risk factor at all was found. Gogas and others suggested a relation between a positive FH and bilateralism, which we cannot confirm.[4,10] De la Rochefordiere noted a high rate of estrogen receptor positivity in patients with BBC.[11] This is also not confirmed by our data.

In a further analysis of localization of the primaries we noted a significantly higher rate of medial localization in women with BBC, something that has not been noted before in the literature. No impact of medial localization on survival or DFS was seen.

The LRR was no worse after BBC than after UBC in breast cancer patients treated with BCT. In our opinion, BCT is not contraindicated for in BBC.

We found that patients with BBC had a significantly higher distant metastasis rate than those with UBC. In our observations, these are in accordance with those of Heron et al., who also noted a trend toward a lower level of local control in BBC.[1] We cannot confirm this last observation. There is no general agreement on whether mastectomy or BCT is the better choice for the primary treatment of BBC. Looking at our local control rate, in accordance with Gollamudi and Mose we believe that the therapeutic strategy in BBC should resemble the treatment procedure applied in UBC.[6,9,12]

Analysis of the DFS reveals a clear trend to a worse DFS in BBC with borderline significance found at 10 years in univariate analysis.

Like Heron and Gustafsson, we noted a worse DSS in patients with BBC.[1,13] Although Heron had a different definition of BBC, with diagnosis of cancer in the second breast up to a year after the diagnosis of the first tumor. This was despite the fact that patients with BBC had significantly more adjuvant systemic therapy (Table 1). Multivariate analysis did not show BBC to be a significant prognostic factor for DSS, in contrast to adjuvant systemic therapy, which was significant with a HR 0.5 (P=0.010; 95% CI 0.3–0.8). Whether adjuvant systemictherapy might be beneficial for BBC is something that needs further investigation.

The numbers are small, and longer follow-up is needed. On the other hand, all reported series are small and will probably remain small in the future, which makes the formulation of general conclusions problematic.

Patients with BBC have a higher rate of distant metastasis and a worse DSS than those with UBC. The incidence of 1.5% is low, which makes it difficult to reach definitive conclusions on outcome and treatment.

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Chapter 5

Effect of external boost volume in breast-conserving therapy on local control with long-term follow-up

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ABSTRACT

Purpose: To determine the effects of boost volume (BV) in relation to margin status and tumor size on the development of local recurrence with breast-conserving therapy.

Methods and Materials: Between 1983 and 1995, 1,073 patients with invasive breast cancer underwent 1,101 breast-conserving therapies. Of these 1,101 BCTs, 967 were eligible for analysis. The BV was categorized into tertiles: <66 cm^3 (*n*=330), 66-98 cm^3 (*n*=326), and >98 cm^3 (*n*=311). The median follow-up was 141 months. Separate analyses were done for women ≤40 years and >40 years.

Results: No significant difference in local recurrence was shown between the tertiles and the recurrence site. The 15-year local recurrence-free survival rate was 87.9% for the first tertile, 88.7% for the second, and 89% for the third. For women ≤40 years old, the corresponding 15-year local recurrence-free survival rate was 80%, 74.5%, and 69.2%. For women >40 years old, the corresponding rate was 88.7%, 89.5%, and 90.9%. At 5 years, women >40 years old had significantly more local failures in the first tertile; this difference disappeared with time. A test for trend showed significance at 5 years (*P*=0.0105) for positive margins for ductal carcinoma in situ in women >40 years of age.

Conclusion: The results of this study have shown that the size of the external BV has no major impact on local control. For women >40 years old, positive margins for ductal carcinoma in situ showed a trend with respect to BV at 5 years. The BV had no influence on local control in the case of positive margins for invasive carcinoma.

INTRODUCTION

Breast-conserving therapy (BCT) is the treatment of choice for early-stage invasive breast cancer.[1-4] The standard treatment consists of lumpectomy, followed by whole breast irradiation with a boost to the tumor bed.

One of the major endpoints of BCT is local control. Some factors associated with optimal local control have been established (margin status and age) and others remain controversial.[5-16]

The Lyon trial is one of three randomized trials that showed that the delivery of a boost to the tumor bed significantly reduced the risk of early local recurrence.[17,18] However, the necessity for a boost to the tumor bed has been questioned in the NSABP B-06 trial.[19] The 10-year results of the European Organization for Research and Treatment of Cancer trial of a boost vs. no boost have shown that the boost leads to a decreased local recurrence rate.[20]

Considerable disagreement persists regarding the required amount of involved breast tissue needed to establish an adequate boost volume (BV). Clinical delineation of the BV carries a significant risk of missing the target. The use of inaccurate planning of the BV has led to a 23–70% reported rate of an inaccurate boost.[21-26] Landis et al.[27] demonstrated that in all but the most well-visualized cases a large variability can exist in the determination of the location and size of the breast lumpectomy cavity for radiotherapy (RT) planning among physicians who specialize in the treatment of breast cancer.

It is generally agreed that demarcating the excision cavity with surgical clips leads to more accurate planning of the BV.[20-22] Despite this, many radiation oncologists must determine the target of the boost by relying primarily on the location of the skin incision, surgical indurations, preoperative mammograms, surgical operation report, and, if possible, the patient's recollection in the case of a palpable mass.

If the interrelationship between the BV, tumor size, and margin status with the development of local recurrence could be more clearly elucidated, radiation oncologists could plan the treatment better. To this end, we reviewed our prospective cohort of all patients with invasive breast cancer treated with BCT with long-term follow-up to determine the effects of the BV in relation to margin status and tumor size in the development of local recurrence. In earlier studies, we demonstrated a statistically significant interaction between margin status and patient age and demonstrated the significance of the margin status.[14,15] We also showed young age to be an important prognostic factor for local control.[14,16] It seems reasonable to suspect a relation among margin status, BV, and local control. We, therefore, performed a separate analysis for margin status and age.

METHODS AND MATERIALS

This prospective cohort of breast cancer patients was started in 1983 when BCT was introduced in our region. All patients in the Twente-Achterhoek region with invasive breast cancer and treated with BCT underwent irradiation at the Radiotherapy Department of the Medisch Spectrum Twente at Enschede. The patient data, including demographics, histologic type, staging information, treatment, and outcome, were recorded prospectively and updated regularly. Between 1983 and 1995, the data of the BVs were recorded until about the data for 1,000 BVs had been collected. In this period, 1,101 BCTs were registered for 1,073 patients. The purpose of this study was to evaluate these BVs at a later point with enough follow-up and events, mainly local recurrence.

Pathologic examination for all BCT was done at the Pathology Laboratory of Oost Nederland. The patients were classified according to the TNM classification, 4th edition, 1997. A family history of breast cancer was recorded to first-degree relatives.

We defined synchronous bilateral breast cancer as cancer diagnosed in both breasts simultaneously or within a 3-month period of diagnosis of the first tumor. Metachronous contralateral breast cancer was defined as breast cancer occurring in the contralateral breast >3 months after the diagnosis of the tumor in the first breast.

Although malignancy grading was recorded when known, it was not routinely reported with the other items of the histology report during the early years, and we had too few patients with a known grade for this factor to be analyzed.

All patients were seen every 3 months for the first 2–3 years and twice a year thereafter. During follow-up, local recurrence, regional recurrence, distant metastasis, and survival were recorded. For the purposes of this study, the cutoff for analysis was February 2007.

Because it is often difficult to differentiate between local recurrence and a new primary in the treated breast, all tumors found in the ipsilateral breast during follow-up were classified as local recurrences. Local recurrences were correlated to the possible boost area and recorded accordingly as within the possible boost area or at the edge of the possible boost area and elsewhere in the breast. Accordingly, local recurrences were divided into those within the BV or at the edge and those elsewhere in the breast.

Margin status

Involvement of the margins of the lumpectomy specimen was defined as the presence of microscopic involvement of invasive carcinoma (IC) or ductal carcinoma in situ (DCIS) in the inked margin. Close margins were recorded as negative. Massive involvement with IC or DCIS of the margins, defined as diffuse or multiple microscopic foci, was regarded as an indication for re-excision. If focal microscopic involvement of the margin was present, re-excision was not

advised. The policy at our department was that minimal microscopic disease could be treated with RT. A total of 72 re-excisions were performed. Negative margins were defined as those with no microscopic IC or DCIS in the inked margin of the lumpectomy specimen or after re-excision. The presence of DCIS in the lumpectomy specimen, independent of involvement at the margin, was recorded separately. The extent of the intraductal carcinoma component was not recorded separately.

Treatment

Breast-conserving therapy consisted of lumpectomy with axillary clearance of Levels I–III, followed by RT to the whole breast, with a supplementary boost to the primary tumor area. In general, BCT was limited to tumors ≤3 cm clinically. The RT regimen consisted of 50 Gy to the whole breast delivered in 2-Gy fractions five times a week using a tangential technique, followed by a boost of 14 Gy to the primary tumor bed in 2-Gy fractions five times a week. The dose to the whole breast was specified on the 95% isodose in the central plane. For planning, wedges were used, and a lung correction was performed. The photon boost technique used multiple fields. In the early years, a boost of 15 Gy, in 2.5–Gy fractions, four times a week, was delivered to 99 patients. The boost dose given was the same in all patients, regardless of margin status. To avoid any bias, because of the small number of iridium boosts, the analyses were limited to the photon and electron boosts only.

Adjuvant therapy

Adjuvant therapy consisted of RT to the regional lymph nodes or the internal mammary chain only and hormonal therapy and/or chemotherapy. The radiation dose was 50 Gy in 2–Gy fractions five times weekly. Regional RT, including the axilla, supraclavicular, and internal mammary chains, was indicated for patients with four or more positive lymph nodes and/or extranodal disease. RT of the internal mammary chain only was indicated for those with fewer than four positive lymph nodes and no extranodal disease. In the case of medial implantation of the breast, the use of a separate anterior field for irradiation of the internal mammary chain was omitted to permit optimal irradiation of the breast.

Until about 1992, premenopausal women received adjuvant chemotherapy when one to three lymph nodes were positive. After 1992, all premenopausal patients with positive lymph nodes received adjuvant chemotherapy. In general, adjuvant chemotherapy was delivered after the primary treatment, surgery plus RT of the breast. For postmenopausal patients with positive estrogen receptor status, adjuvant hormonal therapy was given when positive lymph nodes were present and, in most patients, started directly after surgery.

Determination of external BV

Of the 1,101 BCTs, the BV was unknown in 111 and 23 had been an iridium boost, leaving 967 BCTs for 945 patients for analysis. The location of the BV was determined by the location of the lumpectomy scar, primary tumor site, when known, mammogram findings, and, if possible, radiopaque clips placed in the lumpectomy cavity. Since the early 1990s, the length for a pT1 tumor photon boost was generally 6 cm and was 7 cm for a pT2 tumor. All photon boosts were planned using a two- or three-field technique. The three-field technique was generally two tangential fields and one anterior field. Planning was done in one central plane only. The BV was estimated by measuring the area within the 95% isodose of the central plane multiplied by the length of the boost field. Electron boosts were given by a direct field to the tumor bed. The electron BV was determined by estimating the upper surface of the electron field multiplied by the length of the depth for the 85% isodose. The contour of the breast was not taken into account. We categorized the BV into tertiles: first tertile <66 cm^3, second tertile 66–98 cm^3, and third tertile >98 cm^3.

Statistical analysis

The time to recurrence and the length of follow-up were calculated from the start of treatment. To test the between-group differences for categorical data, chi-square tests were used. Statistical tests for local recurrences and disease-free survival were performed in relation to the number of BCTs performed. Local recurrence-free survival (LRFS) rate was defined as survival without local recurrence.

The statistics for distant metastasis and survival were calculated according to the number of patients using the Kaplan-Meier method. Disease-specific survival (DSS), corrected for intercurrent death, was calculated. Thus, data on patients who died of other causes were regarded as censored data. For comparison of the survival distributions, the log-rank test was used. Multivariate survival analysis was done using Cox regression, including a test for interaction. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented. The reference category was always the first tertile, with the smallest BV, <66 cm^3.

The variables that were univariately related to the outcomes of interest (p<0.10) were entered into the multivariate analyses. A test for trend across the three tertiles was performed. All analyses were performed using STATA (StataCorp, Chicago, IL).[28]

RESULTS

The 967 BVs were divided into three tertiles; 330 were in the first tertile (<66 cm^3), 326 were in the second (66–98 cm^3), and 311 were in the third (>98 cm^3). The patient age range was 27–89

years (median, 57 years). The length of follow-up was 3-253 months (median, 141 months; mean, 136 months).

The patient and tumor characteristics are shown in Table 1. The first tertile had significantly more tumors localized in the lateral upper quadrant. The difference in tumor size for the three tertiles was highly significant (p<0.001), with larger tumors in the third tertile and fewer pT2 tumors in the first.

The treatment characteristics are shown in Table 2. The third tertile had significantly more electron boosts, fraction sizes of 2.5 Gy, and total boost doses of 15.0 Gy. The latter two were linked in a treatment scheme of the 1980s. The third tertile also had more patients who had undergone adjuvant RT.

Local recurrence

The incidence of local recurrence was 8.7% (84 of 967), with 2 unknown. No significant difference was shown among the tertiles. The local recurrence site for the first, second, and third tertile was the boost/edge area vs. elsewhere in 6.4% vs. 2.4%, 6.4% vs. 2.8%, and 5.8% vs. 2.3%, respectively.

The 10-year and 15-year LRFS rate for all BCTs was 93.1% and 88.4%, respectively. The corresponding rate stratified by tertile was 92.4% and 87.9% for the first tertile, 93.1% and 88.7% for the second tertile, and 93.9% and 89% for the third tertile (Figure 1). Because of the possible substantial changes in LRFS in relation to BV during follow-up, separate analyses were done for the 5-year, 10-year, and 15 year LRFS rates. Table 3 shows the HRs and 95% CIs. At 5 years, the HR for the largest BV compared with the smallest was 0.45, but the difference was not significant (p=0.101), possibly because of the small numbers of events (n=31). The difference disappeared during follow-up.

On univariate analysis, taking into account all clinical, histopathologic, and treatment characteristics and the tertiles, significance was shown for two factors: age (p<0.001) and margin status (p<0.001). The presence of in situ carcinoma (p=0.094), primary tumor location (p=0.079), and contralateral breast cancer (p=0.078) showed borderline significance and were included in the multivariate analyses.

The 15-year multivariate Cox regression analysis showed that young age (HR, 3.27; 95% CI, 1.87–5.73; p<0.001) and positive margins (HR, 2.89; 95% CI, 1.73–4.80; p<0.001) were significant. Contralateral breast cancer (HR, 1.83; 95% CI, 0.98–3.42; p=0.059) showed borderline significance for local recurrence.

The analyses also revealed a significant statistical interaction between margin status and age. Therefore, we performed analyses for BV and margin status with regard to LRFS for women ≤40 years (77 BCTs) and >40 years (890 BCTs) separately.

Table 1: Patients and tumor characteristics in 967 BCT stratified by external BV.

	BV (cm^3)			
Characteristics	**<66** *n*=330 (%)	**66-98** *n*=326 (%)	**>98** *n*=311 (%)	***P***
Age category				
≤40 years	33 (10)	17 (5.2)	27 (8.7)	*P*=0.066
>40 years	297 (90)	309 (94.8)	284 (91.3)	
Localization primary				
LUQ	196 (59.4)	163 (50)	153 (49.2)	
LLQ	33 (10)	34 (10.4)	42 (13.5)	
MUQ	58 (17.6)	69 (21.2)	74 (23.8)	*P*=0.025
MLQ	27 (8.2)	37 (11.4)	34 (10.9)	
Central	16 (4.8)	23 (7.1)	8 (2.6)	
Histology				
ductalcarc.	249 (75.4)	251 (77)	255 (82)	
lobularcarc.	38 (11.5)	36 (11)	22 (7.1)	
tubularcarc.	26 (7.9)	20 (6.1)	11 (3.5)	*P*=0.015
medullarcarc.	10 (3.0)	12 (3.7)	6 (1.9)	
rest	7 (2.1)	7 (2.2)	17 (5.5)	
Carcinoma in situ				
DCIS	95 (28.8)	84 (25.8)	67(21.5)	
LCIS	15 (4.5)	19 (5.8)	14 (4.5)	*P*=0.250
none	220 (66.7)	223 (68.4)	230 (74)	
Margin status				
positive IC	26 (7.9)	23 (7.1)	28 (9)	
positive DCIS	15 (4.6)	10 (3.2)	10 (3.2)	
positive IC+DCIS	7 (2.1)	4 (1.2)	7 (2.2)	*P*=0.795
negative	281 (85.2)	286 (87.7)	266 (85.5)	
unknown	1 (0.3)	0	0	
Re-excision				
yes	34 (10.3)	20 (6.1)	18 (5.8)	
none	282 (85.5)	294 (90.2)	283 (91)	*P*=0.157
unknown	14 (4.2)	12 (3.7)	10 (3.2)	
Estrogen receptor				
positive	167 (50.6)	184 (56.4)	191 (61.4)	
negative	54 (16.4)	59 (18.1)	51 (16.4)	*P*=0.025
unknown	109 (33)	83 (25.5)	69 (22.2)	

Characteristics	BV (cm³)			P
	<66 *n*=330 (%)	**66-98** *n*=326 (%)	**>98** *n*=311 (%)	
Progesterone receptor				
positive	138 (41.8)	150 (46)	164 (52.7)	
negative	82 (24.9)	92 (28.2)	76 (24.4)	*P*=0.016
unknown	110 (33.3)	71 (22.8)	71 (22.8)	
Tumor size				
pT1a: <0.6 cm	18 (5.4)	14 (4.3)	12 (3.9)	
pT1b: 0.6–1.0 cm	96 (29.1)	103 (31.6)	48 (15.4)	
pT1c: 1.1–2.0 cm	168 (50.9)	143 (43.9)	165 (53.1)	*P*<0.001
pT1multiple	7 (2.1)	4 (1.2)	8 (2.6)	
pT2: 2.1–5.0 cm	40 (12.1)	61 (18.7)	76 (24.4)	
rest	1 (0.3)	1 (0.3)	2 (0.6)	
Lymph nodes				
1–3 positive	79 (23.9)	67 (20.6)	64 (20.6)	
>3 positive	24 (7.3)	20 (6.1)	23 (7.4)	*P*=0.186
negative	225 (68.2)	236 (72.4)	215 (69.1)	
unknown	2 (0.6)	3 (0.9)	9 (2.9)	

BCT: breast conserving treatment; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; CIS: carcinoma in situ; LUQ: lateral upper quadrant; LLQ: lateral lower quadrant; MUQ: medial upper quadrant; MLQ: medial lower quadrant.

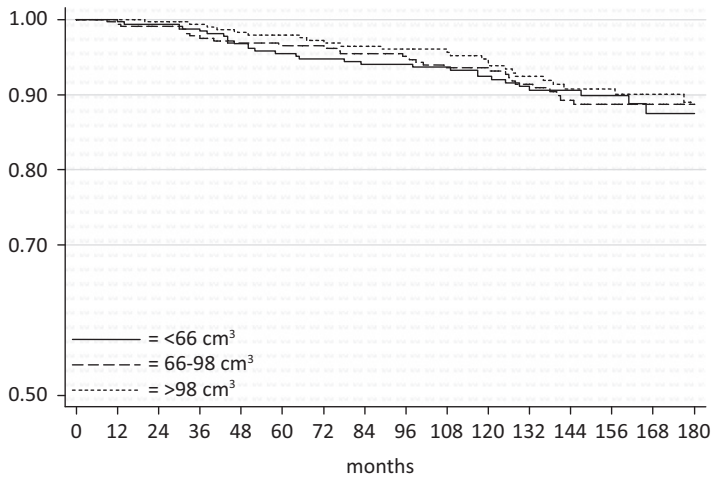

Figure 1: Local relapse-free survival of 965 breast-conserving therapies according to external boost volume.

Local recurrence, BV, and age

Women ≤40 years had significantly more local recurrence at 22.1% compared with women >40 years old at 7.5% (p<0.001).

The local recurrence site for women ≤40 years for the first tertile was the boost/edge area in 15.2% and elsewhere in 0%. For the second and third tertile, the corresponding percentages were 11.8% and 17.6% and 22.2% and 3.7%, respectively. Women >40 years in the first tertile had local recurrence in the boost/edge area in 5.4% and elsewhere in 2.7%. The corresponding percentages were 5.8% and 1.9% and 4.2% and 2.1% for those in the second and third tertile, respectively.

For women ≤40 years, the 10-year and 15-year LRFS rate for was 80% and 80% in the first tertile, 74.5% and 74.5% in the second tertile, and 74.1% and 69.2% in the third tertile, respectively. For women >40 years, the corresponding rates were 93.6% and 88.7% in the first tertile, 94.2% and 89.5% in the second tertile, and 95.8% and 90.9% in the third tertile (Figure 2). For the second and third tertile, the difference was highly significant between the two age categories (p=0.008 and p<0.001, respectively).

Table 3 shows the HRs and 95% CIs for the two age categories. Women >40 years, at 5 years, had significantly fewer local recurrences for the third tertile compared with those in the first tertile (HR, 0.19; p=0.030). No significance difference was seen for women ≤40 years.

