Breast-conserving therapy for ductal carcinoma in situ

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Chapter 1

Introduction and aims of the thesis
Introduction

Background

Invasive breast cancer is the leading cause of death for women aged 25-64 years in western countries. Approximately one out of ten women is faced with the diagnosis of breast cancer, and about half of them will eventually die from the disease. Most, if not all, invasive breast cancers have a pre-invasive stage defined as carcinoma in situ. Ductal carcinoma in situ (DCIS) is a proliferation of malignant epithelial cells which are confined to the mammary ducts and lobules. Because of the absence of invasion there is no metastasising capacity, and therefore adequate treatment of DCIS leads to cure.

The glandular tissue of the breast consists of 15-25 branching duct systems (Figure 1) leading from the collecting ducts at the site of the nipple via segmental and subsegmental ducts to the terminal duct-lobular units, which are the functional site of milk production. DCIS is generally believed to arise at the terminal duct-lobular units (Figure 2). The 15-25 branching glandular “trees” form anatomically non-separable “segments” which may extend over the borders of a breast quadrant. DCIS tends to spread continuously through the ducts of one segment; simultaneously malignant transformation in more than one ductal segment is unlikely to occur. Therefore, DCIS grows typically unicentric, although cross-sectioning of the ductal tree can give a false impression of multifocal growth in the histological slide (Figure 3). Only when the tumour cells penetrate the basement membrane, will extension and invasion into the surrounding stroma occur.

Figure 1 Galactogram of one of the branching ducts
Figure 2 DCIS 'arising' at the terminal duct-lobular unit

Figure 3 Alternation of DCIS and normal breast tissue, giving the (false) impression of multifocal growth
Lesions currently diagnosed as ductal carcinoma in situ were first recognised over a century ago. Bloodgood\(^1\) described "comedo-adenocarcinoma" as an entity in 1893, describing the appearance of "...a benign tumour of the breast.... The moment we cut into and pressed on it, there exuded from its surface many greyish-white, granular cylinders, which I called at that time comedos. From the gross appearance the tumour was diagnosed as malignant, and the radical operation was performed. The nodes were not involved....." The patient was cured of her disease. The concept of non-invasive breast carcinoma was introduced in 1911 by MacCarty\(^2\) by demonstrating that abnormal cells in the ducts were cytologically identical to the cells of invasive carcinoma, and therefore he wondered if it was "......necessary to wait for the penetration of the basement membrane before making a diagnosis of carcinoma". The term carcinoma in situ was first defined in 1932 by Broders\(^3\). Later, Foote and Stewart\(^4\) distinguished lobular carcinoma in situ (LCIS) from DCIS. LCIS is generally considered as a different biological entity with respect to clinical presentation and behaviour and is not further addressed in this thesis. In 1971 Haagensen\(^5\) used the term "intraductal carcinoma" to describe lesions that grow "predominantly" within ducts, but could also show areas of invasion. Also the mixed use of the term "comedocarcinoma", both for invasive lesions and for pure "comedo-type" DCIS, has been subject to confusion for a long time. Only recently has the term DCIS been strictly used for those malignancies that are confined to the lobules and ducts of the breast, without any evidence of invasive growth.

Until the 1980s, DCIS was a rare disease. The lesion accounted for 2-3% of all symptomatic breast cancers, and was diagnosed because it presented with a palpable mass, nipple discharge, or Paget's disease of the nipple. These symptomatic DCIS were usually ill-defined, extensive lesions, spreading through a large part of a segment. At that time, mastectomy was the standard treatment for all operable breast cancers. With this treatment, a virtually 100% cure rate could be obtained for DCIS. Missed invasive foci due to inadequate sampling at the time of diagnosis were considered the origin of the incidentally-observed distant metastases after mastectomy for DCIS (1-3%,\(^6\)-\(^12\)).

