Breast-conserving therapy for ductal carcinoma in situ
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Chapter 9

Discussion
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The high number of DCIS cases detected as a result of screening mammography has raised questions about the clinical significance of these lesions. It has now been proved that screening reduces the mortality from breast cancer. This reduction is achieved by the detection and adequate treatment of 1) invasive carcinomas, not yet metastasised, and 2) DCIS, not yet invasive. It is, however, not clear which cases of DCIS contribute to this mortality reduction. A proportion of DCIS may never have become invasive during the lifetime of the patient, if these had not been detected. At present, identification of those lesions that are likely to become invasive is not possible. Therefore, treatment of every detected case of DCIS is indicated, and should aim to avoid the progression to invasion.

The objectives of this thesis were to investigate breast-conserving treatment (BCT) for DCIS, and included the evaluation of the role of radiotherapy, the risk of invasive and non-invasive recurrence, and the identification of factors related to the risk of recurrence.

Our results clearly show the beneficial effect of radiotherapy: at the median follow-up of 4.25 years, patients treated with excision and radiotherapy had a 38% reduced risk of recurrence, compared with those treated with local excision alone. With these results, the old hypothesis that DCIS would be resistant to irradiation has been abandoned. This hypothesis served as the rationale for the choice of including the surgery alone arm in the trials.

Still, in the radiotherapy arm a 10% local recurrence rate at five years is observed. When this recurrence rate is compared with that after BCT and radiotherapy for invasive carcinoma, several factors should be taken in consideration. First, while the complete surgical excision of an invasive lesion giving rise to a mass is relatively easy to achieve, this is not the case for DCIS, a lesion that is usually non-palpable, ill-defined and often larger than based on mammographic findings. The outcome after BCT for DCIS should be compared with invasive carcinomas surrounded by an extensive intraductal component (EIC). An EIC renders the tumour less clearly defined, and, consequently, the presence of an EIC correlates with the likelihood of residual disease after local excision. EIC accompanying invasive breast cancer is a risk factor for local recurrence after BCT, with reported recurrence rates of around 12-15% at 5 years. If invasive carcinomas accompanied by EIC are removed with histologically-free margins, the risk of recurrence is low.

Secondly, there is a difference in the applied irradiation dose. For invasive cancer a boost of 15-25 Gy is given to the area of the original tumour. For DCIS, this boost is not given. All randomised trials investigating radiotherapy in DCIS have prescribed a dose of 50 Gy to the whole breast, without the use of a boost. This dose, which is much lower than applied in BCT for invasive carcinoma, might not be sufficient.

Finally, while in BCT for DCIS a local recurrence nearly always presents as first event, in BCT for invasive carcinoma the risk of distant metastasis is higher than the risk of local recurrence, which will have implications on the reported rate of local recurrences.
a number of patients with invasive breast cancer will die from disseminated disease before they have the chance of developing a local recurrence, resulting in lower local recurrences.

Recently, several studies have investigated a role for surgery alone in a limited subgroup of patients with invasive breast cancer. Most of these selected patients with small stage I breast cancers, with radically excised tumours. However, even the local recurrence rates in these studies approached 20% at five years. Radiotherapy should thus be part of breast conservation both in invasive cancer and DCIS.

Treatment choice usually is adjusted for the individual patient. Treatment choice depends on the extent of the lesion and on the doctor's and the patient's preferences. In our selection study we found that 60% of all DCIS were treated with BCT, of which half were randomised in the trial. As can be expected, a higher proportion of lesions presenting with clinical symptoms (40%) were too large for BCT, compared with the mammographically-detected lesions (25%). The maximum size limit for entry in the EORTC trial was 5 cm; in practice, lesions of this size cannot safely be treated with BCT. It appeared that only very few randomised lesions were larger than 3 cm.

The results from our selection study show that physicians can make a proper selection of patients suitable for local excision only; patients treated outside the trial with this approach did relatively well: a recurrence rate of 11% was observed in this group. Despite this, our findings indicate that radiotherapy reduces the risk of recurrence in all subgroups of patients. However, the selection study suggests radiotherapy to be less effective in patients treated outside the trial than in the randomised patients. Selection plays a role. It seems that patients with a presumed higher recurrence risk, like having poorly-differentiated DCIS, or involved margins, were treated with excision and radiotherapy outside the trial. This suggests that the magnitude of the effect of radiotherapy, as found in the trial, may not be applicable to all patients with DCIS, and certainly, radiotherapy cannot compensate for insufficient surgery. The selection of patients treated outside the trial with excision alone was based on their - presumed - low-risk profile; the results of this group are similar to those treated with surgery alone in the trial.