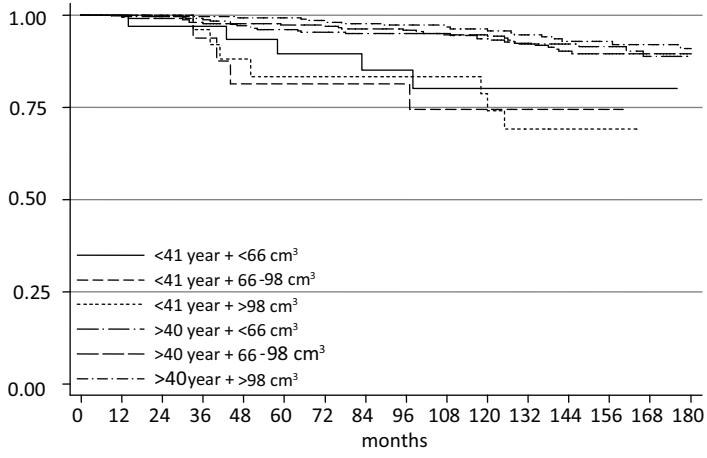

Figure 2: Local relapse-free survival of 965 breast-conserving therapies according to external boost volume and age category.

Table 2: Treatment characteristics of 967 BCTs stratified by external BV.

	BV (cm^3)			
Characteristics	**<66** *n*=330 (%)	**66-98** *n*=326 (%)	**>98** *n*=311 (%)	***P* value**
Type boost dose (Gy)				
photon	328 (99.4)	314 (96.3)	209 (67.2)	<0.001
electron	2 (0.6)	12 (3.7)	102 (32.8)	
Fraction dose (Gy)				
200 cGy	328 (99.4)	321 (98.5)	219 (70.4)	<0.001
250 cGy	2 (0.6)	5 (1.5)	92 (29.6)	
Total boost dose (Gy)				
14 Gy	327 (99.1)	315 (96.6)	216 (69.4)	
15 Gy	1 (0.3)	5 (1.5)	92 (29.6)	<0.001
rest	2 (0.6)	6 (1.8)	3 (1.0)	
Adj. Radiotherapy				
radiotherapy	85 (25.8)	75 (23)	113 (36.3)	<0.001
none	245 (74.2)	251 (77)	198 (63.7)	
Adj. Systemic ther.				
chemother.	40 (12.1)	29 (8.9)	25 (8)	
hormoonther	58 (17.6)	49 (15)	46 (14.8)	0.119
chemo+hormoon	5 (1.5)	4 (1.2)	0	
none	227 (68.8)	244 (74.8)	240 (77.2)	

BCT: breast conserving treatment; DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ; CIS: carcinoma in situ; LUQ: lateral upper quadrant; LLQ: lateral lower quadrant; MUQ: medial upper quadrant; MLQ: medial lower quadrant. Datapresentedasnumberof BCTs,withpercentagesinparentheses.

Local recurrence, BV, age, and margin status for women >40 years

Because of the small number of women #40 years (*n*=77), no analyses of margin status and BV were performed. For women >40 years with margins negative for DCIS, the 5-year, 10-year and 15-year LRFS rates were computed for the three tertiles. Table 3 shows the HRs and 95% CIs. At 5 years, the third tertile had a HR of 0.36 compared with the first tertile, but the difference was not significant (p=0.202).

A test for trend of survivor function was performed for women >40 years with margins positive for DCIS. The test found significance at 5 years (p=0.0105) that had disappeared at 10 and 15 years (Figure 3).

The 5-year, 10-year, and 15-year local failure rate (LFR) for the different tertiles according to margin status for women >40 years is given in Table 4. Positive margins for IC did not result in a significant difference in the LFR for the different BVs. The LFR significantly increased after 10 year for margins positive for IC. Margins positive for DCIS resulted in a significantly greater LFR

compared with margins negative for DCIS and margins positive for IC, irrespective of the different BVs. The first tertile had a greater LFR, but the difference was not significant.

Table 3: Local replapse free-survival for 967 BCTs stratified by external BV.

Boost volume	5-year	10-year	15-year
		All patients (*n*=967)	
<66 cm^3	1	1	1
66–98 cm^3	0.79 (0.36–1.75)	0.89 (0.49–1.65)	0.97 (0.58–1.63)
>98 cm^3	0.45 (0.17–1.17)	0.76 (0.40–1.45)	0.83 (0.48–1.43)
		≤40–years (*n*=77)	
<66 cm^3	1	1	1
66–98 cm^3	1.93 (0.39–9.58)	1.44 (0.38–5.36)	1.44 (0.38–5.36)
>98 cm^3	1.66 (0.37–7.41)	1.37 (0.42–4.49)	1.57 (0.49–4.98)
		>40–years (*n*=890)	
<66 cm^3	1	1	1
66–98 cm^3	0.70 (0.28–1.74)	0.89 (0.45–1.77)	0.97 (0.55–1.70)
>98 cm^3	0.19* (0.42–0.85)	0.61 (0.28–1.33)	0.71 (0.38–1.31)
		>40-years and negative margins for DCIS (*n*=816)	
<66 cm^3	1	1	1
66-98 cm^3	1.13 (0.38–3.38)	1.22 (0.55–2.69)	1.14 (0.61–2.13)
>98 cm^3	0.36 (0.72–1.77)	0.69 (0.27–1.77)	0.69 (0.33–1.43)

The reference boost volume is <66 cm^3. * significant p=0.030. Abbreviations: HR = hazard ratio; CI = confidence interval; other abbreviations as in Table 1. Reference boost volume was <66 cm^3. * Significant at p=0.030.

Disease-specific survival

The 15-year DSS rate for all 945 patients was 83.5%. Stratified by tertile, the 15-year DSS rate was 78.3% for the first tertile, 73.1% for the second, and 75.8% for the third. On univariate analysis, the different BVs did not show a significant difference. The 15-year DSS rate for women ≤40 years was 56.4% for the first tertile, 55.5% for the second, and for the third. For women >40 years, the DSS rate was 80.8% for the first tertile, 74.1% for the second, and 76.1% for the third.

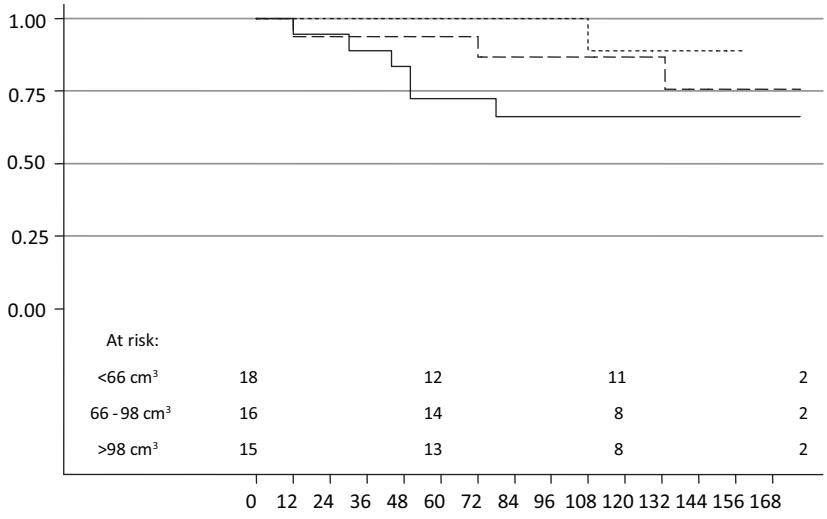

Figure 3: Local relapse-free survival for 49 patients >40 years with margins positive for ductal carcinoma in situ according to external boost volume.

Table 4: Local failure rate for 967 BCTs according to external BV by margin status for 890 BCTs in women >40 years.

	5-year LFR		
Boost volume	**Negative margin** *n*=770	**Positive for IC** *n*=71	**Positive for DCIS** *n*=36
<66 cm³	2.1% (0.01–0.05)	4.4% (0.01–0.27)	28.6% (0.12–0.59)
66–98 cm³	2.3% (0.01–0.05)	4.5% (0.01–0.28)	7.7% (0.01–0.43)
>98 cm³	0.9% (0.00–0.03)	0	0
		10–year LFR	
<66 cm³	4.6% (0.02–0.08)	4.4% (0.01–0.27)	36.5% (0.17–0.67)
66–98 cm³	5.1% (0.03–0.09)	9.3% (0.02–0.32)	16.1% (0.04–0.51)
>98 cm³	4.3% (0.02–0.08)	0	20% (0.03–0.79)
		15–year LFR	
<66 cm³	8.6% (0.05–0.15)	28.3% (0.09–0.69)	36.5% (0.17–0.67)
66–98 cm³	8.7% (0.05–0.14)	20.7% (0.08–0.46)	16.1% (0.04–0.51)
>98 cm³	6.3% (0.04–0.11)	38.4% (0.16–0.74)	0

Abbreviations: LFR = local failure rate; other abbreviations as in Table 1. Data in parentheses are 95% confidence intervals. Because of small patient numbers (*n*=13), no LFR shown for margins positive for IC plus DCIS.

DISCUSSION

The results of this study have demonstrated that the size of the external BV has no major impact on local control. The time to local recurrence in relation to the BV had a HR of 0.45 for the third tertile compared with the first tertile at 5 years, but this disappeared with additional follow-up. The latter was limited to women >40 years. With regard to the different positive margins, only margins positive for DCIS show a trend at 5 years with respect to BV. The BV had no influence on local control in patients with margins positive for IC.

Giving a boost in breast-conserving therapy is currently a topic of discussion. Pezner et al.[29,30] claimed that omitting the boost in patients with tumor-free margins resulted in local control rates comparable to those of other institutions that routinely used a boost. Two trials have shown that the delivery of a boost to the tumor area significantly reduced the risk of local recurrence.[17,18] The recent update of the European Organization for Research and Treatment of Cancer 22881-10882 trial emphasized the value of the boost in relation to local control.[20]

Clinical delineation of the tumor bed carries a significant risk of missing the target. Currently, the BV depends, not only on the size of the primary tumor, but also on the extent of the lumpectomy, the presence of tumor-free margins, and the reproducibility of the clinical delineation of the tumor bed. A boost reconstructed using scar dimensions, mammography, and the presence of surgical clips could lead to missing a substantial portion of the tumor bed, negatively affecting local control.[21-25] Better delineation of the tumor bed using computed tomography, which optimizes coverage of the target volume and spares normal breast tissue, should have the potential to improve local control. That approximately 80% of breast tumor recurrences develop at the site of the original disease supports this idea. To a certain extent, the BV is a surrogate for tumor size, with larger BVs for pT2 tumors. However, we found a large variation in the BV for different tumor sizes.

One of the limitations of this study was that no surgical clips were placed in the tumor bed for most of the BCTs, leaving only the scar, mammogram, and patient recollection to reconstruct the location of the primary. We also must take into account the method of estimation of the BV we used. We can assume that most of the BVs were estimated too large if we consider the geometry of the female breast. We estimated the volume to be a hypothetical square box. It is often difficult to determine whether the local recurrence was located in or near the original boost area; for this reason, we combined the boost and edge area for our analysis.

The aim of giving a boost dose in BCT is to decrease the recurrence rate in the proximity of the lumpectomy. Theoretically, a geographic miss (including BVs that were too small) will lead to more recurrences outside the BV area, and hence to more recurrences elsewhere in the breast.

The hypothesis was that the delineation of the tumor bed must have been inaccurate in an essential part of the BCT, and one should expect a relation between the BV and the local

recurrence incidence. Our working hypothesis was that a larger BV would lead to better coverage of microscopic disease outside the lumpectomy cavity and thereby might lead to a decreased rate of marginal misses. Considering the effect of the BV on local control, we expected that the rate of local recurrence inside the BV area would be the same for the various tertiles. Comparing the various BVs, we wondered whether a large BV would result in less recurrence elsewhere in the breast, leading better overall local control. A large BV would thereby compensate for geographic misses. For the various tumor sizes, we would expect more local recurrence elsewhere in the breast for the first tertile compared with the third tertile.

The analysis showed a large variation in BVs, emphasizing not only the problem of the delineation of the tumor bed, but also interobserver variation. Because of the dispersion and the median of the BVs, we formed three tertiles. The analyses found no influence of BV on the local recurrence site. All three tertiles had the same percentages of recurrences for the different areas, boost/edge vs. elsewhere. According to the hypothesis, one would have expected less recurrence elsewhere for the large BVs.

In analyzing the data, we took into account the results we had had in earlier studies, the statistical interaction between age and margin status, and the difference in local control for the different types of positive margins.[14,15]

Overall, for both age categories, the local recurrence rate for the various tertiles did not differ significantly. Our results showed that women >40 years might benefit from a large BV. In particular, for the first 5 years, a large BV resulted in significantly better local control. According to the HRs, a large BV seemed to postpone local recurrence in this age category. Taking into account the relevance of a margin positive for DCIS in this age category, the significance disappeared, only the trend remained (Table 3). Narrowing our scope to those with a margin positive for DCIS, it seemed that a large BV positively affected local control probability. This is in accordance with the growing pattern of DCIS.[31,32]

In earlier studies, we found a difference in local control for margins positive for IC and DCIS, in particular for women >40 years.[14,15] Margins positive for IC in women >40 years did not result in a greater local recurrence rate. The present analyses with long-term follow-up demonstrated that after 10 years the local recurrence rate significantly increases for this group of patients. Women ≤40 years had a significantly greater local recurrence rate, in accordance with the findings of previous studies.

Because of the small number of women ≤40 years old and the few events, we limited our analysis for this particular age category. We believe that additional analyses with more patients and events are necessary. The present analysis found a trend toward a greater local recurrence rate for large BVs. Whether this was in relation to possible positive margins, tumor size, or other variables is not clear and should be analyzed in a larger cohort.

CONCLUSION

First, the overall BV had no impact on local control. However, there seems to be a relation between BV and the time to local recurrence for a subgroup of patients, by postponing the recurrence. This confirms the conclusions of the Lyon and Hungarian trials that delivery of a boost to the tumor bed significantly reduces the risk of early local recurrence.[17,18] Second, our findings might imply that missing the target in boost irradiation does not lead to an increase in local recurrence or, conversely, that, with accurate boost treatment, extending the BV has no impact on local control. The LRFS rates for the different volumes tended to merge after 15 years. This could imply that despite extending the BVs, ultimately, no differences exist in local control. Finally, the BV seems to have a relation to DCIS. Margins positive for DCIS seemed to benefit from a large BV.

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Chapter 6

Timing of radiotherapy and survival benefit in breast cancer

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ABSTRACT

Purpose: To look at the optimum timing of radiotherapy in breast-conserving therapy (BCT) in relation to outcome in breast cancer.

Methods: We analyzed 1473 BCT on 1446 breast cancer patients from our prospective cohort, stage I or II, node-negative, and without adjuvant systemic therapy. Timing was defined as time from lumpectomy till radiotherapy. Patients were categorized into three timing tertiles: 1-36 days, 37-53 days, and 54-112 days.

Results: The 10-year local relapse-free survival rates did not show significant differences between the three groups. The 10-year Distant Metastasis-Free Survival (DMFS) was 78.9% for the first tertile, versus 86.1% (HR 0.6; P=0.009) for the second, and 90.7% (HR 0.3; P<0.001) for the third. The 10-year Disease-specific Survival (DSS) was 83.8% for the first tertile, versus 90.6% (HR 0.5; P=0.007) for the second, and 97.2% (HR 02; P<0.001) for the third. Also in multivariate Cox regression analysis the second (HR 0.6; P=0.053) and the third tertile (HR 0.3; P=0.002) had significantly better DSS.

Conclusion: Timing of radiotherapy in BCT for breast cancer seems to be highly important in relation to survival. This study shows a 40−70% relative survival benefit with timing after 36 days.

INTRODUCTION

Evidence from randomized clinical trials has demonstrated that the use of radiotherapy is associated with a significantly lower rate of local recurrence in patients treated with breast-conserving treatment (BCT).[1-3]

Although there is a common understanding that delay in starting radiotherapy in BCT may reduce the probability of local control, the optimum time interval between lumpectomy and radiotherapy has not yet been established. Long delays in starting radiotherapy have been linked to increased risk of local recurrence.[4]

Despite the scarce evidence recommendations about the acceptable delays were made. It is generally recommended to start radiotherapy within 6 weeks, because of the adverse effect of delay on local control.

Very few studies have looked at the effect on distant metastasis and survival.[5,6] The majority of the studies are small and basically interested in the effect on local control and timing and sequencing of radiotherapy and adjuvant chemotherapy.[7-11]

The effect of treatment delay on outcome cannot easily be investigated in randomized trials. Therefore observational studies based on high quality routinely recorded data are important.

We were primarily interested in the optimum timing of radiotherapy in BCT for patients with invasive breast cancer in relation to outcome, and wanted to test the hypothesis that starting radiotherapy within 6 weeks of lumpectomy was beneficial with respect to outcome. To avoid any bias from any other adjuvant systemic therapy, chemotherapy and/or hormonal therapy, we selected from our prospective cohort all breast cancer patients without positive nodes and without adjuvant systemic therapy. Also patients presenting with synchronous bilateral breast cancer (BBC) were excluded.

PATIENTS AND METHODS

This prospective cohort of patients was started in 1983 when BCT was introduced in our region. All patients in the Twente-Achterhoek region with invasive breast cancer and treated with BCT received their radiotherapy at the Radiotherapy Department of the Medisch Spectrum Twente at Enschede. From 1983 through 2003 a total of 2506 BCT were registered in 2264 patients. Pathological examination for all BCT was done in the Pathology of Laboratory Oost Nederland. All patient data, including demographics, histology, staging information, treatment, and outcome were recorded and are updated regularly.

Family history (FH) was recorded according to first-degree relative (FDR). We defined BBC as cancer diagnosed in both breasts simultaneously or within a period of 3 months of diagnosis of

the first tumor. Metachronous contra lateral breast cancer (CBC) was defined as breast cancer occurring in the contra lateral breast more than 3 months after the diagnosis of the tumor in the first breast affected.

Involvement of the margins of the lumpectomy specimen was defined as the presence of microscopic involvement of invasive carcinoma and/or carcinoma in situ in the inked margin.

Although the grade of differentiation was recorded when known, it was not routinely reported along with the histology during the early years; and there were too few patients with known grade (48.6%) for this particular factor to be analyzed.

For the purposes of this study, the cut-off for analysis was November 2005.

Treatment

BCT is defined as lumpectomy followed by irradiation of the whole breast with a boost to the primary tumor area. This is accompanied with axillary clearance of levels I–III or since 2000 sentinel node procedure. The radiotherapy consisted in 50 Gy to the whole breast, delivered in 2 Gy fractions five times a week by a tangential technique. This was followed by a boost of 14 Gy to the primary tumor bed, in 2 Gy fractions five times a week, as external photon or electron beam therapy. In the early years a boost of 15 Gy in 2.5 Gy fractions four times a week was delivered (10.3%). The boost dose was the same in all patients, regardless of margin status.

Definition of timing

Timing of radiotherapy was defined as time from lumpectomy till start of irradiation. Of the 2506 BCT, 1486 were node negative, did not receive any systemic adjuvant therapy, and did not have BBC. The time-span ranged from 1 to 196 days after lumpectomy. Patients with a delay of no more than 16 weeks were included in the study. Of 3 patients the exact timing was unknown and 10 patients who had a delay of more than 16 weeks all were excluded, leaving 1473 BCT for analysis.

Patients were categorized into three tertiles: 1-36 days, 37-53 days, and 54-112 days.

Reasons for the delay in starting the radiotherapy were for instance the difference in timing between lumpectomy and axillary dissection. 46.6% did not have their axillary dissection at the same time as the lumpectomy. Lumpectomy-axillary dissection delay was used as a variable in the analysis. Also patients with a re-excision of the lumpectomy, 6.9% showed a significantly longer time interval (Table 1). We also noticed a clear relation in the time period; patients in the eighties and early nineties had a short delay compared to later (Table 2). Other reasons for delay were post-operative wound healing complications, delay in referral to our department, and a waiting list for starting the irradiation. No selection in starting radiotherapy was made on any known prognostic factor.

Statistical methods

Time to recurrence and length of follow-up were calculated from the start of BCT. To test between-group differences for categorical data Chi-square tests were used, and these analyses with regard to local recurrences were performed in relation to the number of BCT. The local recurrence-free survival (LRFS) is defined as survival without local recurrence.

Survival statistics were performed in relation to the number of patients and calculated by the method of Kaplan and Meier. The Disease-specific Survival (DSS), corrected for intercurrent death, was also calculated in relation to the number of patients. This means that data on patients who died of other causes were regarded as censored data. The Distant Metastasis-Free Survival (DMFS) is defined as survival without distant metastasis in patients.

For comparison of survival distributions the log-rank test was used. Variables that were univariately related to the outcomes of interest (P<0.10) were entered in the multivariate analyses.

The Cox proportional hazards model was used to test for the independent effect of timing of radiotherapy after adjusting for known prognostic factors and hazard ratios (HR) estimated with 95% confidence limits are presented. A test for trend across the three ordered tertiles is performed. The tertile with the smallest timing, <37 days, was the referent group. All analyses were performed using STATA.[12]

RESULTS

All 1473 BCT were performed on 1446 patients. About 506 BCT had their radiotherapy in the first tertile, within 37 days of the lumpectomy, 483 in the 2nd tertile, 37-53 days after lumpectomy, and 484 in the 3rd tertile, 54-112 days after lumpectomy.

The length of follow-up ranged from 5-265 months with a median of 90 and a mean of 97 months.

A comparison in terms of clinical and histopathological characteristics between the three tertiles shows differences for age category, histology, estrogen and progesterone receptor status, tumor size, and re-excision (Table 1).

Local recurrence

The 10-year LRFS was 93.1% for the first tertile, versus 92.4% for the second, versus 94.2% for the third tertile.

In the 10-year multivariate Cox regression analysis including the significant variables of the univariate analysis (margin status for invasive and carcinoma in situ, young age, and CBC), timing of radiotherapy was not an independent risk factor.