Although DCIS is the precursor of most, if not all, invasive breast cancers, probably not all DCIS will progress into invasive carcinoma. Little is known about the natural history of DCIS, if left untreated. Autopsy series showed DCIS in the breast with a frequency ranging from 6 to 18% in women who died of causes unrelated to breast cancer\(^13\)-\(^15\). This suggests that a number of DCIS cases never become clinically-apparent invasive tumours. The natural course of the disease has been evaluated in a few studies in cases picked up by review of the histology of breast biopsies for lesions that were originally interpreted as benign. These studies found small numbers of women with misdiagnosed, and therefore untreated DCIS, and report rates of subsequent invasive breast cancer from 11 of 80 cases (14%)\(^16\), to 9 of 28 (32%)\(^17\) and 8 of 15 cases (53%)\(^18\) after long follow-up periods (18-30 years). Morphologically different types of DCIS can be recognised; DCIS with a well-differentiated cell type, resembling that of normal breast...
tissue, is more easily misdiagnosed than DCIS with a poorly differentiated cell type. The subject of different histological types of DCIS will be discussed in greater detail later on in the introduction. The majority of the cases of untreated DCIS with long-term follow-up were low-grade lesions, and the natural course of higher-grade lesions might very well be different. Lewis and Geschickter reported in 1938 eight women with “comedocarcinoma” treated with local excision alone. Six of the tumours recurred locally, and in three of them the axillary lymph nodes were positive. It is unclear whether these lesions described were pure non-invasive lesions.

In the mid-eighties two major changes led to an important breakthrough in the approach to patients with DCIS:

- Improvement of mammography techniques allowed the detection of breast cancer at a non-symptomatic stage. Many cases of DCIS appeared to manifest with microcalcifications on the mammogram (Figure 4a). These calcifications develop either in necrotic areas of the lesion (Figure 4b), or in inspissated secretion of the tumour. The introduction of mammographic screening of asymptomatic women resulted thus in a markedly increased detection of DCIS.
- Breast-conserving therapy (BCT) proved to be a safe alternative compared with mastectomy in patients with operable invasive breast cancer. Therefore the question arose whether the same treatment could be applied for patients with DCIS.

Figure 4a Microcalcifications on the mammogram
Screening

Since the early 1990s, population-based mammographic screening has been introduced in several western countries\(^20\), with the aim of detecting breast cancer at an earlier stage, and so to reduce breast cancer mortality\(^{21-25}\). Currently, 13 countries have national or both national and regional funding of programmes. In the Netherlands, all women between 50 and 75 years of age are offered a biennial screen examination\(^{26}\); this country is one of the few, among which are the United Kingdom and Sweden, that reach a significant proportion of the target population\(^{20}\).

As a result of this screening, there has been an enormous increase in the detection of patients with DCIS. About 15-20\% of all detected breast cancers in screening programmes are DCIS. Overall, the age-adjusted incidence of DCIS has increased five to ten-fold in the past 20 years, with the largest increase after the start of the screening programmes\(^{27-31}\). In recent years, European countries report a DCIS incidence of 6.2 to 9.9 per 100,000 women per year\(^{27-29}\). In the United States guidelines differ and a national funded programme does not exist. Screening usually starts here for women from 40 years of age, resulting in a slightly higher incidence of 13.8 to 15.8 per 100,000 women\(^{30,31}\).
Breast-conserving therapy

When the feasibility of breast-conserving treatment for DCIS is assessed, there are three issues to consider. The first concerns the risk of invasive recurrence resulting in a risk of dying from breast cancer, compared to the achievable 100% cure by the “standard” treatment of mastectomy. The second issue affects the optimal method of breast-conserving treatment, including the role of radiotherapy. The third issue concerns the question whether treatment -, patient - or tumour-factors are related to the risk of recurrence and progression to invasive carcinoma.

Breast-conserving treatment for DCIS

Randomised clinical trials investigating BCT for stage I and II invasive breast cancer showed equivalent results in terms of disease-free survival and overall survival compared to modified radical mastectomy. A breast-conserving procedure seemed therefore also a logical alternative for the increasing number of screen-detected, excellent-prognosis cases of DCIS. However, results from randomised trials investigating BCT for patients with invasive breast cancer cannot directly be extrapolated to patients with DCIS. In the patient with invasive breast cancer the prognosis, both after BCT and mastectomy, depends to a large extent on the risk of metastatic disease, which is mainly related to the tumour characteristics (i.e. pT and histological grade) and to the axillary lymphnode status at the time of the primary diagnosis. Local recurrence after BCT will probably not significantly alter the prognosis. This explains the fact that, as far as prognosis is concerned, BCT is equivalent to mastectomy in invasive cancer. In DCIS, the outcome of BCT should be weighed against the nearly 100% cure rate that can be achieved by ablative treatment. Any type of BCT bears a risk of local recurrence, and any invasive recurrence carries the risk of metastasis and death. BCT for DCIS should therefore aim at all costs to prevent an invasive local recurrence.