Even with optimal treatment, consisting of a complete local excision with radiotherapy, a local recurrence rate of 10% was observed after five years in the trial. Half of the recurrences consisted of invasive carcinomas. As a nearly 100% cure rate can be obtained by mastectomy, BCT should aim at the minimisation of this risk of invasive recurrence. We tried to identify patient, tumour and treatment-related factors that are associated with the risk of recurrence, so that this information could be included in the choice of treatment for patients with DCIS.

Several studies have suggested that the histological type of the DCIS is associated with the risk of recurrence. Poorly-differentiated DCIS is considered to have a higher risk of recurring and progressing to invasive carcinoma than well-differentiated DCIS. This was only partially confirmed by our data. Although the risk of a DCIS recurrence was significantly higher in patients with poorly-differentiated DCIS, the risk of an invasive recurrence was independent of the histological type. The only group of lesions in our
study with an apparently low risk of local recurrence was well-differentiated DCIS with a clinging growth pattern. The study by Eusebi et al.\textsuperscript{14} investigating long-term follow-up in 32 cases of well-differentiated clinging DCIS, observed only two recurrences, these being again well-differentiated DCIS. We feel that radiotherapy can be safely omitted for this group of lesions. In view of their excellent prognosis, that approaches that of the normal population risk for breast cancer, one might question whether the term DCIS should be used. In the United States, other terms are being used for these lesions, that are frequently detected by mammographic screening\textsuperscript{15,16}.

All the other histological types - well-differentiated cribriform DCIS and poorly-differentiated DCIS - were found to have an equivalent risk of invasive recurrence. However, at least at a relatively short duration of follow-up, we did observe that the risk of distant metastasis after BCT was significantly higher in invasive recurrence after poorly-differentiated DCIS. This, at present, unique observation is consistent with the theory that the clinical behaviour is defined early in breast cancer development, and that "dedifferentiation" from a well-differentiated DCIS to a higher-grade lesion is an uncommon event. This theory is confirmed in our study comparing histology and marker expression in primary DCIS and its local recurrence. In this study, only 12\% of the well-differentiated lesions recurred as poorly-differentiated DCIS or grade III carcinomas.

The margin status is the most important factor in the risk of local recurrence for all histological types of DCIS. Complete excision of DCIS is however a technically-difficult procedure, requiring a multidisciplinary approach. The significance of the margin status as assessed by the pathologist has been shown in our risk factor analysis. When the margin status was evaluated as close, or when the margins had not been examined, recurrence rates up to 28\% were observed. Even when no residual DCIS was found at re-excision, a recurrence rate was found of 12\%, reflecting the difficulty of the surgical excision and of the evaluation of the margin status.

There is an important role for the radiologist in optimal treatment of DCIS. Review of mammograms from patients with a recurrence showed evidence of incomplete excision in 31\% of the patients. Although we could only study part of the recurrent cases, these results suggest that a number of recurrences can be avoided with a careful radiological evaluation of the surgical procedure. The extent of DCIS is difficult to assess from the mammogram, and the diameter of the area of calcifications frequently underestimate the histological extent of the DCIS\textsuperscript{1}. Therefore, the excision should aim at a zone of apparently-uninvolved breast tissue of at least 1 cm surrounding the area of calcifications. Furthermore, even with an apparently-complete excision of the area with calcifications, a post-operative mammogram needs to be performed in all cases. The use of magnification views enhances the estimation of the extent and distribution of microcalcifications.
Limitations

Most results of this thesis are based on data from a multicentre randomised clinical trial. We were able to answer many questions related to BCT for DCIS, but there are limitations in making conclusions based upon this study. The EORTC trial 10853 was designed to investigate the role of radiotherapy in BCT for DCIS. At the time of protocol development, no intentions were made to evaluate possible risk factors related to recurrence. As a consequence, important variables like size and margin status were not required in quantified data. A large non-randomised study has suggested that, when DCIS has been removed with wide tumour-free margins, the role of radiotherapy might be limited. It seems logical that if DCIS is completely removed, no adjuvant irradiation may be needed. Ideally, the results of non-randomised studies should be confirmed by randomised clinical trials. However, due to a lack of information about the exact measurement of the width of the tumour-free margin in the trial, the EORTC trial could not identify a margin width in which radiotherapy can be safely omitted.