Table 1: Patients and tumor characteristics in 1473 breast-conserving treatments according to time interval lumpectomy-radiotherapy divided in tertiles.

Characteristics	**< 37 days** *n*=506 (%**)**	**37–53 days** *n*=483 (%)	**54–112 days** *n*=484 (%)	**P value**
Age category				
≤40 years	55 (10.9)	23 (4.8)	10 (2.1)	*P*<0.001
>40 years	451 (89.1)	460 (95.2)	474 (97.9)	
Family history				
Positive	109 (21.5)	118 (24.4)	115 (23.8)	*P*=0.600
None	390 (77.1)	364 (75.4)	369 (76.2)	
Unknown	7 (1.4)	1 (0.2)	0	
Histology				
Ductalcarc.	428 (84.6)	349 (72.3)	327 (67.6)	*P*<0.001
Lobularcarc.	36 (7.1)	65 (13.5)	76 (15.7)	
Tubularcarc.	14 (2.8)	48 (9.9)	61 (12.6)	
Medullarcarc.	12 (2.4)	11 (2.3)	7 (1.4)	
Rest	16 (3.2)	10 (2.1)	13 (2.7)	
Carcinoma in situ				
DCIS	113 (22.3)	100 (20.7)	102 (21.1)	*P*=0.001
LCIS	15 (3.0)	34 (7.0)	48 (9.9)	
None	378 (74.7)	349 (72.3)	334 (69.0)	
Estrogen receptor				
Positive	337 (66.6)	332 (68.7)	378 (78.1)	*P*=0.004
Negative	91 (18.0)	69 (14.3)	55 (11.4)	
Unknown	78 (15.4)	82 (17.0)	51 (10.5)	
Progesterone receptor				
Positive	277 (54.8)	280 (58.0)	313 (64.7)	*P*=0.030
Negative	150 (29.6)	119 (24.6)	115 (23.7)	
Unknown	79 (15.6)	84 (17.4)	56 (11.6)	
Lymph-angioinvasion				
Positive	30 (5.9)	26 (5.4)	21 (4.3)	*P*=0.507
Negative	469 (92.7)	453 (93.8)	460 (95.1)	
Unknown	7 (1.4)	4 (0.8)	3 (0.6)	
Margin invasive carcinoma				
Positive	46 (9.1)	52 (10.8)	30 (6.2)	*P*=0.014
Negative	457 (90.3)	430 (89.0)	453 (93.6)	
Unknown	3 (0.6)	1 (0.2)	1 (0.2)	

Characteristics	< 37 days *n*=506 (%)	37–53 days *n*=483 (%)	54–112 days *n*=484 (%)	P value
Margin carcinoma in situ				
Positive	29 (5.7)	33 (6.8)	30 (6.2)	*P*=0.791
Negative	467 (92.3)	445 (92.1)	451 (93.2)	
Unknown	10 (2.0)	5 (1.1)	3 (0.6)	
Re-excision				
Yes	18 (3.6)	35 (7.2)	48 (9.9)	*P*<0.001
None	475 (93.8)	439 (90.9)	429 (88.6)	
Unknown	13 (2.6)	9 (1.9)	7 (1.5)	
Tumor size				
pT1	409 (80.8)	409 (84.7)	429 (88.6)	*P*=0.002
pT2	97 (19.2)	73 (15.1)	54 (11.2)	
Rest	0	1 (0.2)	1 (0.2)	

DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ

Table 2: Relation between time-period and timing of radiotherapy after lumpectomy for 1473 breast-conserving treatments in 1446 breast cancer patients.

Timing lumpectomy-radiotherapy	Time-period		
	1983–1993 (*n*=504)	**1994–1998** *(n=520)*	**1999–2003** (*n*=449)
<37 days	327 (64.9%)	147 (28.3%)	32 (7.1%)
37-53 days	124 (24.6%)	214 (41.1%)	145 (32.3%)
54-112 days	53 (10.5%)	159 (30.6%)	272 (60.6%)

Distant metastasis

The 10-year DMFS was 78.9% for the first tertile, versus 86.1% (HR 0.6; 95% CI 0.4–0.9; *P*=0.009) for the second, versus 90.7% (HR 0.3; 95% CI 0.2–0.5; *P*<0.001) for the third tertile (Figure 1).

A test for trend across the three groups was highly significant (*P*<0.001).

In multivariate Cox regression analysis including the significant variables of the univariate analysis (young age, family history, presence of in situ carcinoma, histology, tumor size, estrogen and progesterone receptor status, lymph-angioinvasion, and lumpectomy-axillary delay), the second tertile showed a borderline significant (HR 0.7; 95% CI 0.5–1.0; *P*=0.076) and the third tertile a highly significant (HR 0.4; 95% CI 0.2–0.6; *P*=0.001) increased DMFS. Young age (HR 1.8; *P*=0.008), tumor size (pT2) (HR 1.7; *P*=0.05), a positive family history (HR 0.6; *P*=0.033) and positive lymph-angioinvasion (HR 2.3; *P*=0.001) were independent risk factors.

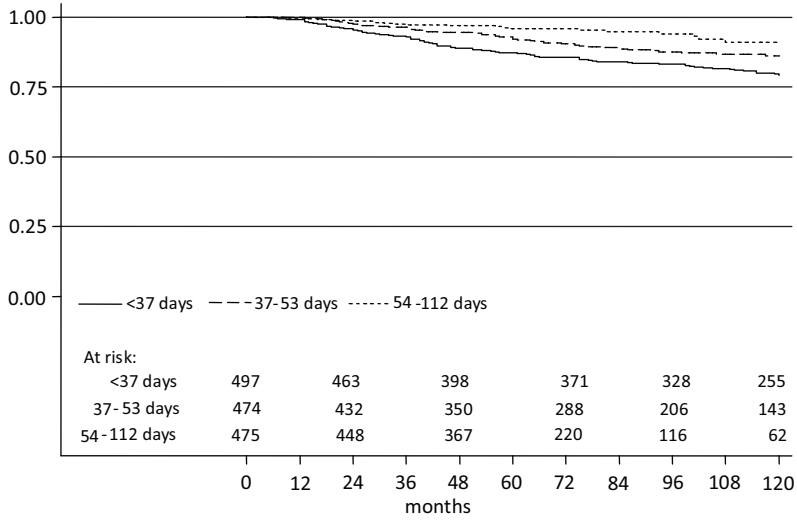

Figure 1: Distant metastasis-free survival for 1446 node-negative patients according to timing of radiotherapy in breast-conserving treatment without adjuvant systemic therapy.

Separated sub-analyses were executed for patients >40 years, tumor size ≤2 cm, and ER-positive. All analyses showed a highly significant trend across the three groups. Also the multivariate analyses showed significance for timing similar to the overall analyses.

Because of possible substantial changes over time in characteristics and adjuvant treatment, analyses were done over certain periods: 1983-1993, 1994-1998, and 1999-2003. Due to small numbers and few events HR's are not always significant (Table 3).

Table 3: Hazard Ratios and 95% Conf. Intervals for the different time period according to timing of radiotherapy for 10-year distant metastases-free survival in 1446 breast cancer patients.

Timing	**Period**		
	1983-1993 (*n*=499**)**	**1994-1998** (*n*=505)	**1999-2003** (*n*=442)
< 37 days	1 (324)	1 (143)	1 (30)
37-53 days	0.28	1.23	0.28
	(0.13–0.58)	(0.73–2.08)	(0.03–3.19)
	(123)	(208)	(143)
54-112 days	(52)	0.51 (0.25–1.03)	0.59 (0.07–4.81)
		(154)	(269)

Disease specific-survival

The 10-year DSS was 83.8% for the first tertile, versus 90.6% (HR 0.55; 95% CI 0.4–0.8; *P*=0.007) for the second, versus 97.2% (HR 0.2; 95% CI 0.13–0.4; *P*<0.001) for the third tertile (Figure 2).

A test for trend across the three groups was highly significant (*P*<0.001).

In multivariate Cox regression analysis including the significant variables of the univariate analysis (young age, presence of in situ carcinoma, histology, tumor size, estrogen and progesterone receptor status, lymph-angioinvasion, family history, and lumpectomy-axillary dissection delay), the second tertile (HR 0.6; 95% CI 0.4–1.0; *P*=0.053) and third tertile (HR 0.3; 95% CI 0.14–0.6; *P*=0.002) were significantly related to an increased DSS. Young age (HR 1.7; *P*=0.030), negative estrogen receptor status (HR 2.5; *P*=0.001), and positive lymph-angioinvasion (HR 3.2; *P*<0.001) were independent risk factors for a decreased DSS.

Separated sub-analyses were executed for patients >40 years, tumor size ≤1 cm, and ER-positive. All analyses showed a highly significant trend across the three groups. Also the multivariate analyses showed significance for timing similar to the overall analyses.

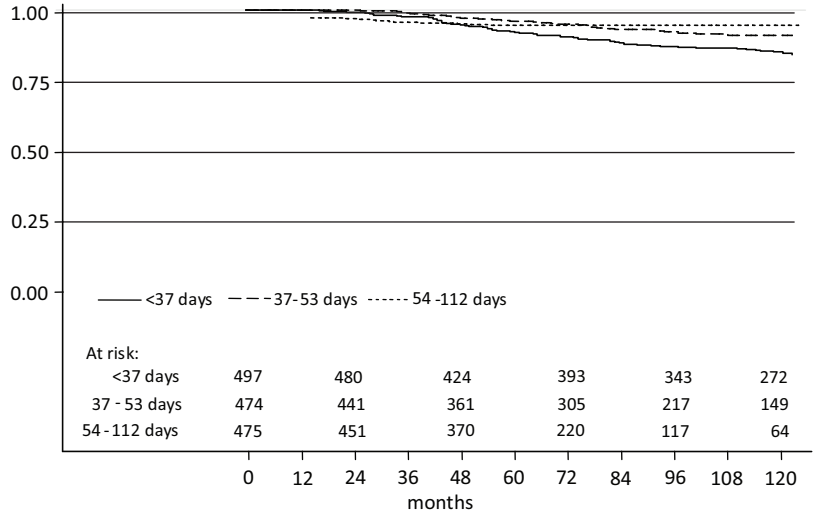

Figure 2: Disease-specific survival for 1446 node-negative patients according to timing of radiotherapy in breast-conserving treatment without adjuvant systemic therapy.

DISCUSSION

The study shows that, completely contrary to the current hypothesis, a longer delay between lumpectomy and radiotherapy had a strong positive and independent effect on the DMFS and DSS. A longer delay, showed a positive effect on DMFS and DSS. We investigated the influence of the different timing in radiotherapy up to and including 16 weeks after lumpectomy. This analysis of a large prospective population based cohort study of all breast cancer patients in Twente who received BCT only, suggest that with a proper timing of radiotherapy in BCT for breast cancer at least a 40% relative survival benefit might be reached. Of course this study has to be confirmed by others, but the trend in survival benefit is very strong and highly significant. Local control was not influenced with the different timings of radiotherapy.

The analyses were done on node-negative breast cancer patients without any adjuvant systemic therapy, chemo- and or hormonal therapy, to exclude any interaction with adjuvant therapy. With regard to any adjuvant systemic therapy, patients were treated according to the treatment policy in The Netherlands at the time of the primary therapy, which meant that patients with this profile did not get any adjuvant systemic therapy.

To our knowledge this is the first study, which extensively looked at the effect of timing of radiotherapy, in relation not only to local control but also to distant metastasis and survival. The advantage of our cohort is that we treat all patients with breast cancer from our region, the selection for only BCT, node-negative, and no adjuvant systemic therapy together with a standardized treatment of radiotherapy during the years creates a very homogeneous cohort of patients. On the other hand comparing the three groups, as can be seen in Table 1, there are significant differences between the three groups for age category, histology, estrogen and progesterone receptor status, tumor size, and re-excision. Despite these factors, timing of radiotherapy was still independently significant in multivariate analyses. Young age, tumor size >2 cm and negative estrogen receptor status are regarded as important prognostic factors in node negative breast cancer. Comparing the three groups showed an imbalance for those variables at the expense of the group with the shortest timing. Separate sub-analyses for women >40, pT1, and positive ER showed the same results with regard to DMFS and DSS in univariate and multivariate analyses. Also we have no reason to believe that these potential confounding factors were a reason for the observed differences in the timing of radiotherapy, thus leading to confounding by indication.

The effect of treatment delay on outcomes cannot easily be investigated in randomized trials, because of ethical reasons. Therefore observational studies based on high quality routinely recorded data are important.

The efficacy of post-operative radiotherapy in preventing or delaying local recurrence in patients who undergo BCT is well established by randomized controlled trials.[1-3] Guidelines

concerning the timing of radiotherapy in BCT are mainly based on expert advice rather than research evidence, and are mainly focused on local control.

Research in starting radiotherapy between 1-16 weeks after lumpectomy has been limited. Only few studies have examined the effect of the surgery-radiotherapy interval, on the short term, in node-negative patients and in the absence of systemic therapy.[6,13-15] Most studies have investigated the timing of radiotherapy in relation to the sequence of radiotherapy and chemotherapy in the treatment of breast cancer. The primary research question was in all of those studies the effect on local recurrence. There is only scant published data in relation to distant metastasis and survival.[5,6]

Four small retrospective studies of node-negative patients and no adjuvant systemic therapy were unable to detect a statistically significant increase in local recurrence if radiotherapy was delayed up to 16 weeks.[6,13-15] One of these, Bahena et al., showed also that a delay over 8 weeks significantly decreased disease-free survival.[6]

In a large retrospective population-based study of 7800 patients Mikeljevic et al. showed that survival was adversely related to longer delays.[5] Patients with a delay of 1-6 weeks had a 5-year survival of 80.1% compared to 84.4% with a delay of 7-12 weeks. However, this study included node-negative and node-positive patients as well as those with adjuvant systemic therapy, which makes it hard to compare with our study. Froud et al., in a retrospective study of node-negative and node-positive patients as well as adjuvant systemic therapy, observed a higher rate of systemic recurrences on univariate analysis with increasing time interval.[8]

We can only speculate on the reasons why a longer delay in radiotherapy seems to be beneficial in our study. The results from this study suggest a negative effect of radiotherapy on the metastatic tumor cells directly after surgery, which changes in the course of the first 16 weeks. In 1979 Gunduz et al. published their study in which they demonstrated that following excision of a C3H primary tumor, changes were observed within 24 h in metastases.[16] There was a transient increase in tumor size. Another study showed that following administration of a dose of radiation to the primary tumor, the growth of the primary was retarded, but an augmentation in the growth in a metastatic focus was observed.[17] The same study also looked at the effect of preoperative irradiation followed by excision of the primary on the metastases. They observed that when the time between irradiation and excision was too long the small transient effect of the radiation had already been experienced and the operation had little additional effect on the kinetics of the metastatic focus. No experiments were done with post-operative radiation. Our hypothesis is now that the contrary might happen too, when the time between surgery and radiation is too long the transient effect of the operation has already been experienced and the radiation has little additional effect on the kinetics of the metastatic focus. Fisher et al. indicated that the removal of a primary tumor is not only a local phenomenon but has other

biological consequences such as metastatic behavior due to interplay of growth factor(s), which can influence the outcome of a host to its tumour.[18] This might explain the results we observed.

Fidler and others showed that tumor cells are able to have minor or major differences in relation to their morphology and function.[19,20] This heterogeneity might be caused by therapy-induced changes on the intrinsic sensitivity and resistance of the tumor cell. This might explain the significant differences we see in local control and distant metastasis in relation to timing of radiotherapy.

CONCLUSION

In this prospective cohort study we tested the hypothesis that irradiation in BCT for breast cancer patients should start as soon as possible. We showed that starting too early might have a detrimental effect on survival and that starting radiotherapy 36 days after the lumpectomy might lead to a 40-70% relative survival benefit. If the results of this study are confirmed by others, it might have major implications on the treatment procedures in breast cancer, and possibly for other tumors too.

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Chapter 7

The value of a positive margin for invasive carcinoma in breast-conservative treatment in relation to local recurrence is limited to young women only

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ABSTRACT

Purpose: To identify the importance of positive margins for invasive carcinoma on local control in patients treated with breast-conservative treatment (BCT).

Methods and Materials: A total of 1752 BCT with known margins were analyzed. Fifty-five patients had a second BCT, leaving 1697 patients for analysis. The margins were positive in 193/1752 BCT (11%). The median follow-up was 78 months.

Results: The 5- and 10-year local recurrence rates (LRR) were 3.1% and 6.9%, respectively, for negative margins vs. 5.6% and 12.2% for positive margins. A statistical interaction between age category and margin status was noted in relation to disease-free survival (DFS) and local relapse-free survival. The 5-year LRR for women ≤40 years was 8.4% for negative margins and 36.9% for positive margins (P=0.005). In a multivariate analysis, a positive margin was significant. The 5-year LRR for women >40 years was 2.6% for negative and 2.2% for positive margins. The 5-year DFS for women ≤40 years was 27.4% for positive and 74.5% for negative margins (P=0.001). The 5-year DFS for women >40 years was 84.3% for positive and 87.2% for negative margins.

Conclusion: Women ≤40 years are a special category of patients in breast cancer. Women ≤40 years must have negative margins for invasive carcinoma when treated with BCT. Minimum surgery for an optimal cosmetic result followed by irradiation, even with microscopic positive margins for invasive carcinoma, yields excellent results with regard to local control in patients older than 40 years.

INTRODUCTION

Many studies have attempted to identify the risk factors for local recurrence in breast-conservative treatment (BCT). A positive margin of the lumpectomy specimen in BCT is generally regarded as a major prognostic factor for local recurrence.[1-7] This leads to a reexcision of the lumpectomy cavity or even sometimes to a mastectomy, resulting in a worse cosmetic result.

Only a few studies have demonstrated that margin status does not influence local control; the numbers have been small, and no subgroup analysis has been done.[8-11]

Positive margins in the literature are not always well defined, and are often regarded as the presence of either invasive carcinoma and/or intraductal carcinoma in situ (CIS) in the margin. No clear difference has been made in the literature with regard to the value of positive margins with either invasive carcinoma or CIS or both in patients with breast cancer. The impact of the presence of invasive carcinoma or CIS in the margin might be quite different.

The recent Phase III studies of CIS as the EORTC Study 10853 showed the value of a positive margin for CIS on local control.[12] Margin status was shown to be the most important factor with regard to local control. This makes it important, in our opinion, to look also at the value of invasive carcinoma with regard to margin and local control.

Data on the use of lumpectomy and radiotherapy in patients with positive margins are limited, and the number of patients with positive margins is often limited.

Because of these unclear and sometimes conflicting data, we investigated the prognostic value of a positive margin for invasive carcinoma on local recurrence and survival in our prospective cohort of breast cancer patients with T1 and T2 tumors, all treated with BCT, and irradiated at the radiotherapy department of the Medisch Spectrum Twente. In particular, we tried to identify the importance of positive margins in subgroups of patients, because this might obviate the need for further mutilation of the breast for a number of patients.

METHODS AND MATERIALS

From the start of this study in 1983, all patients treated with BCT in the Twente-Achterhoek region received radiotherapy, as part of primary treatment, at the radiotherapy department of the Medisch Spectrum Twente. Between 1983 and including 1999, a total of 1760 BCT were registered. All pathology of the lumpectomy specimens was done in the pathology laboratory, Oost Nederland. Because of this, no central pathology review was deemed necessary.

Involvement of the lumpectomy specimen margins was defined as the presence of microscopic involvement of invasive carcinoma in the inked margin. Because the gross surgical margin of the initial lumpectomy is often given only as an estimate, we have chosen not to include this item as a

continuous variable. Massive involvement with invasive tumor of the margins, defined as diffuse or multiple microscopic foci of invasive cancer, was regarded as an indication for a reexcision. When no massive involvement of the margin was present, the surgeon was advised not to do a reexcision. The decision to reexcise was left to the surgeon's discretion. The margin status of the reexcision was not registered. Negative margins were defined as having no microscopic involvement of invasive carcinoma in the inked margin. CIS was recorded when present in the lumpectomy specimen. The presence of ductal carcinoma in situ in the inked margin was not registered. Only invasive tumor in the resection margins was coded as positive margins.

To obtain the most reliable family history, the breast cancer history of only first-degree relatives was recorded, as 0, 1, or more (≥1).

Although the grade of differentiation was recorded when known, it was not routinely reported along with the histology, and there were too few patients with known grade for this particular factor to be analyzed.

BCT consisted of lumpectomy with axillary clearance of Levels I-III, followed by radiotherapy to the whole breast with a boost to the primary tumor area. The radiotherapy consisted of 50 Gy to the whole breast delivered in 2-Gy fractions 5 times a week by tangential technique. This was followed by a boost of 14 Gy to the primary tumor bed in 2-Gy fractions 5 times a week, as external photon or electron beam therapy. The photon boost technique was by multiple fields. The electron boost was delivered as a direct field. In the early years, a boost of 15 Gy, in 2.5-Gy fractions, 4 times a week was delivered to 183 patients (10.4%). Thirty-seven patients were treated by iridium implantation preoperatively with a dose of 15 Gy at a low dosage rate. The same boost dose was given in all patients, regardless of margin status.

Adjuvant therapy consisted of radiotherapy to the regional lymph nodes or to the internal mammary chain only, and hormonal and/or chemotherapy. The radiotherapy dose was 50 Gy in 2-Gy fractions 5 times a week. Regional radiotherapy, which included the axilla and supraclavicular and internal mammary chains, was indicated for patients with 4 or more positive lymph nodes and/or extranodal disease. Radiotherapy of the internal mammary chain only was indicated for those with fewer than four positive lymph nodes and no extranodal disease. In the case of medial implantation of the breast, the use of a separate anterior field for irradiation of the internal mammary chain was omitted to permit optimal irradiation of the breast.