Until the eighties there was no information on the optimal method of BCT in DCIS. Many investigators felt that a complete local excision of the DCIS would be sufficient to cure most patients, and the additional value of radiation therapy was considered limited for this pre-invasive lesion.

Since the mid-eighties, BCT for DCIS has been evaluated by numerous non-randomised – often retrospective – studies. The most important ones are summarised, with those investigating local excision alone in Table 1, and those investigating local excision plus radiotherapy in Table 2. The reported recurrence rates vary from 11 to 63% after local excision, and from 3 to 17% after excision plus radiotherapy. Most studies cover a long period, and include both symptomatically-detected DCIS and mammographically-detected, non-symptomatic lesions. The biology of these lesions might however differ: DCIS giving rise to a palpable lesion can be an expansively-growing, good-prognosis lesion, that might lack the ability to become invasive. On the other hand it can be an
Table 1 Results of non-randomised series of patients treated with local excision for DCIS

<table>
<thead>
<tr>
<th>Author</th>
<th>Period</th>
<th>Median follow-up (months)</th>
<th>Number of patients</th>
<th>DCIS recurrence N (%)</th>
<th>Invasive recurrence N (%)</th>
<th>Total recurrence N (%)</th>
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<tr>
<td>Fisher</td>
<td>76-84</td>
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<td>22</td>
<td>2 (9)</td>
<td>3 (14)</td>
<td>5 (23)</td>
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<td>Carpenter</td>
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<td>38 (mean)</td>
<td>28</td>
<td>4 (14)</td>
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<td>5 (17)</td>
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<td>72-82</td>
<td>9 years</td>
<td>35</td>
<td>10 (29)</td>
<td>12 (34)</td>
<td>22 (63)</td>
</tr>
<tr>
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<td>13</td>
<td>2 (15)</td>
<td>3 (23)</td>
<td>5 (38)</td>
</tr>
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<td>38</td>
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<td>5 (13)</td>
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<td>3 (10)</td>
<td>1 (3)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Vrouenraets</td>
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<td>73 (mean)</td>
<td>14</td>
<td>4 (29)</td>
<td>1 (7)</td>
<td>5 (36)</td>
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<td>25 (22)</td>
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<td>10 (17)</td>
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<tr>
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<td>72</td>
<td>256</td>
<td>22 (9)</td>
<td>16 (6)</td>
<td>38 (15)</td>
</tr>
<tr>
<td>Van Zee</td>
<td>78-90</td>
<td>74</td>
<td>92</td>
<td>(&gt;12)</td>
<td>(&gt;7)</td>
<td>23 (25)</td>
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NA=not available; *histology recurrence unknown in 4 cases

Table 2 Results of non-randomised series of patients treated with local excision + radiotherapy for DCIS