Another limitation of a multicentre randomised trial is the problem of quality assurance. At the start of the trial, in 1986, quality assurance of new therapeutical procedures was not standard practice. The surgical treatment was not monitored and variations in diagnostic and therapeutic procedures were the result. Review of the mammograms and specimen X-rays of all patients would give valuable additional information about the extent of the lesion, and of the completeness of excision. Unfortunately this could not be realised due to logistic problems in collecting this material.

One of the major disadvantages of this trial is that it has not provided data on the cosmetic outcome. Preservation of the breast with good cosmesis should be the major goal of BCT. If, to obtain a complete excision, the excision volume becomes too large, cosmetic outcome after BCT for DCIS may be unsatisfactory. No randomised clinical trial has compared mastectomy with BCT for DCIS. Especially, ablation with direct reconstruction is a very suitable alternative for patients with DCIS. A trial in which patients are randomised between BCT (LE+RT) and mastectomy plus reconstruction will probably have many practical problems. This is, however, the only method to compare cosmetic outcome, quality of life, recurrence and survival between these two treatments.

Finally, as survival is the most important endpoint in BCT for DCIS, long-term follow-up will be needed, to evaluate whether the difference in local recurrence between the two treatments will eventually result in a difference in survival. Also, the observed increased risk of distant metastasis in poorly-differentiated DCIS needs to be confirmed with longer follow-up.

Future prospects

Molecular biological studies of DCIS, using techniques including loss of heterozygosity (LOH), comparative genomic hybridisation (CGH), and micro-array are currently under
development. Until now, no methods have been identified that can be used to distinguish DCIS that are likely to become invasive carcinomas, and indolent lesions. The collected tissue blocks of patients in the EORTC trial will be used for various molecular biological studies. One of the major challenges of future studies will be to identify markers indicative of progression to invasive breast cancer and metastasis. Results of several other randomised clinical trials are under way. It is expected that the first results of the UK DCIS trial will be published within a year. In this trial, both the role of radiotherapy and the effect of tamoxifen in BCT for DCIS are evaluated. 1694 patients have been randomised in this trial, and a pathology review is included as well: the results might give more insight into the role of tamoxifen in BCT for DCIS. The Eastern Cooperative Oncology Group study E5194 evaluates the role of local excision alone for patients with favourable prognosis DCIS, defined as: low or intermediate-grade DCIS up to 2.5 cm or high-grade DCIS up to 1 cm. Patients are not randomised. We have no information on the required margin status. Over 1176 patients are aimed to be registered, a quarter of this number has been reached so far. Finally, the Radiation Therapy Oncology Group study RTOG-98-04 has just started a trial investigating the efficacy of tamoxifen with or without breast irradiation after wide local excision for favourable prognosis DCIS. The lesions must be <2.5 cm, of low or intermediate grade and margins > 3mm. All patients will receive tamoxifen, and will be randomised between radiotherapy and observation after surgery. The target accrual is 2000 patients: it will take several years before the results of this study will be available. Patients with invasive recurrences after well-differentiated DCIS seem to have a low risk of dying from breast cancer, at least after a relatively short follow-up period. This subgroup might be suitable for investigation of further conservative therapies. As most of these lesions express oestrogen receptor, a possible option is randomisation between no further treatment, tamoxifen, and radiotherapy after complete local excision.

An area for further investigation will be the patient’s age as risk factor for recurrence after BCT for DCIS. Young age has also been shown to be a risk factor in BCT for invasive breast cancer. The cases of DCIS in the young age group are a mixture of 1) lesions detected in women who underwent individual screening; 2) symptomatic lesions, with, as shown earlier, a different clinical behaviour. In our study, young patients had a significantly higher rate of symptomatically-detected lesions compared with older patients (63% vs. 24%). The group of young women did not have a higher frequency of poorly-differentiated DCIS compared with the older women. An explanation for the higher recurrence rate in young patients may be that the excisions performed are smaller in view of the cosmetic outcome. Larger studies need to be performed to investigate this group of patients. Until more evidence is available, one should be very careful in the breast-conserving approach for younger patients with DCIS, and aim at a complete excision with 10 mm-free margins followed by radiotherapy in all cases.
Conclusions

The results of the studies presented in this thesis provide insight into the outcome of BCT for DCIS, and into treatment and tumour-related factors that are associated with the risk of recurrence. The achievement of a complete excision is one of the major predictive factors for the success of BCT. A successful treatment of DCIS requires a multidisciplinary approach, performed by an experienced breast team, involving a radiologist, surgeon, pathologist and radiation oncologist.

References


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