Until about 1992, premenopausal women received chemotherapy when four or more lymph nodes were positive. Since 1992, all premenopausal patients with positive lymph nodes have received chemotherapy. In general, the adjuvant chemotherapy was delivered after primary treatment, surgery plus radiotherapy of the breast. For postmenopausal patients, adjuvant hormonal therapy was given when positive lymph nodes were present, and in the majority of patients, it was started directly after the surgery. Since 1999, whether or not adjuvant systemic

therapy is given has depended not only on lymph node status but also, in the case of negative lymph node status, on whether the mitotic activity index is >10.[12]

All patients were seen every 3 months for the first 2-3 years and twice a year thereafter. During follow-up, family history, local recurrence, regional recurrence, distant metastasis, and survival were noted. For the purposes of this study, the cutoff for analysis was March 2003.

Because it is often difficult to differentiate between a local recurrence and a new primary in the treated breast, all tumors found in the same breast during follow-up were classified as local recurrences. Recurrences in the axilla or in the internal mammary chain, or in both, were classified as regional recurrences. Patients were classified according to the TNM classification, 4th edition 1997.

Statistical methods

Time to recurrence and length of follow-up were calculated from the start of the treatment. To test between-group differences for categorical data, Chi-square tests were used. Statistics for local recurrences were calculated based on the number of BCT. The local relapse-free survival (LRFS) is defined as survival without local recurrence.

Survival statistics were calculated according to the number of patients by the Kaplan-Meier method. The disease-specific survival (DSS), corrected for intercurrent death, was calculated. This means that data on patients who died of other causes were regarded as censored data. The disease-free survival (DFS) is defined as survival without any recurrence. For comparison of survival distributions, the log-rank test was used. Multivariate survival analysis was done using Cox regression, including test for interaction. Hazard ratios (HR), relative hazard (RH), and 95% confidence intervals (95% CI) are presented. All analysis was performed using STATA.[13]

RESULTS

Of the 1760 BCT, the margins were unknown in 8, leaving 1752 BCT for analysis. Fifty-five patients had bilateral or contralateral breast cancer with a second BCT, leaving 1697 patients for analysis. The margins were positive in 193/1752 BCT (11%).

The length of follow-up ranged from 3 to 218 months, with a median of 78 and a mean of 85 months.

Table 1 shows a comparison in terms of clinical, histopathologic, and treatment characteristics between patients with positive and negative margins. The two groups were homogeneous in terms of age, localization of the primary, family history, CIS, estrogen and progesterone receptor, and adjuvant treatment. In patients with positive margins, more lobular carcinoma was observed

(*P*=0.002), the number of patients with >3 positive lymph nodes was higher (*P*<0.001), and the tumor size was larger (*P*<0.001).

Local recurrences

The incidence rate of local recurrence was 5% (87/ 1752). In two cases, no information with regard to local recurrence was available. In patients with positive margins, the incidence rate was 8.1% (17/193), compared to 4.5% (70/1,557) in those with negative margins (*P*=0.009). The time to local recurrence ranged from 9 to 177 months with a median of 49 months, with no significant difference between patients with positive or negative margins.

The 5-and 10-year local recurrence rates (LRR) were 3.1% and 6.9%, respectively, for negative margins vs. 5.6% and 12.2% for positive margins (respectively RH 1.7, *P*=0.082, and RH 1.7, *p*=0.0433). Figure 1 shows the LRR according to margin involvement.

In univariate analyses, we demonstrated a relationship between LRFS on the one hand and age (*P*<0.001), contralateral breast cancer (*p*=0.045), margin involvement (*P*=0.002), positive lymph nodes (*P*=0.015), negative estrogen receptor status (*p*=0.003), and adjuvant radiotherapy (*P*=0.018) on the other hand. In a multivariate Cox regression analysis with the above-mentioned variables, a positive margin (HR 2.4, 95% CI 1.4–4.1, *P*=0.002), age ≤40 years (HR 2.9, 95% CI 1.8–4.9, *P*<0.001), and contralateral breast cancer (HR 1.9, 95% CI 1.0-3.6, *P*=0.051) were significantly related to a worse LRFS. Age and margin status showed a borderline statistical interaction (*P*=0.068 HR 2.9). Therefore, we performed the analyses with regard to local recurrence for women ≤40 years and >40 years separately.

Table 1: Clinical, histopathologic, and treatment characteristics of 1752 BCT according to margin lumpectomy.

	Positive, *n*=193 (%)	**Negative,** *n*=1559 (%)	***P* value**
Age category			
≤40 years	20 (10.4)	123 (7.9)	
41–50	55 (28.5)	377 (24.2)	ns
>50	118 (61.1)	1059 (67.9)	
Localization			
LUQ	97 (50.3)	847 (54.3)	
LLQ	30 (15.5)	179 (11.5)	
MUQ	37 (19.2)	15 (20.2)	ns
MLQ	20 (10.4)	140 (9)	
Central	9 (4.7)	78 (5)	

	Positive, *n*=193 (%)	**Negative,** *n*=1559 (%)	***P* value**
Family history			
21 FDR	45 (23.3)	348 (22.3)	
None	145 (75.1)	1200 (77)	ns
Unknown	3 (1.6)	11 (0.7)	
Tumor size			
pT1	125 (64.8)	1248 (80.1)	
pT2	67 (34.7)	301 (19.3)	*p*<0.001
Rest	1 (0.5)	10 (0.6)	
Histology			
Ductal carc.	143 (74.1)	1207 (77.4)	
Lobular carc.	36 (18.7)	157 (10.1)	*p*=0.002
Tubular carc.	8 (4.2)	110 (7.1)	
Medullar carc.	1 (0.5)	42 (2.7)	
Rest	5 (2.6)	43 (2.7)	
No. pos. lymph nodes			
None	120 (62.5)	1128 (72.4)	
1–3	39 (20.2)	320 (20.5)	
>3	27 (14)	97 (6.2)	*p*<0.001
Unknown	6 (3.1)	14 (0.9)	
Carcinoma in situ			
None	122 (63.2)	1098 (70.4)	
DCIS	56 (29)	373 (23.9)	ns
LCIS	15 (7.8)	87 (5.6)	
Unknown		1 (0.1)	
Estrogen receptor			
Positive	136 (70.5)	1013 (65)	
Negative	29 (15)	261 (16.7)	ns
Unknown	28 (14.5)	285 (18.3)	
Progesterone receptor			
Positive	109 (56.5)	855 (54.8)	
Negative	53 (27.5)	402 (25.8)	ns
Unknown	31 (16)	302 (19.4)	
Adj. radiotherapy			
None	139 (72)	1183 (75.9)	ns
Treated	54 (28)	376 (24.1)	
Adj. systemic ther.			
None	124 (64.3)	1118 (71.7)	
Treated	69 (35.7)	441 (28.3)	*p*=0.031

Abbreviations: LUQ=lateral upper quadrant; LLQ=lateral lower quadrant; MUQ=medial upper quadrant; MLQ=edial lower quadrant; DCIS=ductal carcinoma in situ; LCIS=lobular carcinoma in situ; FDR=first-degree relative; BCT=breast-conservative treatment; carc.=carcinoma; adj.=adjuvant.

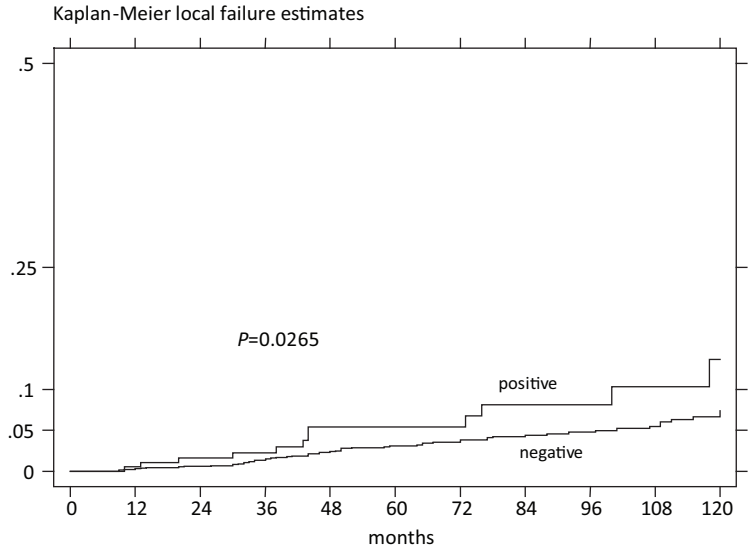

Figure 1: The local recurrence rate in 1752 BCT according to margin involvement of the lumpectomy specimen.

Local recurrence, ≤40 years

The incidence rate of local recurrence for women ≤40 years was 14.7% (21/143).

The 5-and 10-year LRR for women ≤40 years was 8.4% and 15.2%, respectively, for negative margins and 36.9% and 57.9%, respectively, for positive margins (RH 4.3, *P*=0.005, and RH 4.2, *P*=0.003) (Figure 2). Because of the relatively small number of women ≤40 years at 10 years, the LRR is not reliable (Table 2).

In separate univariate analyses, we analyzed LRFS for 143 women ≤40 years. Margin involvement (*P*=0.0007) and bilateral/contralateral breast cancer (*P*=0.0024) were significant predictors of a decreased LRFS. In a multivariate Cox regression analysis including the above variables, both showed significance.

Local recurrence, >40 years

The incidence rate of local recurrence for women >40 years was 4.1% (66/1607).

The 5-and 10-year LRR for women over 40 years was 2.6% and 6.2%, respectively, for negative margins and 2.2% and 6.6%, respectively, for positive margins (Figure 2). The differences were not statistically significant (Table 2).

In univariate analyses, we demonstrated a relationship between LRFS on the one hand and number of positive lymph nodes (p=0.004), estrogen receptor (p=0.0369), and adjuvant radiotherapy (p=0.0369) on the other hand. Margin involvement was not a significant predictor of a worse LRFS.

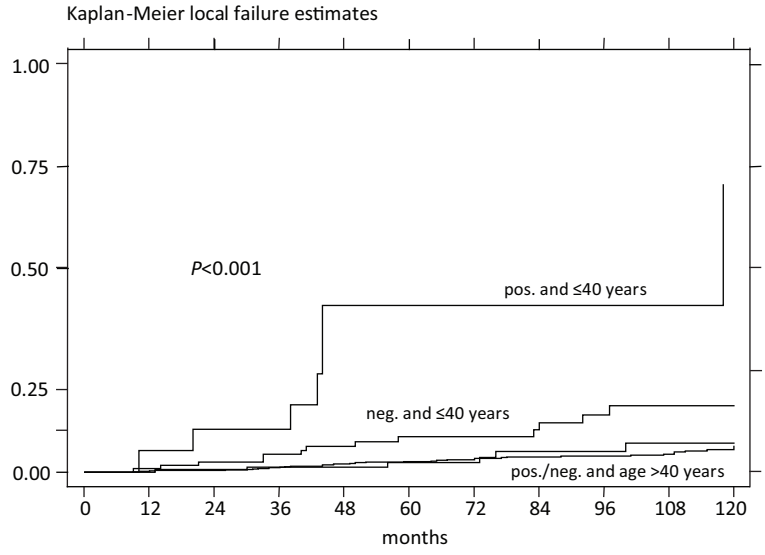

Figure 2: The local recurrence rate in 1752 BCT according to age and margin involvement of the lumpectomy specimen.

Disease-free survival

The 5-and 10-year DFS (survival without any recurrence) rates were 78.3% and 65.3%, respectively, for positive margins and 86.1% and 76.2% for negative margins (respectively RH 1.5, P=0.009, and RH 1.5, P=0.006). In a multivariate Cox regression analysis for DFS, taking into account the significant factors of the univariate analyses (age, positive lymph nodes, CIS, estrogen receptor, progesterone receptor, adjuvant systemic therapy, pathology, tumor size, and adjuvant radiotherapy), along with the other variables, such as age, positive lymph nodes, adjuvant systemic therapy, pathology, tumor size, and adjuvant radiotherapy, a positive margin did show a significantly increased risk (HR 1.5, 95% CI 1.1–2.0, P=0.02). However, there was a statistical interaction between age and margin status (P=0.017, RH 2.4). Therefore, we performed the analyses with regard to DFS for women ≤40 years and >40 years separately.

Table 2: Local recurrence rate in 1750 BCT according to age and margin status.

Age/margin status	Loc. rec. (%)	*n**	*P* value	Rel. hazard
≤40 years (*n*=143)				
5 years				
Negative	8.4	76		
Positive	36.9	8	*P*=0.0007	4.1
7 years (mean)				
Negative	11.5	58		
Positive	36.9	5	*P*=0.0016	3.7
10 years				
Negative	15.2	29		
Positive	57.9	2	*P*=0.0004	3.8
>40 years (*n*=1607)				
5 years				
Negative	2.6	937		
Positive	2.2	97	ns	
7 years (mean)				
Negative	3.7	660		
Positive	4.8	65	ns	
10 years				
Negative	6.2	307		
Positive	6.6	31	ns	

Note: *n* is the number of patients at risk by the end of 5-, 7-, and 10-year follow-up.

Disease-free survival, ≤40 years

In the separate analyses for women ≤40 years, the 5-and 10-year DFS rates were 27.4% and 10.3%, respectively, for positive margins and 74.5% and 62.4% for negative margins (respectively RH 3.2, *P*<0.001, and RH 3.2, *P*<0.001) (Figure 3). Because of the relatively small number of women ≤40 years with positive margin, 19/143, no women were left at 10 years DFS (Table 3).

In univariate analyses, we demonstrated a relationship between DFS on the one hand and tumor size (*P*=0.0362), bilateral/contralateral breast cancer (*P*=0.0027), and margin involvement (*P*<0.001) on the other hand. In a multivariate Cox regression analysis including the above variables, a positive margin (HR 3.6, 95% CI 1.9−6.7, *P*<0.001) and bilateral/contralateral breast cancer (HR 2.6, 95% CI 1.4−4.9, *P* = 0.003) were significant.

Disease-free survival, >40 years

The 5-and 10-year DFS were 84.3% and 73.2%, respectively, for positive margins and 87.2% and 77.5% for negative margins (Figure 3). The differences were not statistically significant (Table 3).

In univariate analyses, we demonstrated a relationship between DFS on the one hand and tumor size (P<0.001), positive lymph nodes (P<0.001), negative estrogen receptor status (P=0.0127), negative progesterone receptor status (P=0.0008), adjuvant radiotherapy (P<0.001), pathology (P=0.0005), CIS (P=0.04), and adjuvant systemic therapy (P<0.001) on the other hand. Margin involvement was not significant.

Table 3: DFS in 1752 BCT according to age and margin status.

Age/margin status	DFS (%)	*n**	*P* value	Rel. hazard
≤40 years (*n*=143)				
5 years				
Negative	74.5	72		
Positive	27.4	5	*P*<0.001	3.2
7 years (mean)				
Negative	67.5	51		
Positive	27.4	5	*P*<0.001	3.2
10 years				
Negative	62.4	27		
Positive	10.3	1	*P*<0.001	3.2
>40 years (*n*=1609)				
5 years				
Negative	87.2	897		
Positive	84.3	94	ns	
7 years (mean)				
Negative	83.1	632		
Positive	78.7	60	ns	
10 years				
Negative	77.5	287		
Positive	73.2	27	ns	

Abbreviations: DFS = disease-free survival; BCT = breast-conservative treatment. * *n* is the number of patients at risk by the end of 5-, 7-, and 10year follow-up.

Distant metastasis

The incidence rate of distant metastasis was 16.3% (276/ 1697 patients) and, according to margin involvement, 20% (38/190) for positive margins and 15.8% (238/1506) for negative margins. In one case, no information was available with regard to metastasis. The 5-and 10-year distant metastasis rates (DMRs) were 12.4% and 19.8%, respectively, for negative margins vs. 19% and 26.6% for positive margins (respectively RH 1.4, P=0.03, and RH 1.4, P=0.04). According to the

age category, the 5-year DMR for women ≤40 years was 77.4% for negative margins vs. 91.7% for positive margins (RH 3.1, *P*<0.001). Because of the small number of women ≤40 years, no 10-year DMR is given. For women >40 years, the 5-and 10-year DMR was 11.6% and 19.1%, respectively, for negative margins and 14% and 21.4% for positive margins. The differences were not statistically significant.

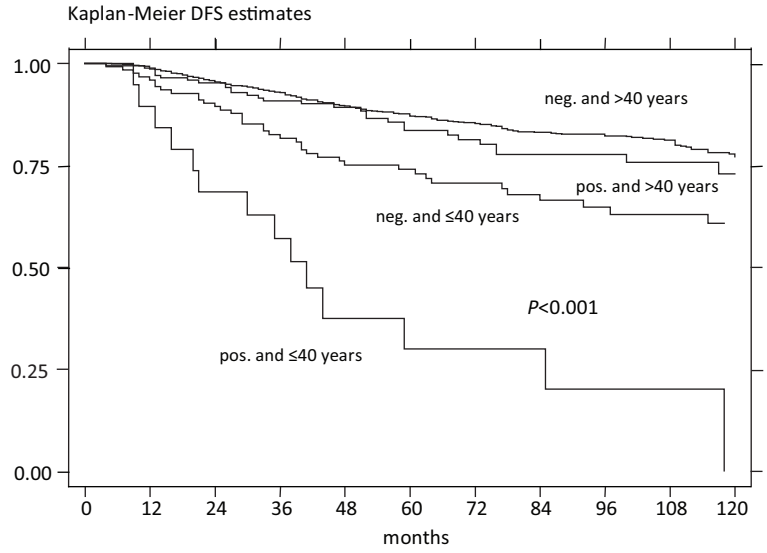

Figure 3: Disease-free survival (DFS) analyses in 1752 BCT according to age and margin involvement of the lumpectomy specimen.

Survival

The 5-and 10-year DSS rates for the 1699 patients were 87.8% and 78.2%, respectively, for patients with positive margins and 92% and 81.4% for negative margins. The differences were not statistically significant.

In the univariate analyses, age, positive lymph nodes, CIS, estrogen receptor, progesterone receptor, adjuvant systemic therapy, pathology, tumor size, bilateral/contralateral breast cancer, and adjuvant radiotherapy were significant. Margin involvement was not a significant predictor.

Subset analyses according to age showed a significantly worse 5-and 10-year DSS of 65.9% and 43.9% for women ≤40 years with positive margins compared to negative margins 83.3% and 68.1% (respectively RH 2.1, *P*=0.022, and RH 2.3, *P*=0.012). For older women, the 5-and 10-year DSS were similar with 90% and 81.4% for positive margins vs. 92.6% and 82.7% for negative margins (Figure 4).

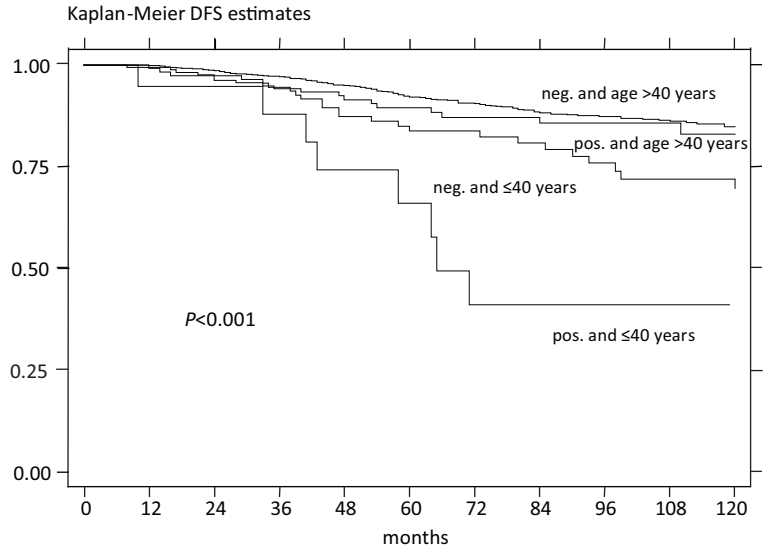

Figure 4: Disease-specific survival (DSS) analyses of 1697 breast cancer patients according to age and margin involvement of the lumpectomy specimen.

DISCUSSION

In general, we can endorse the view that positive margins impair long-term local control. Subgroup analyses, however, revealed that this was restricted to young women only, with a local recurrence rate of 36.9% at 5 years for women ≤40 years and positive margins as compared to 2.6% for older women.

Unfortunately, long-term data are limited on the use of BCT with positive margins for invasive carcinoma. Reports of local recurrence rates after BCT included few patients with positive margins. Microscopic margin involvement in many cases leads to a reexcision of the primary area or even an ablation mamma, resulting in a less optimal cosmetic result. After good local control and survival as a primary goal in BCT, attaining a good cosmetic result is the second most important aim.

Although the subject of microscopic margin assessment is partly a pathologic item with a lot of discussion about the way to assess a positive margin, we will leave this discussion undone.[3]

We tried to establish the clinical relevance of a positive margin for invasive carcinoma irrespective of the CIS status, as reported by the pathologist, on local control, and directly on the primary treatment whether a reexcision might be necessary. The value of this study is that all patients were treated in a single institution, all pathology was performed in a single institution,

and the treatment was relatively standardized during the years of this prospective study. Also, we present in comparison to published literature a rather large group of patients with positive margins.

