Optimizing treatment of low risk breast cancer patients

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Chapter 1

Introduction and outline
Breast cancer

Breast cancer is the most frequently diagnosed malignancy in women worldwide. Incidence rates are the highest in Western European countries. In the Netherlands in 2014 over 14,500 women were diagnosed with invasive breast cancer. This incidence is still rising since the introduction of breast cancer screening in the early nineties, while breast cancer mortality is decreasing. In the majority of women who were diagnosed with breast cancer in the Western world, their disease was detected at an early stage.

The TNM (tumor, node, metastasis) staging system, based on size of the primary tumor (T-stage), the locoregional lymph node status (N-stage) and the absence or presence of distant metastases (M-stage), is used to classify cancer. Based on the T-, N-, and M-stage, different TNM-stages can be identified (table 1). Higher stage disease is associated with worse survival and prognosis; the 5-year survival rate for stage I breast cancer is 98%, stage II 87-92%, stage III 64-82% and for stage IV only 22%. In general, early stage breast cancer means T1-2, N0-2 and M0 tumors (stage 0, I, II or IIIA).

<table>
<thead>
<tr>
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<tbody>
<tr>
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<tr>
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</tr>
<tr>
<td>IA</td>
<td>T0-1N1mi</td>
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<tr>
<td>IB</td>
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<tr>
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<td>T2N1 or T3N0</td>
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<td>T0-2N2 or T3N1-2</td>
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<td>Any T N3</td>
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<tr>
<td>IV</td>
<td>Any TN M1</td>
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</table>

Table 1: Staging

Standard of care for most women with early stage breast cancer is nowadays breast conserving therapy (BCT), which consists of a wide local excision of the tumor followed by adjuvant radiotherapy (RT) to the breast with or without adjuvant systemic therapy. Several studies have shown that BCT is at least equally effective as mastectomy.

Radiotherapy

In BCT RT is usually given to the whole breast, with or without an additional boost dose at the lumpectomy area/cavity. Adjuvant RT decreases the risk of a local recurrence, with approximately 50% as shown by the latest Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) overview. In the European Organisation for Research and Treatment of Cancer (EORTC) boost-no boost
study it was found that by adding a boost dose local control is further improved for all patients groups. The largest absolute effect was seen in young patients. In older patients (> 60 years) the effect of a boost was small, even after prolonged follow up, as a consequence a boost dose is no longer advised in these patients. Many studies have demonstrated that young age is an independent risk factor for locoregional recurrences, while on the other hand in elderly patients the risk of local recurrence is very low. The approach to optimize breast cancer treatment for individual patients is therefore different for elderly patients compared to younger patients.

**Hypofractionation**

Standard fractionation of whole breast RT consists of 2 Gray (Gy) per fraction regimen to a total dose of 50 to 66 Gy over a treatment period of 5-7 weeks. Several randomized trials have compared the standard fraction to treatment schedules that use larger doses per treatment and fewer total treatments (hypofractionating). Two UK trials (START trials) and a Canadian hypofractionation trial of whole breast irradiation showed that hypofractionating (in 13-16 fractions) was equally effective in terms of local control and late side effects. This has led in the Netherlands to a decreased treatment period of 3-5 weeks. Further acceleration up to 26 or 27 Gy in 5 fractions is currently under investigation (FAST-Forward trial). Reduced overall treatment time can result in less health care costs and decreased inconvenience for patients.

**Partial breast irradiation**

Another alternative to whole breast irradiation in elderly patients with low risk of local recurrence that has been studied is accelerated partial breast irradiation (PBI). Due to the fact that after BCT most ipsilateral local recurrences occur at or close to the original tumor bed, irradiation of the whole breast may be omitted, limiting the radiation dose to normal tissue. Due to smaller treatment volumes higher radiation doses in a shorter treatment period can be delivered. Several methods of PBI have been considered and introduced in the clinic; interstitial brachytherapy, intracavitary brachytherapy (Mammosite), intra-operative RT and three-dimensional conformal external-beam RT. Results showing the effects on local control in PBI are limited; three randomized trials have been published until now. In a study of Polgar et al., in which patients with invasive breast cancer were randomized between whole breast RT versus multicatheter brachytherapy or electron beam irradiation, there was equal local control in the two arms after 10.2 years follow up. The two other randomized trials randomized between intra-operative RT and whole breast RT both showed slightly higher local recurrence rates in the PBI group compared to the whole breast RT group. The local control results of external beam PBI come from phase I and phase II studies; overall low local recurrence rates are thus far available, only after limited follow up time.

An important advance of external beam RT is the fact that it is widely available and non-invasive. Another important advantage is the availability of pathology information at the time of treatment.
There are however several studies on postoperative external beam PBI that reported suboptimal outcomes concerning toxicity and cosmetic outcome. Hepel et al. showed 8% grade 3-4 soft tissue fibrosis 29 and Jagsi et al. showed 21% unacceptably poor cosmesis at a median follow up of 2.5 years 30. In the randomized RAPID trial, in which patients were randomized between external beam PBI and whole breast RT, there were significantly more poor cosmetic results in the PBI group compared to the whole breast RT group at 5 years (33% versus 13%, respectively). In this study more poor cosmetic outcome was seen with longer follow up 31. All studies have linked unfavorable cosmetic results with large treatment volumes. Irradiation of smaller volumes of normal tissue in the breast leads to less adverse effects of RT and better cosmetic outcome 32. Due to large inter-observer variability in delineating the target volume in a postoperative situation 33, 34, there is a treatment uncertainty leading to potentially larger target volumes.

