Optimizing treatment of low risk breast cancer patients
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Chapter 9

General discussion and future prospects
General discussion

The clinical outcome after breast conserving therapy (BCT) has greatly improved over the years; locoregional recurrence rates have decreased and survival has improved \(^1,^2\). Local treatment has improved as a result of better surgical techniques and innovations in radiotherapy (RT) techniques \(^3\). Adjuvant systemic treatment has led to improved survival and has also contributed to reduction of locoregional recurrences; in addition, over the years more effective combinations of drugs have been introduced and the use of adjuvant systemic therapy has increased substantially \(^4,^5\). In this thesis we have described studies of risk factors for locoregional recurrence after BCT and methods to optimize breast cancer treatment in patients with early stage breast cancer and low risk of recurrence. There is a need for improved prognostic and predictive tools for breast cancer in general, aiming at treatment optimization and on the other hand prevention of overtreatment of patients, particularly in low risk, elderly, breast cancer patients.

Estimation of the risk of locoregional recurrence (LRR) is based on traditional clinicopathological factors, especially age, differentiation grade and axillary lymph node involvement, as described in chapter 2. Elderly patients have lower risk on LRR compared to younger patients (< 50 years). Based on gene-expression profiling studies using DNA microarrays, breast cancer can be classified into five molecular subtypes: estrogen receptor (ER)-positive luminal A, ER-positive luminal B, human epidermal growth factor receptor (HER)-2 enriched, basal-like/triple negative and normal breast-like subtypes \(^6-^8\). Immunohistochemical analysis of ER and HER2 status provides a reasonably accurate surrogate for this molecular classification. Luminal subtypes are hormone receptor positive tumors. Luminal A and luminal B subtypes can be distinguished by ER, progesterone receptor (PR), HER2 and Ki-67 staining. Luminal B subtype can be subdivided according to HER2 status and Ki-67 staining or grade in luminal B and luminal B HER2 \(^9\). Classification of breast cancer into these different subtypes can be used in addition to classification based on traditional factors such as nodal status and differentiation grade. The subtypes have been shown to be associated with different patient outcomes, but data are variable regarding their predictive value for LRR after BCT. There are several studies showing a difference in local and/or regional recurrence rates after BCT for the different breast cancer subtypes \(^10-^15\). However, in a recent large study of Metzger-Filho et al. of more than 1900 node-negative early stage breast cancer patients there was no significant difference in LRR risk after 13 years follow up between all subtypes \(^16\). Also in the study of Laurberg et al. there was no association found between the 10- and 20 year risk of LRR and the different molecular subtypes in a cohort of 514 node negative breast cancer patients \(^17\). They observed a higher risk of LRR among younger patients (≤ 45 years) with low risk breast cancer compared with older patients. This difference was not associated with subtype \(^17\).
Chapter 9

The second part of this thesis focuses on partial breast irradiation (PBI), which is an alternative to standard whole breast irradiation in elderly patients with low risk of local recurrence. Due to the fact that after BCT most ipsilateral local recurrences occur at or close to the original tumor bed, RT of the whole breast might be overtreatment in defined low risk patients. In chapter 3 the first results of the Preoperative Accelerated Partial Breast Irradiation (PAPBI) trial are described. Patients with early stage low-risk (>60 years, cT1-2pN0) breast carcinomas were treated with preoperative external beam PBI, and after 6 weeks breast conserving surgery was performed. In contrast with postoperative external beam PBI trials the results in terms of fibrosis and cosmesis of patients treated in the PAPBI trial are favorable until now. For example in the large national Canadian RAPID trial, where 2135 patients were randomized between external beam PBI and whole breast RT, there was more poor cosmetic outcome with longer follow up in the PBI group. In this trial the volume of breast that receives 95% of the prescribed dose was restricted to <35%. In the PAPBI trial fibrosis was only present in a small volume of the breast. Also, the majority of the patients had no or only mild fibrosis; at 1, 2 and 3 years of follow up respectively 89%, 98% and 100% of patients. The cosmetic outcome was good to excellent in 88% of the patients after 2 year (n=41) as scored by the treating physician. A large volume of breast tissue that receives a relatively high dose of RT will lead to poorer cosmetic results, as described in postoperative external beam PBI studies. Due to more accurate target definition it is expected that preoperative external beam PBI leads to smaller treatment volumes compared to postoperative external beam PBI. Large inter-observer variability in delineating the target volume in a postoperative situation leads to potential large target volumes. In the PAPBI trial the planning target volume (PTV)/breast ratio had to be less than 25%. The PTV/breast ratio in the PAPBI trial was only 13% and the mean PTV was 122 cc. The good results in terms of cosmesis and fibrosis in the PAPBI trial are likely to be explained by this small RT volume. In addition, the breast tissue that received the highest RT dose is surgically removed after completion of the RT, which results in less fibrotic tissue in the breast and lower grade of fibrosis. In chapter 4 we describe the comparison of preoperative versus postoperative target volume delineation in a dataset of 24 breast cancer patients. There was considerably less inter-observer variation in the preoperative target delineation group, but the clinical target volume was comparable between the pre- and postoperative situation. This minimal difference between pre- and postoperative PTVs was the result of using the information on histological free margins by subtracting this from the prescribed CTV margin extension in the postoperative situation. In a side study of the recently started PAPBI-2 trial we will investigate the pre- and postoperatively delineated volumes of patients actually treated with postoperative PBI.