We defined involvement of the margin of the lumpectomy specimen as having microscopic involvement of invasive carcinoma in the inked margin. It should be noted that almost all of the clinical studies in which margin status has been related to local recurrence risk are based on evaluation of inked margins. In our study, no distinction was made between extensive or focal involvement. Also, we should keep in mind that massive involvement of the inked margins with invasive carcinoma was regarded as an indication for a reexcision.

Most studies have shown that positive microscopic margins have a significantly higher rate of local recurrence.[2,14–16] In contrast, Solin et al.[8] and de Jong et al.[17] showed a negative result. Recent studies also indicate that the extent of margin involvement, extensive vs. focal, seems to be important.[14,18]

Along with others, we did find a detrimental influence of a positive margin on local control. However, a strong statistical interaction between age category and margin status was noted in relation to DFS and a borderline interaction to LRFS. This means that the population of women should be analyzed separately for those ≤40 years and those >40 years. This revealed that the prognostic value of a positive margin for invasive carcinoma was restricted to women ≤40 years only. Solin et al. could not identify any subgroup; however, their group of patients was rather small.[8]

Cowen et al. tried to identify the relationship between margin involvement and local and distant failures in a fairly homogenous group of patients.[19] Unfortunately, the authors failed to define a "pathologic involved margin" with regard to invasive and/or intraductal carcinoma. The problem again remains that we still do not know from this study what the main contributing factor is. Schnitt et al. also tried to identify a subgroup of patients with positive margins for BCT, but the group of patients was too small.[20]

Looking at our results and those presented in the literature, we realize that the value of a reexcision in the case of positive margin with invasive carcinoma, regardless of the presence of CIS, should be looked at differently for different age categories. For the majority of women >40 years, no influence on local recurrence was noted for a positive margin for invasive carcinoma. On the other hand, it seems extremely important for women ≤40 years to have negative margins for invasive carcinoma, which might partly explain the high local recurrence rate in our cohort of young women. On the other hand, age ≤40 years is also an important prognostic factor for local control, as we already have shown in an earlier study.[21]

Looking at the results of the recent ductal carcinoma in situ studies with respect to the value of a positive margin on local control, the presence of CIS in the margin might be a main contributing factor for local recurrence for the whole population.[12]

We found an excellent LRR for women over 40 years, even with positive margins, compared to the EORTC trial boost vs. no boost.[22] We can confirm the conclusion of Solin et al.[8] that adequate local control in patients with positive microscopic pathology margins is true for most patients. For only a subgroup of patients, this leads to a poorer LRFS and DFS.

Whether age or margin involvement is the predominant factor remains the question. Age is not only a major prognostic factor in breast cancer as we have shown in an earlier study, but also an important factor when looking at the value of a positive margin for invasive carcinoma.[21] As Nixon et al. suggested, tumors in young women might be biologically distinct with an independently worse prognosis.[23] Also the latest EORTC trial "boost vs. no boost" underlined the importance of age as a risk factor.[22] Until this is resolved, reexcision has to be advised in young women with positive margins for invasive carcinoma. This might lead to not only an improved LRFS but also a better DFS and DSS in this age category of women.

CONCLUSION

Women ≤40 years are a special category of breast cancer patients. Our results show that a positive margin for invasive carcinoma is of prognostic value in relation to LRFS, DFS, and DSS only for women ≤40 years. Women ≤40 years must have negative margins for invasive carcinoma when treated with breast-conservative treatment.

Our treatment results also indicate that minimum surgery for an optimal cosmetic result followed by irradiation, even with microscopic positive margins for invasive carcinoma, yields excellent results with regard to local control in patients older than 40 years.

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Chapter 8

Differences in outcome for positive margins in a large cohort of breast cancer patients treated with breast-conserving therapy

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ABSTRACT

A study of the possible difference in outcome for positive margins for invasive carcinoma (IC) versus ductal carcinoma in situ (DCIS), and with regard to different age categories in a large prospective cohort of patients with invasive breast cancer. A total of 2 291 BCT were analyzed. Margins were positive for IC in 8.7% and for DCIS in 4.6%. The median follow-up was 83 months. The 10-year local recurrence-free survival for negative margins vs. positive margins for IC vs. positive for DCIS for women ≤40 years were 84.4% vs. 34.6% (HR 4.5) vs. 67.5%, and for women >40 years 94.7% vs. 92.6% vs. 82.6% (HR4.2). The 10-year distant disease-free survival for negative margins vs. positive margins for IC vs. positive for DCIS women ≤40 years were 72.0% vs. 39.7% (HR 3.4) vs. 77.8%. The disease-specific survival showed a significant relation to positive margins for IC in young women. The effect of positive margin for IC seems to be limited to young women only, and is not only restricted to local control, but also to distant metastasis and survival. On the other hand a positive margin for DCIS is a risk factor for local control in women >40 years.

INTRODUCTION

Positive resection margins in breast-conserving treatment (BCT) for breast cancer patients are often an indication for a re-excision or even an ablation. In recent phase III studies and newly designed studies negative margins are a prerequisite for inclusion. The general opinion is that a positive margin is associated with a worse prognosis with regard to local control.[1-8]

No phase III studies have been or will be designed to look at the problem of a positive margin. Sub analyses from phase III studies and retrospective studies have addressed the issue of positive margins. Margins of patients with invasive breast cancer can be positive for invasive carcinoma (IC) as well as for ductal carcinoma in situ (DCIS) or both. The outcome is diverse and in many studies no difference is being made whether the margin is positive for IC or DCIS. Neither is a distinction made in terms of patient's categories.

The aim of this study is to look in a large prospective cohort of patients with invasive breast cancer at the possible difference in outcome for positive margins for IC and DCIS, and with regard to age category.

PATIENTS AND METHODS

This prospective cohort of patients was started in 1983 when BCT was introduced in our region. All patients in the Twente-Achterhoek region with invasive breast cancer and treated with BCT received their radiotherapy at the Radiotherapy Department of the Medisch Spectrum Twente at Enschede. From 1983 through 2002, a total of 2 335 BCT were registered in 2 267 patients with invasive breast cancer. Pathological examination for all BCT was done in the Pathology Laboratory Oost Nederland. All patient data, including demographics, histology, staging information, treatment, and outcome were recorded and are updated regularly. Patients were classified according to the TNM-classification, 4th edition 1997. For the purposes of this study, the cut-off for analysis was December 2005.

Family history (FH) was recorded according to first-degree relative (FDR).

We defined synchronous bilateral breast cancer (BBC) as cancer diagnosed in both breasts simultaneously or within a period of three months of diagnosis of the first tumour. Metachronous contra lateral breast cancer (CBC) was defined as breast cancer occurring in the contra lateral breast more than three months after the diagnosis of the tumour in the first breast affected.

Although the grade of differentiation was recorded when known, it was not routinely reported along with the histology during the early years; and there were too few patients with known grade (51.5%) for this particular factor to be analyzed.

Margin status

Involvement of the margins of the lumpectomy specimen was defined as the presence of microscopic involvement of IC or DCIS in the inked margin. Close margins were recorded as negative. Massive involvement with IC or DCIS of the margins, defined as diffuse or multiple microscopic foci, was regarded as an indication for a re-excision. In case of focal microscopic involvement of the margin was present the surgeon was advised not to do a re-excision. The policy in our department was that minimal microscopic disease could be treated with radiotherapy. A total of 152 re-excisions were performed. Negative margins were defined as having no microscopic involvement of IC or DCIS in the inked margin of the lumpectomy specimen or after re-excision. The presence of DCIS in the lumpectomy specimen, independently of involvement of the margin with DCIS, was recorded separately. The extensive intra ductal carcinoma component was not recorded separately. Of the 2 267 patients with 2 335 BCT the margins were unknown in 3 BCT and 41 BCT were positive for both IC and DCIS. To get a clear view on the impact of IC versus DCIS at the margin, and also because of the small number, BCT with margins positive for both were excluded, leaving 2 291 BCT in 2 223 patients with invasive breast cancer for analysis.

Treatment

BCT consisted of lumpectomy with axillary clearance of levels I-III, followed by radiotherapy to the whole breast with a boost to the primary tumour area. The radiotherapy consisted in 50 Gy to the whole breast, followed by a boost of 14 Gy to the primary tumour bed. The boost dose given was the same in all patients, regardless of margin status. The localisation of the boost was determined by the location of the scar, the primary tumour location, the mammography, and if possible by placed radiopaque clips.

Adjuvant therapy consisted of radiotherapy to the regional lymph nodes or to the internal mammary chain only, and hormonal and/or chemotherapy. Regional radiotherapy, which included the axilla and the supraclavicular, and internal mammary chains, was indicated for patients with four or more positive lymph nodes and/or extra nodal disease (EN). Radiotherapy of the internal mammary chain only was indicated for those with fewer than four positive lymph nodes and no EN. In the case of medial implantation of the breast, the use of a separate anterior field for irradiation of the internal mammary chain was omitted to permit optimal irradiation of the breast.

In the late eighties adjuvant systemic therapy was introduced for patients with positive nodes. From 1992 on, all premenopausal patients with positive lymph nodes have received chemotherapy. For postmenopausal patients adjuvant hormonal therapy was given when positive lymph nodes were present. Since 1999 indications for adjuvant systemic therapy have depended not only on the lymph node status, but also in the case of a negative lymph node status on the mitotic activity index, histological grade and tumour size. Premenopausal women

received chemotherapy and endocrine therapy when the oestrogen receptor status was positive. Postmenopausal women received primarily endocrine therapy and were offered chemotherapy when their age was <70 years. When the hormone receptor status was negative, patients were offered chemotherapy.

Statistical methods

Time to recurrence and length of follow-up were calculated from the start of BCT. To test between-group differences for categorical data $\chi 2$ tests were used, and these analyses with regard to local recurrences were performed in relation to the number of BCT. For all survival analyses, patients were censored if they had not experienced an event (local recurrence, distant metastasis) at the time of analysis or if they were lost to follow-up or were dead at the time of analysis. The local recurrence-free survival (LRFS) is defined as survival without local recurrence. An event was defined as the occurrence of a local recurrence in the treated breast.

Statistics for distant metastasis and survival were performed in relation to the number of patients and calculated by the method of Kaplan and Meier. The disease-specific survival (DSS), corrected for inter-current death, was also calculated in relation to the number of patients. This means that for this particular analysis, data on patients who died of other causes than breast cancer were regarded as censored data. An event was defined as death due to breast cancer. The distant disease-free survival (DDFS) is defined as survival without distant metastasis in patients. An event was defined as the occurrence of a distant metastasis in the patient.

For comparison of survival distributions the log-rank test was used. Variables that were univariately related to the outcomes of interest (p<0.10) were entered in the multivariate analyses.

The Cox proportional hazards model was used to test for the independent effect of margins status after adjusting for known prognostic factors and hazard ratios (HR) estimated with 95% confidence limits are presented. All analyses were performed using STATA.[9]

RESULTS

Of the 2 291 BCT in 2 223 breast cancer patients the margins were positive for IC in 8.6% (198/2291), and in 4.6% for DCIS (108/2291). The length of follow-up ranged from 3 to 265 months, with a median of 83 and a mean of 93 months.

Characteristics of the three groups, negative margins and positive margins for either IC or DCIS are presented in Table 1. Patients with a positive margin for DCIS showed more positive lymph nodes, more lateral localisation, and received more adjuvant therapy, while patients with a positive margin for IC more often have larger tumours, and lobular carcinoma. Lymph-angioinvasion was more associated with positive margins for IC and DCIS.

Table 1: Distribution of the different clinical, pathohistological, and treatment characteristics for the 2 291 breast-conserving treatments in 2 223 breast cancer patients, according to margin status for invasive carcinoma (IC) and ductal carcinoma in situ (DCIS).

Characteristics	**Negative Margin** *n*=1 985 (%)	**Positive Margin IC** *n*=198 (%)	**Positive Margin DCIS** *n*=108 (%)	***P* value**
Age				
≤40 years	141 (7.1)	14 (7.1)	10 (9.3)	ns
>40 years	1844 (92.9)	184 (992.9)	98 (90.7)	
Family history				
Positive	452 (22.8)	52 (26.3)	19 (17.6)	ns
Negative	1521 (76.6)	146 (73.7)	88 (81.5)	
Unknown	12 (0.6)		1 (0.9)	
Localisation primary				
Lateral	1270 (64)	127 (64.1)	86 (79.6)	
Medial	616 (31)	62 (31.3)	20 (18.5)	
Central	99 (5)	9 (4.6)	2 (1.9)	*P*=0.023
Histology				
Ductal carcinoma	1522 (76.7)	142 (71.7)	102 (94.4)	*P*<0.001
Lobular carcinoma	223 (11.2)	43 (21.7)	1 (0.9)	
Tubular carcinoma	150 (7.6)	7 (3.5)	2 (1.8)	
Medullar carcinoma	43 (2.7)	2 (1)	1 (0.9)	
Rest	47 (2.4)	4 (2.1)	2 (1.8)	
Lymph-angioinvasion				
Positive	150 (7.6)	29 (16.7)	18 (16.7)	*P*<0.001
Negative	1797 (90.5)	162 (81.8)	86 (79.6)	
Unknown	39 (1.9)	7 (3.5)	4 (3.7)	
Oestrogen receptor				
Positive	1393 (70.2)	149 (75.2)	69 (63.9)	ns
Negative	337 (17)	29 (14.7)	25 (23.2)	
Unknown	255 (12.8)	20 (10.1)	14 (12.9)	
Progesterone receptor				
Positive	1173 (59.1)	116 (58.6)	57 (52.8)	ns
Negative	545 (27.5)	61 (30.8)	37 (34.3)	
Unknown	267 (13.4)	21 (10.6)	14 (12.9)	
Presence of CIS				
DCIS	386 (19.4)	25 (12.6)	108	
LCIS	122 (6.2)	18 (9.1)		
None	1477 (74.4)	155 (78.3)		

Characteristics	Negative Margin *n*=1 985 (%)	Positive Margin IC *n*=198 (%)	Positive Margin DCIS *n*=108 (%)	*P* value
Re-excision				
Yes	137 (6.9)	6 (3.0)	6 (5.5)	
None	1 780 (89.7)	181 (91.4)	95 (88)	ns
Unknown	68 (3.4)	11 (5.6)	7 (6.5)	
Tumour size				
PT1	1555 (78.3)	129 (65.1)	89 (82.4)	
PT2	420 (21.2)	69 (34.9)	19 (17.6)	*P*<0.001
Rest	10 (0.5)	0	0	
Lymph nodes				
PN0	1432 (72.1)	126 (63.6)	60 (55.6)	
PN1	514 (25.9)	65 (32.8)	44 (40.7)	*P*=0.001
Rest	39 (2.0)	7 (3.6)	4 (3.7)	
Adjuvant Systemic Therapy				
Yes	657 (33.1)	83 (41.9)	58 (53.7)	
None	1328 (66.9)	115 (58.1)	50 (46.3)	*p*=0.001
Adjuvant Radiotherapy				
Yes	411 (20.7)	49 (24.7)	39 (36.1)	
None	1574 (79.3)	149 (75.3)	69 (63.9)	p<0.001

The analyses showed a significant statistical interaction between margin status for IC and age. Therefore we performed the analyses with regard to outcome for women ≤40 years (165 BCT) and >40 years (2 126 BCT) separately.

Local recurrence

≤40 years

Of the 165 BCT margins were positive for IC in 8.4% (14/165) and in 6% for DCIS (10/ 165). The length of follow-up ranged from 9 to 234 months, with a median of 87 and a mean of 98 months. The 10-year LRFS rates of negative margins vs. positive margins for IC vs. positive margin for DCIS were 84.4% vs. 34.6% (HR4.5; 95% CI 1.5−13.8; *P*=0.008) vs. 67.5% (HR 2.1; 95% CI 0.5−9.3; *P*=0.316) (Figure 1).

In multivariate Cox regression analysis including the only significant variable of the univariate analysis, histology and margin status, margin involvement for IC was highly significant (HR 4.6; 95% CI 1.4−15.1; *P*=0.012). Margin involvement for DCIS showed no significance (HR 2.0; 95% CI 0.58.9; *P*=0.348).

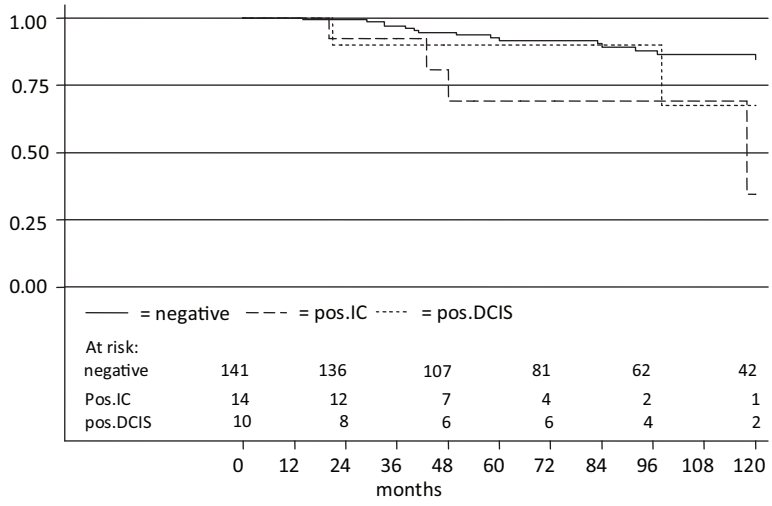

Figure 1: The local relapse-free survival in 165 breast-conserving treatments according to margin status for women ≤40 years.

>40 years

Of the 2 126 BCT margins were positive for IC in 8.6% (184/2126), and in 4.6% for DCIS (98/2126). The length of follow-up ranged from 3 to 265 months, with a median of 83 and a mean of 93 months. The 10-year LRFS rates of negative margins vs. positive margins for IC vs. positive margin for DCIS were 94.7% vs. 92.6% (HR1.6; 95% CI 0.8−3.2; *P*=0.192) vs. 82.6% (HR 4.2; 95% CI 2.2−7.9; *P*<0.001) (Figure 2).

In multivariate Cox regression analysis including the significant variables of the univariate analysis (lymph-angioinvasion, presence of in situ carcinoma, and margin status) margin involvement for DCIS was highly significant (HR 3.5; 95% CI 1.6−7.7; *P*=0.002), whereas margin involvement for IC was not (HR 1.4; 95% CI 0.7-2.8; *P*=0.393).

Distant metastasis

≤40 years

The 10-year DDFS rates for negative margins vs. positive margins for IC vs. positive margin for DCIS were 72% vs. 39.7% (HR 3.4; 95% CI 1.6−7.3; *P*=0.002) vs. 77.8% (HR 0.8; 95% CI 0.2−3.2; *P*=0.711).

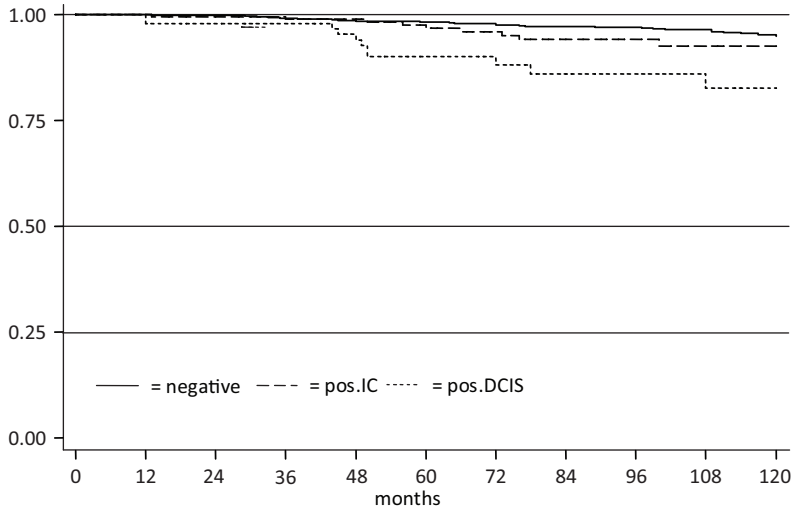

Figure 2: The local relapse-free survival in 2 126 breast-conserving treatments according to margin status for women >40 years.

In multivariate Cox regression analysis including the significant variables of the univariate analysis, lymph-angioinvasion, BBC, and margin status, margin involvement for IC was significant (HR 2.4; 95% CI 1.0–5.6; *P*=0.050). Margin involvement for DCIS showed no significance (HR 0.6; 95% CI 0.1–2.4; *P*=0.435).

>40 years

The 10-year DDFS rates for negative margins vs. positive margins for IC vs. positive margin for DCIS were 81.7% vs. 72.9% (HR 1.4; 95% CI 1.0–2.1; *P*=0.038) vs. 79.8% (HR 1.5; 95% CI 0.9–2.5; *P*=0.100).

In multivariate Cox regression analyses including the significant variables of the univariate analysis (BBC, tumour size, histology, positive lymph nodes, presence of in situ carcinoma, oestrogen receptor status, progesterone receptor status, lymph-angioinvasion, adjuvant systemic therapy and radiotherapy, and margin status) a positive margins for IC (HR 1.2; *P*=0.223) or DCIS (HR 1.2; *P*=0.602) did not show significance.

Disease-specific survival

≤40 years

The 10-year DSS rates for negative margins vs. positive margins for IC vs. positive margin for DCIS were 73.4% vs. 33.2% (HR 4.0; 95% CI 1.8-8.9; *P*=0.001) vs. 77.8% (HR 0.9; 95% CI 0.2-4.0; *P*=0.949) (Figure 3).