**Preoperative Accelerated Partial Breast Irradiation**

In preoperative PBI the tumor is still in situ and visible, which can lead to more accurate tumor delineation compared to the postoperative situation, and potentially smaller volumes can be treated. After RT the breast tumor is surgically removed and herewith also the area of the breast that received the highest RT dose. These factors will lead to a lower radiation dose to normal breast tissue and less side-effects. These considerations have led to the development of the Preoperative Accelerated Partial Breast Irradiation (PAPBI) trial, described in the second part of this thesis.

**Breast imaging**

Besides conventional imaging, consisting of mammography and ultrasound, contrast-enhanced magnetic resonance imaging (MRI) is a diagnostic tool used to detect breast lesions. MRI has a high sensitivity to detect breast cancer. In patients treated with neoadjuvant chemotherapy, given prior to surgery, MRI is used to monitor response to treatment 35. In the PAPBI trial MRI is used to determine whether the breast lesion is unifocal as well as for RT response evaluation. Positron emission tomography (PET) is a radiotracer imaging technique in which compounds are injected intravenously. The most frequently used tracer in breast cancer is combination of the isotope fluorine-18 (18F) with the tracer compound fluorodeoxyglucose (FDG), which enters a similar metabolic pathway to glucose. Proliferating cancer cells have a higher rate of glucose metabolism than normal cells. The difference in FDG uptake can be visualized by PET. 18F-FDG PET in combination with computed tomography (CT), for providing anatomical information, is used for staging of locally advanced breast cancer 36. PET/CT can also be used to evaluate response to neoadjuvant chemotherapy 37, 38. In the PAPBI trial PET/CT is used for RT response evaluation.
Patient selection for optimizing treatment

RT treatment adds costs to the health care system\(^\text{39}\) and it has some (late term) toxicity\(^\text{40}\). Due to the fact that RT has limited effect on local recurrence rates and overall survival in selected low risk patient groups there is a need for identification of tools to identify patients who can be treated less by reducing or omitting RT. Patients undergoing BCT today have very low local recurrence rates\(^\text{41}\), and from those results it can be concluded that less intensive therapy will also lead to low local recurrence rates in selected patients.

Several clinical and histopathological factors, such as age, tumor size, grade, lymphovascular invasion (LVI), estrogen-receptor status (ER), progesterone-receptor status (PR), Human Epidermal growth factor Receptor-2 (HER2) and involvement of the axillary lymph nodes, are known predictors for local recurrence. Predicting the risk for recurrence for an individual patient is however challenging.

Gene-expression profiling studies have identified prognostic gene expression profiles to predict outcome in breast cancer\(^\text{42-44}\). For example, the 70-gene signature (MammaPrint\(^\text{\textregistered}\), Agendia NV, Amsterdam, the Netherlands) is a gene expression classifier used to predict the risk of distant recurrence\(^\text{42, 45}\). Recently it was shown that the 70-gene signature is also a predictive factor for local recurrence after BCT\(^\text{46}\). The search for a gene-expression profile that is predictive for local recurrence after BCT and can be used to guide this therapy in clinical practice is ongoing.

If a reliable gene expression profile associated with local recurrence can be identified, this will help in clinical decision making; i.e. the selection of patients who need tumor excision alone (without RT), patients who need tumor excision followed by whole breast irradiation and patients who are best treated with PBI. Developing diagnostic tools for more individualized breast cancer treatment; where both over- and under treatment of patients can be decreased by patient-tailored treatment is an important goal in breast cancer research.

Rationale and outline of this thesis

The aim of this thesis is to evaluate tools to optimize breast cancer treatment in patients with early stage breast cancer with low risk of local recurrence.

The first part of this thesis, chapter 2, provides an overview of the predictive and prognostic factors for local recurrence after mastectomy and after BCT, and describes the role of sensitivity to RT in local recurrence risk.

The second part of this thesis focuses on PBI. In chapter 3 we describe the first results of a preoperative PBI trial, the PAPBI trial, focusing on toxicity and cosmetic outcome. We compared target volume delineation pre-operatively versus post-operatively with respect to inter-observer variation and differences in size of delineated volumes in chapter 4. In chapter 5 the value of
PET/CT in T1 breast cancer is assessed, based on PET/CT scans made in early stage breast cancer patients. In chapter 6 the response to RT of tumors of patients treated in the PAPBI trial is described by comparing the response assessed by histopathologic examination, with the response assessed by MRI or PET/CT.

The third part of this thesis focuses on the outcome of patients treated in the Netherlands Cancer Institute with BCT over a period of 28 years. In chapter 7 all patients treated with BCT between 1980 and 2008 for early stage breast cancer were studied. Clinical characteristics, treatment and outcome were compared between groups treated over the years (1980-1987; 1988-1998; 1999-2008). In chapter 8 we describe all patients ≥ 65 years old from the same cohort, analyzing prognostic factors and risk of recurrences in elderly breast cancer patients.

This thesis ends with concluding remarks and future prospects in chapter 9 and a summary of the results presented in chapter 10.
References