<table>
<thead>
<tr>
<th>Author</th>
<th>Period</th>
<th>Median follow-up (months)</th>
<th>Number of patients</th>
<th>DCIS recurrence N (%)</th>
<th>Invasive recurrence N (%)</th>
<th>Total recurrence N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisher</td>
<td>76-84</td>
<td>39 (mean)</td>
<td>29</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Temple</td>
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<td>6 years</td>
<td>17</td>
<td>0</td>
<td>2 (12)</td>
<td>2 (12)</td>
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<tr>
<td>Vrouenraets</td>
<td>74-87</td>
<td>73 (mean)</td>
<td>28</td>
<td>0</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
<tr>
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<td>94</td>
<td>34</td>
<td>0</td>
<td>3 (9)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Cutuli</td>
<td>75-87</td>
<td>56</td>
<td>34</td>
<td>1</td>
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<td>3 (9)</td>
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<td>Ray</td>
<td>76-90</td>
<td>61</td>
<td>58</td>
<td>NA</td>
<td>NA</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Sneige</td>
<td>68-91</td>
<td>86</td>
<td>49</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Solin</td>
<td>67-85</td>
<td>10.3 years</td>
<td>270*</td>
<td>21 (8)</td>
<td>24 (9)</td>
<td>45 (17)</td>
</tr>
<tr>
<td>Amichetti</td>
<td>80-90</td>
<td>81</td>
<td>139</td>
<td>7 (5)</td>
<td>6 (4)</td>
<td>13 (9)</td>
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<tr>
<td>Silverstein</td>
<td>72-98</td>
<td>92</td>
<td>213</td>
<td>18 (8)</td>
<td>19 (9)</td>
<td>37 (17)</td>
</tr>
<tr>
<td>Van Zee</td>
<td>78-90</td>
<td>74</td>
<td>65</td>
<td>(&gt;6)*</td>
<td>(&gt;3)*</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Kestin</td>
<td>80-93</td>
<td>7.2 years</td>
<td>146</td>
<td>4 (3)</td>
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<td>17 (12)</td>
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NA=not available; *multicentre retrospective study, **histology recurrence unknown in 1 case
extensively-growing lesion, in which the risk of missed invasive foci increases with the tumour size\textsuperscript{12,47}. Screen-detected cases of DCIS consist of lesions that are either typically small, pre-invasive lesions, which will probably become invasive if not adequately treated, or lesions that might have never become clinically-apparent carcinomas.

The findings of the non-randomised studies suggest that radiotherapy reduces the risk of local recurrence. However, most studies comprise small numbers of patients, have variable lengths of follow-up, and due to highly selected groups of patients, especially with respect to the indications for radiotherapy, no firm conclusions can be drawn.

Breast-conserving therapy for DCIS has been investigated in several randomised clinical trials that started in the mid-eighties throughout the world\textsuperscript{58}. The majority aimed to evaluate the role of radiotherapy in BCT. Most trials had a similar design, with patients being randomly assigned to radiotherapy versus no further treatment after complete local excision of the lesion. In 1993 the National Surgical Breast and Bowel project (NSABP) B-17 study was the first to publish its results at a median follow-up of 3.6 years\textsuperscript{59}. The results of this trial indicate that radiotherapy prolongs local recurrence-free interval after local excision, findings that were confirmed at an update after a median follow-up of 7.5 years\textsuperscript{60}. More randomised studies are needed to confirm the findings of one trial, but many other randomised clinical trials have had accrual problems\textsuperscript{61}. For the European Organization for Research and Treatment of Cancer (EORTC) trial 10853 it took ten years for the required number of patients to be reached. The first results, described in chapter two of this thesis, were published in early 2000, and confirmed the beneficial effect of radiotherapy in BCT for DCIS\textsuperscript{62}.

Although radiotherapy seems to reduce the risk of local recurrence, even with radiotherapy the recurrence rates are rather high, and both trials report rates of 9-10% at five years. Approximately half of the recurrences are invasive carcinomas, and may thus become life-threatening\textsuperscript{15,50,62}.