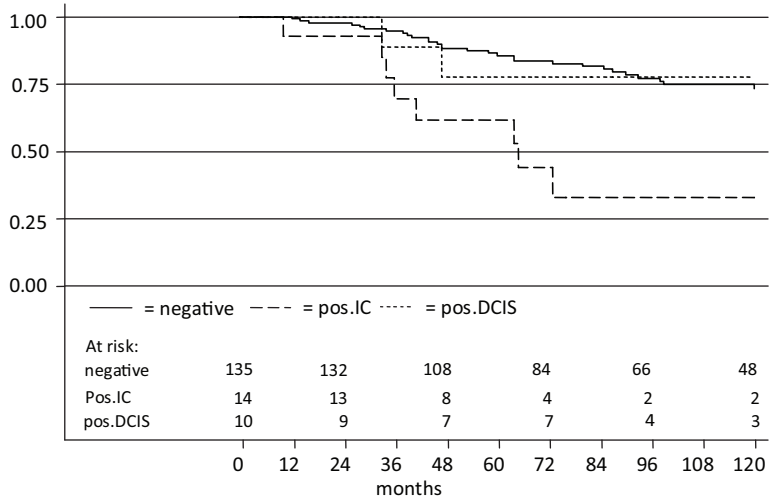

Figure 3: The disease specific survival in 159 patients with 165 BCT according to margin status for women ≤40 years.

In multivariate Cox regression analysis including lymph-angioinvasion, BBC, and margin status, the significant variables of the univariate analysis, margin involvement for IC was significant (HR 2.8; 95% CI 1.1−6.7; *p*=0.024). Margin involvement for DCIS showed no significance (HR 0.6; 95% CI 0.1−2.8; *p*=0.555).

>40 years

The 10-year DSS rates for negative margins vs. positive margins for IC vs. positive margin for DCIS were 87.0% vs. 84.1% (HR 1.2; 95% CI 0.9−1.9; *P*=0.374) vs. 76.7% (HR 1.9; 95% CI 1.1−3.2; *P*=0.018) (Figure 4).

In multivariate Cox regression analyses including the significant variables of the univariate analysis (FH, tumour size, histology, positive lymph nodes, presence of in situ carcinoma, oestrogen receptor status, progesterone receptor status, lymph-angioinvasion, adjuvant systemic

therapy and radiotherapy, and margins status) a positive margins for IC (HR 1.1; *P*=0.653) nor DCIS (HR 1.2; *P*=0.526) were significant.

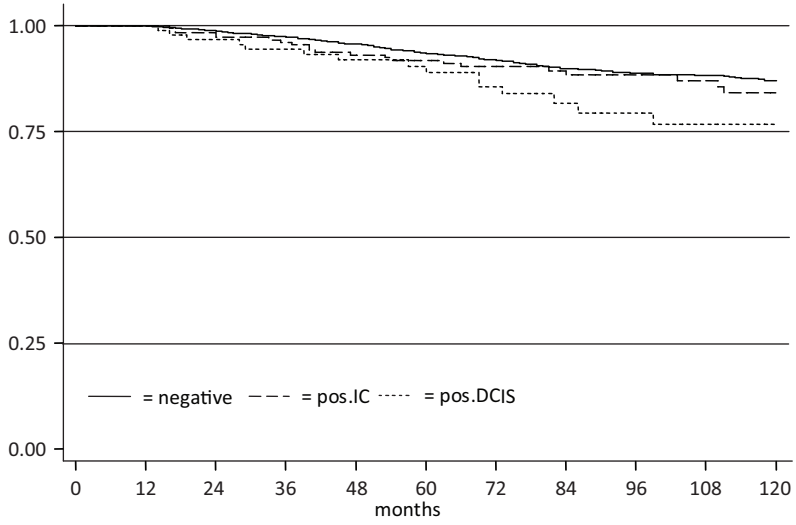

Figure 4: The disease specific survival in 2 064 patients according to margin status for women >40 years.

DISCUSSION

This study shows a diverse effect of a positive margin on outcome. The effect is not only dependent on whether the margin contains IC or DCIS, but also on the age of the patient. Young women, ≤40 years, a positive margin for IC results in a significantly higher local recurrence rate, distant metastasis rate, and lower survival. A positive margin for DCIS did not show these results, although this might be due to the small numbers. For women >40 years, a positive margin for DCIS is significantly related to a higher local recurrence rate and lower survival, although the latter is not significant in multivariate analyses. In contradistinction to young women a positive margin for IC in women >40 years does not result in a significant higher local recurrence rate or lower survival.

In this study we tried to establish the clinical relevance of a positive margin for DCIS in comparison to IC, as reported by the pathologist, on outcome. The value of this prospective study is that these are all patients from one region in The Netherlands. All patients were irradiated in

a single institution, all pathology was performed in a single institution, and the treatment was relatively standardized during the years of this prospective study. Also, we present a rather large group of patients with positive margins compared to the published literature. On the other hand, due to the relative small number of women ≤40 years with positive margins the results have to be interpreted with caution.

In the eighties and early nineties grading of the pathology was not common in our region, resulting in a rather large percentage of patients without grading, which might be regarded as an omission of this study.

Randomized studies have established wide excision and radiation as an equal alternative to mastectomy in the treatment of breast cancer.[10-12] The early studies mandated pathologically negative margins for those undergoing radiation. The absolute necessity of free margins is uncertain.[13] The surgical margin status after breast-conserving surgery is considered mainly a strong predictor for local failure.[1-8,14-16] In a recent review from Horst et al. they concluded that an adequate resection, as assessed by the status of the excisional margins on pathological examination, is a predictive factor with regard to local control.[17] Although many papers have been published with regard to positive margins, most papers do not make a distinction between IC and DCIS.

Cowen et al. is one of the few who looked at positive margins for IC and DCIS in BCT, however the numbers are small.[14] They analyzed 152 patients with positive margins, 39.7% IC, 41.1% DCIS, and 19.2% both. Similar to our results, they also found more local recurrences with margin involvement for DCIS (21.7%) as compared to invasive (15.5%), but the numbers are too small to reach statistical significance. They only concluded that margins with exclusively DCIS were not an indicator of a reduced relapse rate. Gage et al. showed that margin involvement for DCIS was a better indicator of local relapse than extensive intraductal carcinoma.[19] Freedman et al. also looked separately at the invasive and in situ component, but could not establish a difference, although they did not make a distinction in age category.[20] In 142 patients with a positive margin for invasive tumour and 49 for DCIS, they found 7% local recurrences in both categories.

Women ≤40 year are generally regarded as a separate entity in breast cancer with regard to prognosis and survival. Investigators from a number of centres have found that women younger than approximately 35-40 years at the time of diagnosis had a substantially higher risk of breast recurrence than older women.[17,18,21-26] In earlier studies we showed age ≤40 years to be an important prognostic factor for local control.[24,27]

In the present analysis we also established a significant statistical interaction by age category, implicating the importance of analyzing the different age categories separately. Few studies also stress the importance of young age as a determinant factor for risk of local failure.[17,21,22,24] Our study showed not only a significant relation of a positive margin for IC to local control, but also to distant metastasis and survival for young women in univariate and multivariate analyses.

With regard to positive margin for DCIS in young women our analyses showed a possible trend to higher local recurrence rate. This study stresses the importance to have clear margins, in particularly for IC in women ≤40 years, not only in relation to local control but also in relation to distant metastasis. The reasons for different outcomes in relation to age are unclear; are we dealing with different tumours or is the endocrinological status of the young patient the reason?

In our analysis the incidence rate of local recurrence with positive margin for DCIS was 17.4% at 10-year in women >40 years, more than four times higher compared to negative margins. This is comparable to the local recurrence rate in the EORTC trial 10853 for a free margin status.[28] This EORTC trial is one of the few studies in which the value of a positive margin for DCIS can be evaluated. One of the main conclusions of the trial was that the margin status was the most important factor in success for BCT. The NSABP trial B-17 also proved the radio sensitivity of DCIS.[29] The aim of this trial was to test the hypothesis that local excision of DCIS followed by radiotherapy was more effective than lumpectomy alone. Free margins for DCIS are the predominant risk factor in women >40 years. Boyages et al. in a meta analyses on local recurrence in patients with DCIS confirmed margin status in BCT for DCIS to be a predictor of local recurrence.[30]

One of the questions which arises from this analysis is why we find a difference in local control with regard to positive margins for DCIS in comparison to IC? Is there a difference in histological growth patterns? Is DCIS in the breast a more extensive disease compared to IC? Holland et al. showed the extension of DCIS to be greater in comparison to IC.[31,32] These findings are consistent with the hypothesis that positive margins for DCIS results in higher rate of local recurrence than do positive margins for IC using the same principles in designing the boost volume. Holland et al. also showed that DCIS does not have a multicentric distribution, meaning that a 'one piece' complete resection should be possible. However they found that in about 25% in their series tumours were very large. Incomplete resection might lead to a large residual tumour burden of DCIS. Re-excision with positive margin for DCIS should be more extensive and might even lead to an ablation.

Looking at the whole population we noticed also a negative outcome on distant metastasis of patients with a positive margin for IC. For the young patients the multivariate analysis showed significance with a HR 2.4, which is despite the small number important. Although for the older patients the multivariate analysis did not show significance the HR 1.4 at 10 years in univariate analysis is impressive looking at the large number of patients. Patients >40 years did not show a difference in local control, which might implicate that positive margins for IC is more a predictive factor for distant metastasis as for local recurrence.

We also noticed a relation between margin status and survival for the young patients. For patients >40 years the LRFS was significantly worse for positive margins for DCIS in women >40 years. This was translated in a significant worse survival with a HR of 1.9 for this group in univariate analysis, probably because of the increased local recurrence rate.

CONCLUSION

We showed a difference in outcome for positive margins for IC versus DCIS with regard to local control and also in relation to age. The impact of positive margin for IC seems to be limited to young women only, and is not only restricted to local control, but also to distant metastasis and survival. On the other hand a positive margin for DCIS is a risk factor for local control in women over 40 years. A positive margin for IC in this age category seems to have no impact on local control.

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Chapter 9

The impact of margin status in breast-conserving therapy for lobular carcinoma is age related

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ABSTRACT

Purpose: The aim is to look at the impact of margin status and outcome of invasive lobular carcinoma (ILC) treated with breast-conserving therapy (BCT).

Methods: This manuscript describes an analysis on 330 BCT in 318 patients with ILC.

Results: The 12-year local relapse free survival (LRFS) is 89%. In multivariate analysis, positive margin status, age >50 years, contra lateral breast cancer, and adjuvant systemic therapy were significant predictors of local relapse free survival. In a separate analysis limited to a positive margin for invasive carcinoma or carcinoma in situ, only a positive margin for invasive carcinoma was a significant predictor of local relapse free survival. This was limited to women ≤50 years. The 12-year disease-specific survival (DSS) was 85%. In multivariate Cox regression analysis grade 3 compared to grade 2 (HR 7.2), and a tumour size of pT2 (HR 2.5) were significant independent predictors of disease-specific survival (DSS). These factors were also relevant for distant metastasis-free survival (DMFS) and disease-free survival (DSS).

Conclusions: Positive margins for invasive carcinoma seem to be a strong predictor for local recurrence in particular for women ≤50-years. Our study showed grade 3 and tumour size to be strong predictors of DMFS, DFS, and DSS. Margin status was not.

INTRODUCTION

Over the last two decades, the trend in breast cancer management has been towards less invasive treatment strategies. Several large-scale studies have demonstrated that breast-conserving therapy (BCT) consisting of lumpectomy and radiation treatment is as effective as mastectomy.[1,2]

These studies validating the use of BCT were not designed to look at histology as an independent variable affecting the outcome. The overall outcome has been heavily weighted by the most common histological type, invasive ductal carcinoma. Invasive lobular carcinoma (ILC) is the second most common type, accounting for 8–16% of all invasive breast cancers.[3,4]

Because of differences in histological features for ILC, such as a more infiltrative growth pattern, a more frequent discontinuity, and a less defined thickening, and the differences in clinical behaviour, there has been a preference towards treating patients with more aggressive surgery instead of BCT.[5] And, hence, not entering these patients in BCT trials.

Because studies show that the incidence of ILC has increased over the last 10–20 years, particularly in postmenopausal women, ILC has been the subject of increasing interest.[4,5,6]

Irrespective of histology, many studies have focused on identifying factors that may affect local control after BCT such as margin status, presence of in situ carcinoma, tumour size, and grade. In earlier studies we established a difference in outcome for the different involvements of the margin by invasive carcinoma or carcinoma in situ, but these studies were heavily weighted by invasive ductal carcinoma too.[7,8]

In a large study by Sastre-garau et al. no difference was shown in local control between ILC and non-ILC.[9] In a large sized study derived from the National Cancer Data Base, Winchester et al. found no difference in overall survival between ILC and non-ILC cases comparing BCT to mastectomy.[10]

The purpose of the current study is to look at the long-term outcome and the impact of margin status of ILC treated with BCT from a single region in the Netherlands during the last twenty years.

PATIENTS AND METHODS

This prospective cohort of breast cancer patients was started in 1983 when BCT was introduced in our region. All patients in the Twente-Achterhoek region with invasive breast cancer, treated with BCT received their irradiation at the Radiotherapy Department of the Medisch Spectrum Twente at Enschede. All patient data, including demographics, histology, staging information, treatment, and outcome were recorded prospectively and updated regularly by the first author. From 1983 through 2005 a total of 2923 BCT were registered in 2836 patients. The histology from

these 2923 BCT consisted of 2227 (76%) invasive ductal carcinoma, 330 (11%) invasive lobular carcinoma (ILC), 124 (4%) invasive tubular carcinoma, 51 (2%) medullar carcinoma, and the rest mucinous carcinoma, undifferentiated carcinoma, or a combination of invasive ductal, lobular, or tubular carcinoma. This manuscript describes an analysis on the 330 BCT in 318 patients with ILC. None of the patients was lost to follow-up.

Histological examination for all BCT was done in the Pathology of Laboratory Oost Nederland. When missing the histological criteria of the ILC were updated before analysis and reviewed by one pathologist. Patients were classified according to the TNM-classification, 4th edition 1997.

We defined synchronous bilateral breast cancer (BBC) as cancer diagnosed in both breasts simultaneously or within a period of 3 months of diagnosis of the first tumour. Metachronous contra lateral breast cancer (CBC) was defined as breast cancer occurring in the contra lateral breast more than 3 months after the diagnosis of the tumour in the first breast affected.

As it is often difficult to differentiate between a local recurrence and a new primary in the treated breast, all tumours found in the ipsi-lateral breast during follow-up were classified as local recurrences.

All patients were seen every 3 months for the first 2 years and twice a year thereafter. During follow-up local recurrence, regional recurrence, distant metastasis, and survival were noted. For the purposes of this study, the cut-off for analysis was September 2008.

Margin status

Involvement of the margins of the lumpectomy specimen was defined as the presence of microscopic involvement of invasive carcinoma (IC) or carcinoma in situ (CIS) at the inked margin. Close margins were recorded as negative. Massive involvement with IC or CIS of the margins, defined as diffuse or multiple microscopic foci, was regarded as an indication for a re-excision. In case of focal microscopic involvement of the margin the surgeon was advised not to re-excise. The policy in our department was that minimal microscopic disease should be treated with radiotherapy. After our first study in 2003 this was changed, the aim was to have clear margins.[8]

In total 33 re-excisions were performed. Negative margins were defined as having no microscopic involvement of the inked margin with IC and/or CIS of the lumpectomy specimen or after re-excision.

Of all 318 patients accounting for 330 BCT the status of the resection margins was known.

Treatment

BCT consisted of lumpectomy with axillary clearance of levels I-III or sentinel node procedure, the latter being introduced in 2001, followed by radiotherapy to the whole breast with a boost to the primary tumour area. The radiotherapy regimen consisted of 50 Gy to the whole breast, followed by a 14 Gy boost to the primary tumour bed. The boost dose given was similar for all patients,

regardless of margin status. The localization of the boost was determined by the location of the scar, the primary tumour location, the mammography, and if possible by radiopaque clips placed during the lumpectomy procedure.

Adjuvant therapy consisted of radiotherapy to the regional lymph nodes or to the internal mammary chain only and hormonal and/or chemotherapy. Regional radiotherapy, which included the axilla and the supraclavicular, and internal mammary chains, was indicated for patients with four or more positive lymph nodes and/or extra nodal disease (EN). Radiotherapy of the internal mammary chain only was indicated for those patients with less than four positive lymph nodes and no EN. In case of medial implantation of the breast, the use of a separate anterior field for irradiation of the internal mammary chain was omitted to permit optimal irradiation of the breast.

In the late eighties adjuvant systemic therapy was introduced for patients with positive nodes. From 1992 on, all premenopausal patients with positive lymph nodes received chemotherapy. For postmenopausal patients adjuvant hormonal therapy was given when positive lymph nodes were present. Since 1999 indications for adjuvant systemic therapy depended not only on the lymph node status, but also in case of a negative lymph node status on the mitotic activity index, histological grade and tumour size. Premenopausal women received chemotherapy and endocrine therapy when the estrogens receptor status was positive. Postmenopausal women received primarily endocrine therapy and were offered chemotherapy if younger than <70 years. With a hormone receptor negative status patients were offered chemotherapy.

Statistical methods

Time to recurrence and length of follow-up were calculated from the start of BCT. To test between-group differences for categorical data Chi-square tests were used, and these analyses with regard to local recurrences were performed in relation to the number of BCT. For all survival analyses, patients were censored if they had not experienced an event (local recurrence, distant metastasis) at the time of analysis or if they were lost to follow-up or were dead, without disease, at the time of analysis. The local recurrence-free survival (LRFS) is defined as survival without local recurrence. An event was defined as the occurrence of a local recurrence in the treated breast.

Statistics for distant metastasis and survival were performed in relation to the number of patients and calculated by the method of Kaplan and Meier. The disease-specific survival (DSS), corrected for intercurrent death, was also calculated in relation to the number of patients. This means that for this particular analysis, data on patients who died of other causes than breast cancer were regarded as censored data. An event was defined as death due to breast cancer. The distant metastasis-free survival (DMFS) is defined as survival without distant metastasis in patients. An event was defined as the occurrence of distant metastasis in the patient.

For comparison of survival distributions the log-rank test was used. Variables that were univariately related to the outcomes of interest ($P<0.05$) were entered in the multivariate analyses.

The Cox proportional hazards model was used to test for the independent effect of margins status after adjusting for known prognostic factors and hazard ratios (HR) estimated with 95% confidence limits are presented. With an overall median follow-up of 95 months all analysis were performed on 12-year follow-up.

In the univariate analysis we used the following variables: age, localisation of the primary in the breast, family history, re-excision status, margin status, grade of differentiation, presence of lymph vascular space involvement, oestrogen status, progesterone status, mitotic activity index, tumour size, lymph node status, BBC, CBC, adjuvant radiotherapy, and adjuvant systemic therapy. All analyses were performed using STATA.[11]

RESULTS

Of the 318 patients with ILC and treated with 330 BCT the age ranged from 34 to 83 years with a mean and median age of 60 years. Only 7 patients (2%) were aged <40-years.

The clinical, patho-histological, and treatment characteristics of all 330 BCT are presented in Tables 1 and 2.

Three patients (1%) presented with BBC, and 33 patients (10%) developed CBC. The median time to CBC was 57 months.

Local control

Of the 330 BCT 6% (21/330) developed a local recurrence during follow-up. The 5-, 10-, and 12-year local relapse free survival (LRFS) is 97%, 92.2%, and 89% respectively. The time to local recurrence ranged from 18 to 199 months with a median of 83 months.

The univariate analysis showed age, CBC, positive margins for invasive carcinoma (IC) and/or lobular carcinoma in situ (LCIS), and adjuvant systemic therapy to be significant predictors for local recurrence.

In the multivariate analysis with the above mentioned factors, positive margin status (HR 3.5; 95% CI 1.37–9.03; $P=0.009$), age >50-years (HR 0.25; 95% CI 0.09–0.63; $P=0.003$), CBC (HR 4.9; 95% CI 1.77–13.63; $P=0.002$), and adjuvant systemic therapy (HR 0.13; 95% CI 0.02–0.99; $P=0.049$) were independent significant predictors for local recurrence.

In a separate analysis on positive margin status for IC, LCIS and IC plus LCIS, only positive margin for IC (HR 3.5) and positive for IC plus LCIS (HR 4.9) showed significance (Table 3). This increased risk is most pronounced in women ≤50 years (Figure 1). Due to the small numbers for

LCIS and also for the women ≤50 years the confidence intervals are large and results should be interpreted with caution.

Table 1: Clinical and pathological characteristics of 330 invasive lobular carcinomas all treated with breast-conserving therapy.