In chapter 3 we also describe the treatment efficacy of preoperative partial breast RT in the PAPBI trial. Thus far, three local recurrences have been observed in this study. Our first published report describes two local recurrences and one additional recurrence occurred in our institute after publication. All three recurrences were a true recurrence, based on loss of heterozygosity analysis.
of tumor DNA. Two patients initially had a grade 2 tumor, one had a grade 1 tumor. One of three patients received adjuvant systemic treatment (Tamoxifen). In 2 patients the recurrence was visible and palpable near the biopsy tracts, in the subcutaneous tissue. This finding was confirmed with imaging. In one patient the local recurrence was discovered by finding lymphadenopathy in the axilla first. Additional imaging (ultrasound and PET/CT) showed that the location of the recurrence probably was located in the biopsy tract. One patient was treated with a second wide local excision after the local recurrence. Adjuvant treatment consisted of hormonal therapy (tamoxifen) without adjuvant RT. After a follow up of 24 months she developed a second recurrence. This recurrence was discovered on MRI during regular follow up; again the location was probably the primary biopsy tract. The other two patients were treated with a breast ablation. Thus, in all three patients with an ipsilateral breast recurrence (IBTR) this was located in or close to the needle tract of the diagnostic core needle biopsy. This led to protocol modification of the PAPBI trial; since then part of the biopsy needle tract is excised as part of the breast conserving surgery, similarly as performed in skin-sparing mastectomy. All three patients suited the published criteria for selecting patients who are suitable for PBI by both European Society for Therapeutic Radiology and Oncology (ESTRO) and American Society of Therapeutic Radiotherapists (ASTRO) 25, 26.

In other PBI trials, to the best of our knowledge, there is no mandatory treatment involving the biopsy tract. In the ELIOT trial the 5 year event rate for IBTR was 4.4% (95% CI 2.7-6.1) in the intraoperative radiotherapy (IORT) group and 0.4% in the whole breast external beam radiotherapy group 27. Unfavorable factors such as tumor size greater than 2 cm, the presence of four or more positive lymph nodes, a poorly differentiated tumor, and triple-negative subtype increased the risk of IBTR with an overall 5-year occurrence of IBTR of 11.3% for patients who had at least one of these unfavorable characteristics. 40% of the patients with an IBTR in the ELIOT trial had a recurrence ‘elsewhere’ 27. This could be due to multicentric tumor foci located beyond the limits of irradiation 28, while part could be due to a recurrence in the needle tract. In the recent Cochrane overview comparing the results of PBI with whole breast irradiation more local recurrences and more new primary tumors in the ipsilateral breast are described 29, perhaps due to the same issue. There are several papers reporting recurrent cancer along the needle tract in breast cancer 30-33. For breast conserving therapy, preoperative core needle biopsy does not seem to have impact on local recurrence and overall survival most likely because surgery is combined with postoperative whole breast RT 34. Longer follow up and more careful reconstruction with imaging of recurrence location are needed to conclude more about IBTR rates and their patterns in other PBI studies. This is especially important in view of increasing use of PBI.