\textbf{Risk factors for recurrence}

Many studies have attempted to identify factors that are associated with the risk of local recurrence. One of the most discussed is the histological type of the lesion. DCIS encompasses a morphologically-heterogeneous group of lesions. Several DCIS classification systems have been launched during the past ten years to identify histological types with presumed different risks of recurrence and progression. A good classification correlates with clinical outcome, is unambiguous and easy to apply for pathologists and has a low inter-observer variability\textsuperscript{53}. Most of the available classifications are, however, based on retrospective studies inducing a selection bias, with often small numbers of patients at risk. To date no classification has been found able to predict the progression to invasion and the risk of distant metastasis. Moreover, many of them are prone to a large inter-observer variability, even among experienced breast pathologists\textsuperscript{61,63}.
The traditional classification of DCIS was based on the predominant architectural pattern in which comedo, solid, cribriform, micropapillary, and clinging growth patterns were recognised. This classification lacked reproducibility, mainly because different patterns are frequently present within the same tumour. Furthermore, architecture was not sufficiently related to clinical outcome. Consequently, in the past ten years, several new classifications for DCIS have been proposed\textsuperscript{66-72}. Lagios was one of the first to argue that nuclear grade is more predictive for recurrence than architecture\textsuperscript{66}. He focused on nuclear grade, but also took the presence of necrosis and the architectural pattern into account\textsuperscript{67}. Later, several other classification systems followed, many of them based on nuclear grade\textsuperscript{68-72}. The Nottingham classification is based only on the presence of necrosis, recognising DCIS without necrosis, DCIS with non-pure comedo necrosis, and comedo DCIS\textsuperscript{69}. The rationale behind this classification is that necrosis is easy to recognise and usually associated with more aggressive biological behaviour. The Van Nuys classification also takes necrosis into account, but primarily focuses on nuclear grade\textsuperscript{71}. It divides DCIS into three groups, by first recognising lesions with a high nuclear grade to select the most "aggressive" group, and then dividing the remaining non-high-grade lesions by the presence or absence of necrosis. Holland and co-workers\textsuperscript{70} based their system on a combination of cytonuclear differentiation and cell polarisation, and did not include the presence of necrosis as a discriminative factor.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{example-of-well-differentiated-dcis.png}
\caption{Example of well-differentiated DCIS (250x)}
\end{figure}
Figure 6 Example of intermediately-differentiated DCIS (200x)

Polarisation refers to the cell apex orientation towards a lumen, resulting in glandular growth patterns and considered as a sign of differentiation. The classification divides DCIS into a well, an intermediate and a poorly-differentiated type. Examples of the three subtypes are given in Figures 5 to 7. This system approaches the generally-applied Bloom and Richardson grading system adapted by Elston and Ellis\textsuperscript{73} for invasive breast cancer, in which cytonuclear grade, amount of tubular formation (corresponding to the cellular polarisation in DCIS), and number of mitoses are taken into account. This grading system for invasive lesions has proved to correlate well with clinical outcome. Furthermore, in tumours where both are present, the grade of the invasive tumour has been shown to correlate well with the histological type of its associated DCIS component classified according to the method described by Holland et al\textsuperscript{74}. For these reasons the Holland classification will be applied in this thesis.

Several other factors have been reported to relate to the risk of recurrence\textsuperscript{44-46,49,51,75-77}. An important element is evaluating completeness of the excision of the DCIS\textsuperscript{45}. The extent of the lesion and the width of the tumour-free margin status have been shown to correlate with the risk of residual disease\textsuperscript{78-80}. Assessing the margin status of the resection is very important in evaluating adequacy of excision. Controversy exists on what should be considered a safe margin width, and various different techniques of
Introduction and aims of the thesis

Figure 7 Example of poorly-differentiated DCIS (400x)

surgical excision and margin evaluation have been recommended\textsuperscript{81-83}. To date, there is no consensus on optimal diagnostic and therapeutic procedures to achieve complete excision. The surgical removal of a non-palpable lesion has to be guided by a needle localisation procedure, and is a technically difficult procedure. Furthermore, although DCIS has a typically unifocal growth, “gaps” of uninvolved breast tissue may be seen\textsuperscript{84} (Figure 3). Therefore, at histology one can have the impression of a free margin status, even with DCIS left behind in the residual breast tissue.

A randomised clinical trial is the most appropriate setting for evaluating factors that are associated with the risk of local recurrence when treatment factors are included, since the random allocation of patients to the treatment arms will guarantee an equal distribution of possible treatment, tumour and patient-related risk factors between the different arms.

A randomised clinical trial is considered the gold standard for evidence-based therapy. Selection of patients for randomised trials may, however, have a large impact on the applicability of the study results to the general population with the disease\textsuperscript{85}. When studying the applicability of BCT in DCIS, it is necessary to evaluate how many patients with DCIS will in fact be suitable for BCT, and which proportion of patients is included in the trial. It might be that the effect of radiotherapy is not applicable to all
patients treated with breast conservation. The only method of evaluating generalisability is to compare randomised with non-entered patients. Other issues can be raised regarding BCT for DCIS. Although recurrence after conservative surgery is likely to be the result of residual disease, a second primary tumour may also develop. Recurrences found remote from the initial lesion would be more likely to be second primaries. Recurrence as a result of residual disease will have morphological similarities with the original DCIS. Studies on the histological types of local recurrence after BCT for DCIS are currently not available, and there is no insight into the incidence of second primary tumours.