Characteristics	***n*=330 (%)**
Age	
<50 years	69 (21.7)
51-60 years	93 (29.2)
>60 years	156 (49.1)
Family history	
Positive	74 (23.3)
Negative	244 (76.7)
Localisation primary	
Lateral	207 (62.7)
Medial/central	123 (37.3)
Differentiation grade	
Grade 1	75 (22.7)
Grade 2	218 (66.1)
Grade 3	32 (9.7)
Unknown	5 (1.5)
Lymph vascular space invasion	
Positive	9 (2.7)
Negative	318 (96.4)
Unknown	3 (0.9)
Oestrogen receptor	
Positive	306 (92.7)
Negative	20 (6.1)
Unknown	4 (1.2)
Progesterone receptor	
Positive	253 (76.7)
Negative	71 (21.5)
Unknown	6 (1.8)
Presence of CIS	
DCIS	15 (4.5)
LCIS	118 (35.8)
None	197 (59.7)

Characteristics	*n*=330 (%)
Mitotic activity index	
Low: <13	285 (86.4)
High: >12	37 (11.2)
Unknown	8 (2.4)
Re-excision	
Yes	33 (10)
None	294 (89.1)
Unknown	3 (0.9)
Margin status	
Negative	258 (78.2)
Positive IC	38 (11.5)
Positive LCIS	25 (7.6)
Positive IC + LCIS	9 (2.7)
Tumour size	
≤10 mm	89 (27)
11-20 mm	157 (47.6)
21-50 mm	73 (22.1)
PT1mult	11 (3.3)
Lymph node status	
Negative	247 (74.8)
1-3 positive nodes	Tumour size 62 (18.8)
>3 positive nodes	Tumour size 21 (6.4)

IC: invasive carcinoma; LCIS: lobular carcinoma in situ. The patient-related characteristics are based on 318 patients, while carcinoma-related characteristics are based on 330 carcinomas.

Table 2: Adjuvant treatment characteristics of 330 breast-conserving treatments of invasive lobular carcinoma of the breast.

Characteristics	Number (%)
Adjuvant regional radiotherapy	
Yes	58 (17.6)
None	272 (82.4)
Adjuvant systemic therapy	
Chemotherapy	10 (3.0)
Hormonal therapy	75 (22.7)
Chemo + hormonal therapy	24 (7.3)
None	221 (67.0)

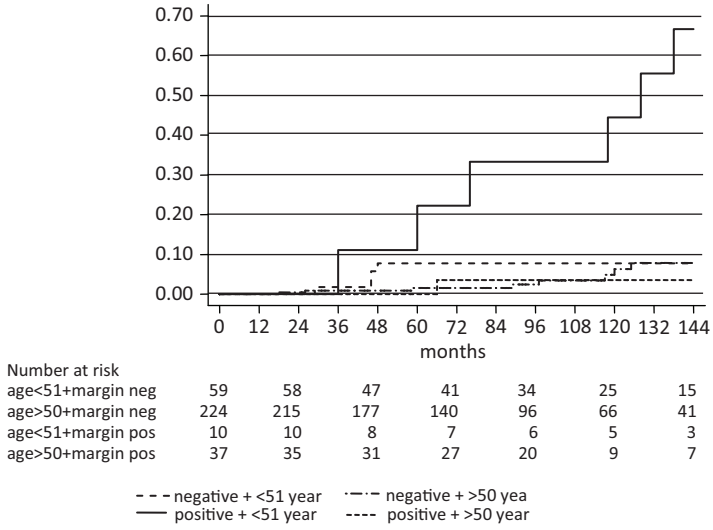

Figure 1: The 12-year local failure rate for 330 lobular carcinoma of breast cancer treated with breast-conserving therapy according to positive margin status for invasive carcinoma and age category.

Distant metastasis

The incidence rate for distant metastasis of the 318 patients was 13% (42/318). The 5-, 10-, and 12-years distant metastasis-free survival (DMFS) was 91%, 84.5%, and 83%, respectively. Time to metastasis ranged from 9 to 215 months with a median of 58 months.

The univariate analysis showed significance for the following characteristics: differentiation grade, tumour size, lymph node status, adjuvant radiotherapy and systemic therapy.

In multivariate Cox regression analysis including the above mentioned factors grade 3 compared to grade 2 (HR 6.9; 95% CI 3.2–15.0; $P<0.001$) was a significant predictor of distant metastasis, as well as a tumour size of pT2 (HR 3.2; 95% CI 1.7–6.3; $P<0.001$), and a tumour positive lymph node status (HR 7.7; 95% CI 2.2–27.2; $P=0.001$).

Disease-free survival

The 5-, 10-, and 12-year disease-free survival (DFS) for the 318 patients was 90%, 80 and 77%, respectively.

Univariate analysis showed differentiation grade, tumour size, and margin status for IC and/or LCIS to be significantly related to DFS.

In multivariate Cox regression analysis grade 3 compared to grade 2 (HR 3.3; 95% CI 1.7−6.5; *P*<0.001) and large tumour size (pT2) (HR 2.4; 95% CI 1.3−4.4; *P*=0.004) were independent predictors of DFS.

Disease-specific survival

The 5-, 10-, and 12-year disease-specific survival (DSS) for the 318 patients was 97%, 93%, and 85%, respectively.

The univariate analysis showed differentiation grade (Figure 2), tumour size, lymph node status, adjuvant radiotherapy, and systemic therapy to be significantly related to DSS.

In multivariate Cox regression analysis grade 3 compared to grade 2 (HR 7.2; 95% CI 2.8−18.9; *P*<0.001) and a tumour size of pT2 (HR 2.5; 95% CI 1.1−5.9; *P*=0.034) were an independent predictor of DSS. Tumour positive lymph nodes (HR 4.4; 95% CI 0.9−20.2; *P*=0.060) showed borderline significance.

Table 3: Hazard ratios, confidence interval and p-value for local recurrence at 12-years according to margin status and age category.

Margin status	Hazard ratio	95% Confidence interval	*P* value
	All ages (*n*=330)		
Negative (*n*=258)	1		
Positive IC (*n*=38)	3.5	1.20−10.3	0.022
Positive IC + LCIS (*n*=9)	4.9	1.08−22.5	0.040
Positive LCIS (*n*=25)	2.6	0.57−12.1	0.214
	Age ≤50-years (*n*=69)		
Negative (*n*=54)	1		
Positive IC (*n*=7)	7.3	1.83−29.5	0.005
Positive IC + LCIS (*n*=3)	7.1	1.30−39.5	0.024
Positive LCIS (*n*=5)	__a	__	__
	Age >50-years (*n*=261)		
Negative (*n*=204)	1		
Positive IC (*n*=31)	1.2	0.14−9.7	0.888
Positive IC + LCIS (*n*=6)	__a	__	
Positive LCIS (*n*=20)	4.5	0.89−22.7	0.067

IC: invasive carcinoma; LCIS: lobular carcinoma in situ. [a] Cannot be calculated because no local recurrences were observed.

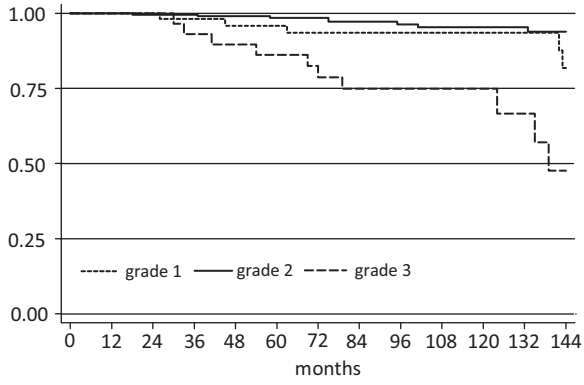

Figure 2: The 12-year disease-specific survival for 318 patients with lobular carcinoma for breast cancer and all treated with breast-conserving therapy according to differentiation grade.

DISCUSSION

This study shows positive margins for IC to be a predictive factor for local recurrence in women with invasive lobular carcinoma, but this seem limited to women ≤50-years. With respect to distant metastasis and survival the usual suspect such as grading, tumour size, and lymph node status are important prognostic factors, but margin status was not.

This prospective cohort of all breast cancer patients treated with BCT was started in 1987 by the first author.

The data are updated regularly on recurrence status, family history and status of the patient. All patients are followed even when they move to other parts of the country, keeping the loss to follow-up to an absolute minimum. Data are checked before entering the dataset by the first author personally.

Local control and margin status

The local recurrence rate of 8% at 10-years for ILC in our study is comparable to the overall 10-year local recurrence rate of for instance EORTC 22881-10882 trial and our own results.[7,8,12]

Despite the acceptance of BCT to be the primary treatment in early staged breast cancer, there is still debate over what is the appropriate margin. It is generally accepted that involved margins are associated with a higher local recurrence rate, only there is no consensus on the definition of clear surgical margins. As mentioned earlier, positive margins in this study were those with invasive carcinoma or carcinoma in situ in the inked margin.[13,14]

ILC may infiltrate the breast stroma and adipose tissue insidiously without producing a discrete mass. So, it is conceivable that in some patients with ILC after lumpectomy a considerable tumour burden still remained in the vicinity of the lumpectomy cavity. This might not only explain the high percentage of positive resection margins 18-63% in the literature, but also the reported high local recurrence rates.[15,16,17,18,19] In this respect a positive margin status might be an important risk factor for developing local recurrence after BCT.[20] However this was not confirmed by a recent study in 416 patients with ILC by van den Broek et al.[21]

In our study 30% (100/330) of the cases showed positive margins after first excision. After 33 re-excisions 22% (72/330) cases with positive margins for IC, CIS or both remained. This is a rather high percentage but can be explained by our policy in the early years not to re-excise cases with only focal positive margins.[7,8] The high rate of positive margins did however not translate into a high local recurrence rate. Looking at the relation between positive margin status and local control, we found significance for positive margin for IC and for both, LCIS and IC. LCIS alone did not show significance in relation to local control. Further analysis showed a relation between age and margin status with respect to local control. In an earlier study we showed a statistical interaction between age and margin status, but these studies were heavily weighted by the most common histological type, invasive ductal carcinoma.[7,8]

This study also showed that a positive margin status for IC resulted in high local recurrence rate for women ≤40years. In the present study we could not show statistical interaction between margin status and age, but still found a strong correlation between age and margin status for IC. Women ≤50-years with positive margins for IC had a seven times higher risk of local recurrence compared to women with negative margins. In general the age of 40 is accepted as an important turning point for patients with breast cancer, and those who are younger show a significantly worse outcome compared to the older category. However, most studies are heavily weighted by invasive ductal carcinoma. Our study with only 7 women ≤40-years and a median age of 60 years shows that ILC seems to be seen mostly in an older age category compared to invasive ductal carcinoma. In our series of only ILC we found a possible turning point at 50 years, but only for local control, suggesting positive margin status for ILC to be particularly important for women ≤50-years. Age was not an important factor for either distant metastasis or survival for patients with ILC.

The presence of lobular carcinoma in situ (LCIS) at the lumpectomy margin is in general regarded as irrelevant. Some investigators have noted that ILC and ILC coexisting with LCIS have an increased risk of in-breast events, but in both scenarios the excess breast events tend to occur over a protracted follow-up. This suggests an increased long-term risk of developing new primary breast lesions.[22,23] Our study shows a trend towards an increased local recurrence rate with positive margins for LCIS, only this seems limited to women >50-years.

Metastasis and survival

As expected, histological grading, tumour size, and lymph node status were the most important predictive factors for DMFS, DFS, and DSS.

A study by Møller Talman et al. including 860 ILC showed a significant worse prognosis for grade 3 tumours compared to grade 2 regarding both DFS and overall survival.[6] The Nottingham group showed that histological grading was the most important factor in predicting prognosis.[22] Our material included 330 ILC with 17% grade 1, 72% grade 2, and 10% grade 3 tumours. We also found a worse prognosis for grade 3 compared to grade 2 for DMFS, DFS and DSS. Singletary et al. in a large series showed tumour size and lymph node status to be the most important predictive factors for DFS[5]. A recent paper of Rakha et al. showed lymph node status to be the strongest predictor of both DSS and DFS for patients with ILC followed by grade, vascular invasion, size, and ER status.[18] Our study showed tumour size and in particularly lymph node status to be strong predictors of DMFS, DFS, and DSS.

Invasive lobular carcinoma has been associated with a higher risk of contra lateral tumours compared to ductal carcinoma. In accordance with the literature we found 1% BBC and 10% CBC rate.[3,8,19,20]

CONCLUSION

Positive margins for IC seem to be a predictive factor for local recurrence in women with invasive lobular carcinoma, but this seems limited to women ≤50-years. Our study showed differentiation grade and tumour size to be strong predictors of DMFS, DFS, and DSS.

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Chapter 10

Discussion

Breast-conserving therapy in early staged invasive breast cancer includes a combination of resection of the primary tumor and a sufficient rim of normal breast tissue, axillary staging, preferably by a sentinel node procedure, and radiotherapy of the breast (with or without a boost dose). The primary aim is to obtain a satisfying cosmetic result, without compromising to local tumor control or survival probability.

A number of randomized trials have shown that breast-conserving therapy in well-selected patients with invasive breast cancer leads to a survival rate comparable to that after mastectomy. The efficacy of breast-conserving therapy depends on: 1) an adequate selection of patients and 2) a correct implementation of the recommended treatment modalities. Important criteria in the selection of patients for breast-conserving therapy are: 1) removal of the primary tumor should not lead to serious cosmetic malformations and 2) the probability of locally recurrent disease is acceptably low.

In the selection of patients suitable for breast-conserving therapy, the following three groups of variables have to be taken into account: a) patients variables, b) clinical variables, and c) histopathological variables. Longitudinal prospective cohort studies are best suited to evaluate these variables.

TOTAL DOSE AND FRACTIONATION IN BREAST CANCER RADIOTHERAPY

The concept of an “all or none cancerocidal dose” has dominated radiotherapy since the discovery of radium and x-rays at the end of the 19th century. The effective radiation dose for sterilising cancer was taken as being 110% of the skin erythema dose, based on the belief that a dose slightly higher than the one needed to kill the epithelium of the mother organ would eradicate tumors originating from the epithelium. The applied total dose was not fractionated but was administered in a single session.

It was believed that the radio-sensitivity of tumors was determined by the radio-sensitivity of the tissue of origin. Historical data showed that for adenocarcinoma of the breast a certain dose was necessary to eradicate >90% of the tumor cells. It was also noted that for a given cancer type the volume was the major factor determining the rate of local control. Subclinical disease includes not only microscopic disease but also aggregates of cancer cells, which are too small to be detected clinically. Fletcher stated that for subclinical deposits of adenocarcinoma of the breast, a dose of 50.0 Gy administered in 5 weeks would eradicate close to 100% of all subclinical disease.

In the early eighties of the 20th century this concept was the background for treatment guidelines in breast-conserving therapy concerning the optimal radiotherapy dose of 50.0 Gy to the whole breast plus a boost of 14.0-16.0 Gy administered to the tumor bed, irrespective

of margin status. Taking into account that a dose of 50.0 Gy should be enough to eradicate subclinical disease, expected after a lumpectomy, an extra boost of 14.0-16.0 Gy to the tumor area seems more than enough. In fact this boost dose covers the extra dose needed in cases of a tumor positive resection margin, in which case theoretically more cancer cells than usual might be present in the vicinity of the tumor bed area. This might also result in a larger area of remaining cancer cells. There is no convincing evidence available to justify administering an even higher boost dose in cases with a tumor positive resection margin. The latter can be regarded as a way to cope with uncertainty.

A 4% 5-year and 8% 10-year local recurrence rate in our cohort of patients with breast-conserving therapy is comparable to that of the published literature, and, thereby, justifies our treatment policy.

New phase III studies have looked at the value of the boost, for instance the EORTC “Boost versus no boost” mega trial. The main conclusion was that the efficacy of a boost dose was age dependent. In 2004 we adapted our radiation protocol, so that no boost would be administered anymore to older patients with clear margins and limited tumor size.

Other phase III studies have looked at different radiation schemes with shorter treatment time and a larger fraction dose, the so-called hypofractionation schemes. Hypofractionation had results comparable to those of standard fractionation. In our center, this resulted in the introduction of hypofractionation for breast-conserving treatment from a maximum of 32 fractions to a scheme of a minimum of 16 fractions; all applied five times a week.

PATIENT FACTORS

In early breast cancer the personal preference of the patient determines to a great extent whether to opt for either a modified radical mastectomy or breast-conserving therapy. Others factors such as age, hereditary breast cancer, and family history are also important in treatment choice as well as in predicting the occurrence of recurrent disease. The impact of these patient factors, and especially treatment preference, cannot be adequately investigated in randomized trials comparing treatment options, so prospective cohort studies are pre-eminently better suited to study those factors.

By setting up such a population-based cohort of all patients in our region treated with breast-conserving therapy we had the opportunity to look at the influence of e.g. age and family history (FH) without being influenced by any form of selection. In this respect, we not only had the opportunity to look at the impact of those factors on recurrent disease and on survival at a certain time, but also to look at the influence of time with respect to the impact of those factor on recurrent disease and on survival.

Family history

In a first analysis published in 2000 we reported on the impact of FH on outcome in breast-conserving therapy. The validity of the FH in oncology has been well recognized. A positive FH is a function of the number of relatives, the background risk and the etiologic heterogeneity of the disease, and the age distribution of relatives. FH-based studies have the disadvantage of grouping true hereditary cases with those of familial clustering. Differences in defining FH and study methodology (e.g. matched control patients or a population-based study) are probably responsible for the discrepancies in the impact of FH as a prognostic factor.

Nevertheless, in our opinion, reporting results for women with a positive FH is extremely important, because most women know their FH when diagnosed with breast cancer, but are not aware whether they have hereditary breast cancer or not. Primary treatment should be based on the knowledge of the impact of family history.

In this analysis on FH we included 1.204 patients with a median follow-up of 65 months. A positive FH for first-degree relatives was seen in 20.5%, of whom 17.5% had one first-degree relative and 3% two or more first-degree relatives. It appeared that having two or more first-degree relatives with breast cancer did not negatively affect outcome; in fact it seemed to have a positive effect. Overall a positive FH for first-degree relatives did not have a negative effect on outcome either. For the future, it would be of interest to confirm not only if this statement stands with longer follow-up and in a much larger sample size, but also to analyze if an association exists between FH and BRCA1-2 positivity. At the moment we are participating in a large study looking at the impact of BRCA1-2 positivity on outcome in breast cancer for patients under the age of 50-years. Hopefully we will have the opportunity to look at a possible relation between FH and BRCA1-2 and outcome in this age category. These studies are of importance, because relevant decisions in the treatment of breast cancer are associated with (possible) BRCA1-2 positivity.
Sub-analyses for different age categories revealed that patients under 40-years and a positive FH showed a significant higher local recurrence rate, although this was not confirmed in multivariate analysis in this study.

This brings us to another important patient factor: age.

Age

Age is generally seen as an important prognostic factor in breast cancer. Many studies have demonstrated that young women at the time of diagnosis have a substantially higher risk of local failure after breast-conserving therapy than older patients do. Younger age is also correlated with an inferior survival and higher incidence of negative clinico-pathologic features. Young age was and is often seen as a contraindication for breast-conserving therapy due to the observed high local recurrence rate. On the other hand, from a psychological and social point of view breast-conserving therapy offer young women a better treatment than mastectomy. In this respect,

young women suffering from early breast cancer are an important group of patients. This raises the question whether breast-conserving therapy is the proper treatment for young women or whether other factors should be considered besides age. Do we offer young women with mastectomy a better prognosis, not only in relation to local control but also more importantly, with respect to survival?

Of course a prospective cohort study such as we have performed cannot adequately answer this question. However, we were able to look at factors, which might have interfered with local control in particular in young women, and we could also look at the relationship between age and distant metastasis rate and survival. This might lead to a more differentiated approach for young women to be offered breast-conserving therapy. In 2001 we published our first paper on the relevance of age. This study consisted of 1.085 women diagnosed with a pT1 tumor and a median follow-up of 71 months. We concluded that young women, ≤ 40 years, with pT1 breast cancer fared significantly worse compared to women over 40 years in terms of local control, distant metastasis and survival. Sub-analysis revealed that the adverse effect of young age on outcome appeared to be limited to the node-negative patients and those with a positive family history. Analyses with a long-term follow-up are of importance to this age category, because theoretically young women have a long life expectancy.

In another paper, published in 2003, we showed that in particular women under the age of 40 years should have negative margins for invasive carcinoma. Minimal surgery for an optimal cosmetic result followed by irradiation, even with focally microscopic positive resection margins for invasive carcinoma, yielded excellent results with regard to local control in patients over 40-years. In the histopathological factors section we will further discuss the relation of age and resection margin status.

CLINICAL FACTORS

Clinical factors such as tumor size and regional lymph node metastases are well known as important variables determining outcome. Others variables such as the presence of bilateral breast cancer, the presence of contra lateral breast cancer, boost volume, and timing of treatment are not generally regarded as important variables in relation to outcome. This might be due to the diversity in studies performed on these items. Timing of radiotherapy is mostly studied in relation to local control or in relation to the sequence of radiotherapy and chemotherapy. With respect to bilateral breast cancer and contra lateral breast cancer many studies do not differentiate between these two variables. However, the occurrence of synchronous bilateral breast cancer compared to metachronous contra lateral breast cancer is of interest to thorough analysis. Are we dealing with the same patient category or is there a difference in outcome,

locally and in survival? Other clinical and therapeutically factors, such as timing of radiotherapy and the size of the boost volume could also be analyzed.

Bilateral breast cancer

In 2003 we published a paper on synchronous, bilateral breast cancer: prognostic value and incidence. Synchronous, bilateral breast cancer is uncommon and published papers are scarce. Most papers deal with bilateral or contra lateral breast cancer, and they hardly ever differentiate between synchronous and metachronous contra-lateral breast cancer. In our study we showed (after multivariate analyses) a significant higher rate of distant metastasis rate for patients with bilateral breast cancer when compared to patients with unilateral breast cancer. All this translated to a worse disease-specific survival for patients with bilateral breast cancer. Due to the small number of publications together with the small sample sizes on synchronous bilateral breast cancer, no definite conclusions can be drawn. Looking at our results one might consider to take synchronous bilateral breast cancer as a poor prognostic factor in the decision for adjuvant systemic therapy. An update with more patients and longer follow-up seems necessary to obtain a more precise picture of the impact of synchronous bilateral breast cancer.