Paget’s disease of the nipple is a special manifestation of breast cancer. Poorly-differentiated ductal cells originating from an underlying DCIS or invasive carcinoma spread into the epidermis of the nipple, resulting clinically in eczematous changes. This rare type of breast cancer is standardly treated with mastectomy; recently small studies have suggested a role for BCT in this type of lesions as well. Especially those cases with a limited underlying DCIS would be suitable for this kind of treatment. The currently available data are however too limited to draw any firm conclusions about the risk of recurrence after BCT.

The EORTC

The European Organization for Research and Treatment of Cancer (EORTC), founded in 1962, is an international cancer research organisation registered under Belgian law. The organisation promotes, conducts and coordinates experimental and clinical cancer research in 32 countries, through a network of more than 2,500 investigators, in 350 cancer centres and clinics. Overall, there are more than 6,500 cancer patients treated each year according to EORTC trial protocols. Specialists from the various cancer fields are organised into 20 different cooperative groups. The EORTC Data Center, located in Brussels, is involved in the coordination of phase II and III clinical trials.

In 1986, the EORTC Breast Cancer Group started, in collaboration with the Radiotherapy Group, a randomised phase III trial comparing local excision with local excision + radiotherapy in patients with DCIS (protocol 10853).

Since 1989, the EORTC has convened four international workshops on DCIS with the aim of exchanging existing knowledge, reaching consensus and discussing new issues that required further investigation on all aspects of DCIS. The EORTC trial, originally designed to investigate the role of radiotherapy in BCT for DCIS, with 1,010 randomised patients from 43 institutes, has served as a basis for an attempt to answer many additional questions regarding breast-conserving treatment for patients with DCIS. Most of the work described in this thesis is related to this trial.
This thesis

The aims of this thesis are:
- To investigate the role of radiotherapy in breast-conserving therapy for DCIS by evaluating the risk of recurrence after local excision only and after local excision plus radiotherapy;
- To identify patient, tumour and treatment-related factors that are associated with an increased risk of recurrence and, eventually, metastases;
- To analyse the effect of patient selection on generalisability of the trial results;
- To study, in the patients who developed a local recurrence, whether the recurrence is likely to reflect residual disease or represents a second primary tumour, and whether radiological signs of failure of a complete excision can be identified.

Thesis outline
Chapter 2: The role of radiotherapy in BCT for DCIS is studied. The first results of the EORTC trial 10853 are presented, in which 1,010 patients were randomised between radiotherapy and no further treatment after complete local excision of DCIS. The main endpoints are local recurrence, either DCIS or invasive.
Chapter 3: The impact of the quality of the initially-followed diagnostic and therapeutic procedures on outcome of patients randomised in the EORTC trial 10853 is evaluated. Data are presented from a review of the medical files of 824 patients during site visits.
Chapter 4: The selection of patients for the EORTC trial 10853 is studied in 910 patients with DCIS from five participating centres. Reasons for non-entry are presented, and outcome of the non-entered patients is compared with the randomised cases. The impact of the findings on the generalisability of the trial results is discussed.
Chapter 5: Clinical and pathological risk factors for local recurrence and distant metastasis are investigated. The pathology data are derived from a central pathology review of 863 of the randomised patients.
Chapter 6: The histological type and several immunohistochemical markers (oestrogen and progesterone receptor, HER2/Neu and p53) of the primary DCIS are compared with its local recurrence, both DCIS and invasive. This was performed to obtain insight into the incidence of second primary tumours after BCT for DCIS, and to analyse whether dedifferentiation of well-differentiated DCIS to higher-grade lesions occurs.
Chapter 7: Pre-operative and follow-up mammograms of 53 patients with a local recurrence from the EORTC trial 10853 have been reviewed, to assess the role of mammography in the evaluation of adequacy of the surgical excision and detection of local recurrence.
Chapter 8: The feasibility of breast-conserving therapy for Paget’s disease of the nipple with or without associated DCIS is studied in 61 patients. The results of an EORTC registration study (protocol 10873) are presented.
Chapter 9: The results are discussed and suggestions for future studies are given.
References

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2H 2H Chapter I


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