Boost

Since the introduction of breast-conserving therapy, radiotherapy comprised irradiation of the whole breast, possibly preceded or followed by a boost to the tumor area. Traditionally the overall treatment time amounted to 6-7 weeks. Over the years many have questioned the need to irradiate both the whole breast and the tumor area. One of the last large studies on this item was the EORTC-trial 'Boost versus no boost'. The question in all those studies can be reduced to: what is the growth pattern of the tumor, how does it spread, what is the relevance of the spreading and what is the optimal dose regimen. It is therefore relevant to know how large the ideal boost volume should be. Is there a relation between the size of the boost volume and the incidence of local recurrences? On the other hand we have to realize the limited accuracy in positioning our boost during each fraction dose. After breast-conserving surgery women are referred to the department of radiotherapy. At that time information on the exact position and the size of the primary tumor bed in the breast is limited. First of all, the mammography is performed, although the way the breast is positioned for the mammography is not the same as the position in which the breast is irradiated. Next, we have the surgical scar, possible postoperative changes (seromas, hematomas, and infections), information from the patient, and a simulation photo. Overall, this makes it difficult to be absolutely sure of irradiating the right target volume each time. Hence, the possibility of a geographical miss is not unrealistic. Since the start of the new century the introduction of the CT-simulator and the use of surgical clips in demarcating the lumpectomy area increased the accuracy of the boost area. Taking all these uncertainties into account we

published a paper in 2008 on the effect of external boost volume on local control. For this study we included all patients treated in a period from 1984 till 1995 with an external boost. The median follow-up period was 141 months, and 967 patients with breast-conserving treatments were suitable for analyses. Boost volumes were categorized into tertiles, < 66 $cm^{3,}$ 66-98 $cm^{3,}$ and > 98 cm^3. The size of the boost volume had no major impact on local control. In a paper on the impact of margin status in 2003 we demonstrated a statistical interaction between margin status and age. This urged us to do separate analyses for women ≤ 40 years compared to those over 40 years. The local control for women over 40 years was significantly better compared to that for young women, but no relation to boost volume could be demonstrated. With regard to resection margins, we noted a trend at 5- year with respect to boost volume for tumor positive resection margins positive for ductal carcinoma in situ (DCIS), whereas boost volume had no influence on local control in patients with tumor positive resection margins for invasive carcinoma. Taking into account the possibility of inaccurate targeting of the boost volume, by some estimated from 23-70%, our findings might imply that missing the target in boost irradiation does not lead to an increase in local recurrence or, conversely, that, with accurate boost treatment, extending the boost volume has no impact on local control.

Timing

As mentioned before, the overall time for the thirty-two fractions of radiotherapy, as part of the breast-conserving therapy, was nearly seven weeks. With the start of the breast-conserving therapy two disciplines were involved, surgery and radiotherapy. Over the years systemic therapy has become an integral part of the treatment of breast cancer. Starting in the eighties with chemotherapy or hormonal therapy for a well defined group of patients with positive nodes, it has been extended from patients with positive nodes, to patients with certain characteristics in tumor size, differentiation grade, or other prognostic factors. Only a small part of the patients with breast cancer nowadays does not receive any form of adjuvant systemic therapy. With the implementation of all these treatment modalities, timing has become a very relevant issue. In this respect, it has become important to know whether the radiation treatment should start immediately after surgery or at a later point in time. Naturally, one might argue that keeping in mind the outcome of numerous phase III studies in the eighties showing that radiotherapy in breast-conserving therapy is an integral part of the primary treatment, and any adjuvant therapy consequently starts afterwards. On the other hand, the question of whether starting the treatment within 4 weeks of surgery or for instance after 12 weeks has any impact on local control and survival is relevant. This is of importance to radiotherapy as well as to adjuvant systemic therapy and both may very well determine (in part) the patients' prognosis. Although there is a common understanding that delay in starting radiotherapy in BCT may reduce the probability of local control, the optimum time interval between lumpectomy and radiotherapy

has not yet been established. Long delays in starting radiotherapy have been linked to increased risk of local recurrence. Most studies on timing of radiotherapy have looked at the impact on local control and only very few also focus on the impact on distant metastasis. Most studies are also performed; looking at the sequence of chemotherapy and radiotherapy and not from the point of view of what is the optimum time interval. The effect of timing of the different therapies cannot easily be investigated in randomized trials. Having a database as we have now, up to date and with large numbers of patients and long-term follow-up, we were able to look at the impact of timing of radiotherapy on outcome in breast-conserving therapy. We were primarily interested in the optimum timing of radiotherapy in BCT with respect to outcome. Our hypothesis was, that starting radiotherapy within six weeks of lumpectomy was beneficial with respect to outcome. In 2006 we published our paper on timing in radiotherapy. We analyzed 1.473 breast-conserving treatments on 1.446 breast cancer patients. To avoid any bias from adjuvant systemic therapy, chemotherapy and/or hormonal therapy, we selected all patients without tumor positive axillary lymph nodes and without adjuvant systemic therapy. Also patients presented with synchronous bilateral breast cancer were excluded. Patients were categorized into three interval tertiles: 1-36 days, 37-53 days, and 54-112 days. We concluded that the local relapse-free survival did not differ between the three groups. On the other hand we showed, that later timing of radiotherapy seemed to be strongly related to improved distant metastasis-free survival, resulting in an improved survival. This result was a surprise, which we could not and still cannot explain. From laboratory experiments it is known that immediately after surgery an increase in circulating tumor cells was noted. The same study also showed that following the administration of a dose of radiation to the primary tumor, the growth of the primary tumor was delayed, but an increase in the proliferative capacity in metastatic foci was observed. Looking at the outcome of our study it seems that radiotherapy shortly after surgery enhances this effect and confirms the hypothesis of an increased proliferative capacity in metastatic foci. It is imperative that others look in the same category of patients with breast-conserving therapy at the impact of timing, and compare their results with ours.

Looking at the outcome of this study it is interesting to look in the near future at the impact of timing in radiotherapy to patients bearing tumor positive regional lymph nodes and/or treated with adjuvant systemic therapy. Not only to observe whether there is a difference in outcome, but in particular whether adjuvant systemic therapy in node negative patients would change the outcome in relation to survival with extending the time to radiotherapy.

HISTOPATHOLOGICAL FACTORS

In breast-conserving therapy histopathological factors play an important part, not only in the judgment on the primary treatment, but also in relation to outcome. Known factors are histological subtype, Bloom Richardson grading, the presence or absence of lymph vascular space invasion, mitotic activity index, presence or absence of carcinoma in situ, and tumor resection margin status.

Margin status has been a point of discussion since the introduction of breast-conserving therapy. When do we regard the margin negative? Is it relevant that there is no invasive carcinoma in the inked resection margin or should the distance from the inked margin to the nearest tumor be one, two or more millimeters? Do we also have to look at the ductal carcinoma in situ component in relation to the resection margin? Can we combine these in our judgment or do we have to look at them separately? In this discussion it is also important to look at the growth pattern of invasive carcinoma and carcinoma in situ. From studies performed by Holland et al. we know that ductal carcinoma in situ has a more wide spread growth pattern which may be translated to a more insecure margin status in comparison to that of the invasive carcinoma component. Theoretically, a close or focally tumor positive resection margin for ductal carcinoma in situ will imply a greater probability of having a positive re-excision in comparing to that of invasive carcinoma. Daily practice reveals that most re-excisions after the finding of tumor positive margins for invasive carcinoma are histological tumor negative. On the other hand knowledge of the more diffuse growing pattern of carcinoma in situ might lead one to expect more local recurrences in the presence of extensive carcinoma in situ or carcinoma in situ close to the margin.

Tumor positive resection margins in breast-conserving therapy are frequently a reason for applying an extra high boost dose to the primary tumor area. Keeping in mind that we are dealing with a possible microscopic involvement of the margins of the lumpectomy, the question arises whether an extra dose to this area is needed. As mentioned before, in case of subclinical or microscopic deposits of carcinoma in the breast, 50.0 Gy in 5 weeks eradicates close to 100% of subclinical disease. We administered to every patient a boost of 14.0 Gy. In our opinion, not only is an extra high boost unnecessary in cases with tumor positive resection margins, but also the need for a re-excision in case of a positive margin might be questioned. It was our policy in the eighties and nineties not to advise a re-excision with focally positive margins.

Margin

In 2003 we published our first paper on margin status and showed a statistical interaction between age and margin status. One of the main conclusions from that paper was that the value of a positive margin for invasive carcinoma in relation to local control was limited only to young

women. In the literature, this difference between young and older patients is not taken into account.

In our opinion it is important to differentiate between positive margins for invasive carcinoma when compared to positive margins with ductal carcinoma in situ. We showed that a focally positive margin for invasive carcinoma is of prognostic value in relation to local control, disease-free survival and disease-specific survival for women of 40-years and younger. On the other hand, focally positive margin did not have an impact in patients older than 40-years, indicating that minimal surgery for an optimal cosmetic result followed by irradiation, even with positive margins for invasive carcinoma in this age category yields excellent results.

In a second paper on margin status in 2007 with more patients and a longer follow-up period we confirmed our earlier finding that positive margins for invasive carcinoma are an important risk factor in young women with respect to local control. However, we also found that ductal carcinoma in situ was related to a higher rate of local recurrences in patients older than forty years. One of the questions arising from these analyses is, why we find a difference in local control with regard to positive margins for ductal carcinoma in situ in comparison to that of invasive carcinoma? As we mentioned before, the growth pattern of carcinoma in situ is different from that of invasive carcinoma. This might theoretically imply that the growth pattern of carcinoma in situ leads to larger probability of finding carcinoma in situ cells in the remaining breast compared to invasive carcinoma. These findings are consistent with the hypothesis that positive margins for ductal carcinoma in situ results in higher rates for local recurrence than do positive margins for invasive carcinoma using the same principles in treating the breast. Incomplete resection for carcinoma in situ should not only lead to a re-excision, but also to a more extensive re-excision in comparison to that for invasive carcinoma keeping the growth pattern in mind. Our analysis confirmed the hypothesis for women over 40 years. We could not confirm the hypothesis in women of 40-years and younger. In fact, positive margins for invasive carcinoma were highly related to local recurrence. The difference in local recurrence between the two age categories raises many questions. One of the key questions should be are we dealing with the same tumor? A question we are not able to answer at this moment, but looking at the outcome of our studies and also at the differences mentioned in the literature, the suggestion is that we are possibly dealing with two different tumors. New techniques such as for instance micro arrays might give us new information regarding this item.

Histology

Ductal carcinoma is the main histological subtype in breast cancer accounting for about 80% of all breast cancers. The second most common subtype is lobular carcinoma, accounting for 8-16% of all cases. Most studies in breast cancer have been heavily weighed by the most common type, invasive ductal carcinoma, and were not designed to look at histology as an independent variable

affecting the outcome. The differences in histological features for lobular carcinoma compared to ductal carcinoma, such as more infiltrative growth, more frequent discontinuity, and less defined thickening, and the differences in clinical behavior makes histology an interesting risk factor to look at. Local control in lobular carcinoma was comparable to that of ductal carcinoma. Looking at the more frequent discontinuity occurring with lobular carcinoma one would expect a relation between positive margin for invasive carcinoma and local control for all women. But as with ductal carcinoma, we demonstrated that in particular for young women a high correlation existed for local control with margin status for invasive carcinoma, only this time the turning point is not 40-years but 50-years, a whole decade later. Again the question arises, why do young women do worse?

FUTURE

Twenty-one years of input of data on breast-conserving treatment has not only created a large database, but also has given insight into the actual treatment results compared to those from the published literature, and revealed the impact of different risk factors. The present database with more than 3.800 BCT cases, the extensive cooperation with the pathologists, and the regular updates resulting in an up-to-date database with long-term follow-up, give us the opportunity to publish more interesting papers.

Looking at our results with respect to the outcome of timing in BCT we hope to publish an update of this result in the near future with more patients and longer follow-up. Also, we will look at the effect of adjuvant systemic therapy in node negative patients. Does adjuvant systemic therapy have any effect on the timing of radiotherapy, does it correct for a worse timing of radiotherapy? These are interesting questions. Also, it would be of interest to investigate the effect of timing of radiotherapy in patients with positive nodes and adjuvant systemic therapy.

We are also planning to look at the impact of the mitotic activity index. An update of the histological variables of those with a known mitotic activity index is in process, and with 1.800 patients this will be one of the largest series on which we hope to publish in the near future.

This database of presently over 3.800 patients has much potential for research on breast cancer. It is up to date and concerns real life treatment without any selection. This makes it unique.

Summary

A large cohort study on breast cancer was started that included patients treated with breast-conserving therapy, from the early start of this treatment in the Twente – Achterhoek region, till today, with more than 3.800 breast-conserving treatments. Recruitment is still continuing.

In **chapter 2**, on family history, we were able to show that a positive family history with regard to first degree relatives does not result in a worse outcome; on the contrary we demonstrated a trend to a better outcome.

In **chapter 3** we could establish a young age as a risk factor for local control in breast cancer in accordance with the literature.

We also looked at the incidence and outcome for patients with bilateral synchronous breast cancer. We demonstrated that bilateral breast cancer has a poor outcome compared with unilateral breast cancer, in particular in relation to distant metastasis (**chapter 4**).

Boost irradiation in breast-conserving therapy has been an important issue since many years. Not only with regard to the question of the necessity of the boost, but also with regard to the accuracy of delivering the boost to the tumour area. The latest has become more interesting after the introduction of the CT-localisation. We published one of the few papers on external boost volume in breast-conserving therapy (**chapter 5**) from before the era of the CT-localisation. Most studies describe the impact of boost volume in brachytherapy. We showed no relation of the boost volume to local control despite the fact that probably the accuracy of the boost area was questionable.

Timing in breast cancer has become an important item due to the extended treatment with surgery, radiotherapy and systemic therapy. Most studies published focus on local control. We demonstrated in **chapter 6** no effect on local control with the start of radiotherapy till twelve weeks after surgery. Surprisingly we also found that a longer time interval leads to favourable results with respect to distant metastasis and survival.

One of the items what intrigued us was margin status. We published three papers on this item (chapters 7, 8, and 9). The main contribution to the already existing literature was that we could show a statistical interaction between age and margin status. In our first paper in 2003 (**chapter 7**) we demonstrated that the value of positive margins for invasive carcinoma was limited to young women. Our second paper in 2007 (**chapter 8**) on a larger cohort and with long-term follow-up did not only confirm the findings in the first paper, but also showed that the effect of a positive margin was not limited to local control only, but also to distant metastasis and survival. We also demonstrated that a positive margin for ductal carcinoma in situ was a risk factor for local control in women over 40-years. In our last paper (**chapter 9**) on margin status we restricted ourselves to lobular carcinoma, and demonstrated the same effect of positive margins for invasive carcinoma as with ductal carcinoma, only this time the turning point was not 40-years but 50-years. This

means that in clinical practice analysis of the importance of margin status should always be done according to age category.

This thesis is not the end of all publications concerning breast cancer from this cohort. In the near future we will publish more data on timing, family history in relation to BRCA-1/2, and prognostic factors as the mitotic activity index.

Samenvatting

Vanaf het vroege begin van de borstsparende behandeling in de regio Twente-Achterhoek werd een grote cohort studie gestart met patiënten die behandeld werden met borstsparende therapie. Tot op heden zijn meer dan 3800 borstsparende behandelingen uitgevoerd en het cohort wordt nog steeds uitgebreid.

Hoofdstuk 2 laat zien dat een positieve familiegeschiedenis van eerstegraads familieleden niet resulteert in een slechte uitkomst. Integendeel, er lijkt een trend naar een betere uitkomst aanwezig te zijn.

In **hoofdstuk 3** blijkt dat een jonge leeftijd een risicofactor is voor locale controle in borstkanker, wat in overeenstemming is met de literatuur hierover.

Ook werden incidentie en uitkomst onderzocht voor patiënten met bilaterale synchrone borstkanker. We toonden aan dat bilaterale borstkanker een slechter resultaat geeft vergeleken met unilaterale borstkanker, in het bijzonder in relatie tot metastasen op afstand (**hoofdstuk 4**).

Boost-bestraling in borstsparende behandeling is een belangrijk item sinds vele jaren, niet alleen met betrekking tot de vraag naar noodzakelijkheid van de boost, maar ook met betrekking tot de nauwkeurigheid van plaatsing van de boost in het tumorgebied. Dit laatste wordt steeds interessanter na de introductie van de CT-localisatie. De publikatie in **hoofdstuk 5** is een van de weinige artikelen over externe boost volumina van vóór het tijdperk van CT-localisatie; de meeste studies beschrijven de resultaten van het boost volume in brachytherapie. Er bleek geen relatie te bestaat tussen het volume van de boost en de locale controle, ondanks de waarschijnlijk twijfelachtige accuratesse van het bestralingsgebied.

Timing is van de behandeling bij borstkanker is een steeds belangrijker item geworden ten gevolge van de uitgebreide behandeling met chirurgie, radiotherapie en systemische therapie. De meeste gepubliceerde studies leggen de nadruk op locale controle. In **hoofdstuk 6** wordt aangetoond dat er geen effect is op locale controle na de start van radiotherapie tot wel twaalf weken na de chirurgische ingreep. Tot onze verbazing en verrassing vonden we ook dat een lange tijdsinterval tot meer wenselijke resultaten leidde met betrekking tot metastasen op afstand en overleving.

Eén van de intrigerende onderwerpen was de invloed van de status van de snijranden. We publiceerden drie artikelen over dit onderwerp (hoofdstukken 7, 8 en 9). De belangrijkste bijdrage aan de reeds bestaande literatuur was dat we een statistische interactie tussen leeftijd en status van snijranden konden laten zien. In ons eerste artikel in 2003 (**hoofdstuk 7**) toonden we aan dat de waarde van positieve snijranden voor invasieve carcinomen beperkt was tot jonge vrouwen. Het tweede artikel in 2007 (**hoofdstuk 8**), over een inmiddels veel groter aantal patiënten en met een langere follow-up, bevestigde niet alleen de bevindingen uit de eerste studie, maar liet ook zien dat het effect van positieve snijranden niet beperkt was tot alleen locale controle, maar ook

tot metastasen op afstand en overleving. We toonden ook aan dat een positieve snijrand voor ductale carcinoma in situ een risicofactor was voor locale controle bij vrouwen ouder dan 40 jaar. Het laatste artikel (**hoofdstuk 9**) over snijranden beperkt zich tot lobulaire carcinoma en toonde hetzelfde effect van positieve snijranden aan voor invasieve carcinoma als bij ductale carcinoma, waarbij het omslagpunt niet bij 40 maar bij 50 jaar lag. Dit betekent dat in de klinische praktijk de analyse van het belang van snijrandbepalingen altijd gedaan moet worden, rekening houdend met de leeftijd van de patiënt.

Dit proefschrift is zeker niet het einde van een reeks van publicaties betreffende borstkanker uit deze cohort studie. In de nabije toekomst zullen meer data gepubliceerd worden over timing, familiegeschiedenis in relatie tot BRCA-1/2 en voorspellende factoren zoals de mitotische activiviteit index.

Dankwoord

Op deze manier wil ik een ieder binnen de afdeling Radiotherapie en daar buiten danken, die mij op enigerlei wijze heeft geholpen en mij in de toekomst hopelijk zal blijven helpen bij het blijven volgen van de al bestaande patiënten, het verzamelen van gegevens van nieuwe patiënten, het opsporen van statussen, en het schrijven van de diverse artikelen, et cetera.

Het laboratorium pathologie Oost-Nederland wil ik danken voor de welwillendheid waarmee ik telkens werd geholpen bij ontbrekende gegevens en tevens de pathologen die bereid waren en zijn bij het updaten van de ontbrekende histologische gegevens.

Zonder iemand te kort te willen doen wil ik graag twee mensen noemen. Allereerst Job van der Palen die mij niet alleen vanaf het begin heeft begeleidt bij het analyseren en schrijven, maar tevens een bijzonder inspirerende werking op het onderzoek en schrijven heeft gehad. Daarnaast Henk Struikmans, die mij steeds overtuigd heeft van het belang van het onderzoek.

Tevens dank aan de leden van de promotiecommissie, die direct bereid waren zitting te nemen in de commissie.

Ma en ook pa, hoewel hij dit helaas niet meer heeft mogen meemaken, ben ik dankbaar voor het vertrouwen en de mogelijkheid die jullie mij geboden hebben.

En als laatste, maar niet onbelangrijk mijn partner, flightgenote, vriendin en echtgenote Edith, dank voor de steun en interesse en alles wat wij kunnen delen.

Curriculum Vitae

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Education

Graduated secondary schooling at 'de Rijks Hoger Burgerschool' in Vlissingen in 1970.
Study Medicine 1970 – 1978 Erasmus University Rotterdam. Registration of Medicine April 1978
From 1978 – 1980 worked as an Assistant Gynaecologist during one year and later as an Assistant Surgeon.
Training for Radiation-Oncologist 1980 – 1984 Dr. Daniel den Hoed Clinic Rotterdam. Registration of Radiotherapy June 1984.

Professional activity

Radiation-Oncologist: 1984 –1986 Department of Oncology, Academic Hospital Leiden
Since 1987 Department of Radiation Oncology,
Medisch Spectrum Twente, Enschede.

Married with Edith Owel and two kids, Janneke en Wouter. Janneke has studied dentistry and is working as a dentist nowadays. Wouter has done training in hotel and event management, but did not finish it. At the moment working in the hospitality business. He will start a new education in health care this year.

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