The sensitivity of tumor cells to RT is of interest as a local recurrence is the result of tumor cells not removed by surgery, combined with the resistance of these cells to RT. Several studies investigated gene expression signatures associated with RT sensitivity in cell lines 35, 36. Recently Speers et al.
studied the intrinsic sensitivity to RT of human breast cancer cell lines and used this to develop a signature that can discriminate between women prone to develop a LRR and women not prone to recur. Their results suggest that intrinsic RT sensitivity is not dependent on breast cancer molecular subtypes. Gene expression profiling techniques can be used to evaluate the association of the expression of genes with local recurrence after BCT. Several studies have been performed in order to find a signature predicting local recurrence, all based on retrospective analyses. These results need to be validated in other databases and preferably confirmed in prospective randomized trials. In such a trial it can be tested whether in a low risk patient group, based on a low risk gene expression signature, RT can be safely omitted. With the PAPBI study we have a model to study response of the tumor to RT, as the tumor is still in situ during the preoperative irradiation. One of the objectives of the PAPBI trial is to develop a gene expression signature for radiosensitivity, which is still work in progress.

In chapter 5 we show the value of 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in T1 breast cancer, based on PET/CT scans made in sixty-two early stage breast cancer patients. In the majority of patients (54/62) the tumor was visible on PET/CT, while tumors with prognostically unfavorable characteristics (node-positive, triple negative, grade 3, high proliferation index) were more likely to be eligible for response monitoring. In chapter 6 we describe the evaluation of the tumor response to RT in the PAPBI trial by comparing the histopathological response and the response assessed by imaging: magnetic resonance imaging (MRI) and FDG PET/CT. We used two different scoring methods for the MRI (RECIST and largest diameter at late enhancement (plateau/washout)) and the PET/CT (visually complete metabolic response and SUVmax difference) to determine response to RT. Patients in the PAPBI trial have tumors with prognostically favorable characteristics. Six weeks after breast irradiation only 20% of tumors of 60 early stage breast cancer patients showed a (near) complete pathological response. This is in line with the only other study which described pathological response after preoperative partial breast RT; in this study 4 complete pathological responses out of 27 patients were observed. The sensitivity of the MRI and PET/CT is around 70-80% and the specificity 60-80% making the prediction of pathological responders using only MRI or PET/CT difficult. The results described in this chapter will be used in a prospective study to search for genes which are important in RT response in tumor tissue from patients treated in the trial, with the goal to detect a gene expression profile to predict RT sensitivity.

Local recurrence rates in early stage breast cancer are low, as we describe in chapter 7 and chapter 8. In our cohort of 8485 patients treated between 1980 and 2008 IBTR rates are 2 and 5% at 5 and 10 years respectively. Over the years the IBTR rate has remained stable while the use of the RT boost declined. This could be well explained by the fact that the effects of reduction in the number of patients receiving a boost is counteracted by increased use of adjuvant systemic
therapy. For elderly patients (≥ 65 years old) the local recurrence rate was even lower with rates of 1-2 % and 3 % at 5 and 10 years respectively. Several studies have been performed to determine whether RT could be omitted in elderly low risk patients. None of these studies have led to practice changing policy, despite the fact that only slightly higher, but acceptable, IBRT risks were described in these studies, with no negative effect on distant metastases or overall survival, when RT was omitted. Most patients continue to undergo RT as part of BCT. All patients in the trials where RT was omitted were treated with endocrine therapy. Side effects of endocrine therapy are frequently reported in elderly patients, and up to almost 50% of patients after 5 years of follow up did not continue treatment. In chapter 8 we aimed to identify subgroups in low risk elderly breast cancer patients that do not benefit from intensified treatment. Our defined subgroup of low risk patients in this early stage elderly breast cancer cohort consisted of patients with a T1, ER positive, node negative, grade 1 or 2 tumor. This subgroup had similar LRR rates compared to a higher risk subgroup of patients (defined as patients with grade 3 and/or node positive tumors). The low risk group had however lower risk to develop distant metastases and had better overall survival. The low risk group probably is overtreated with currently used standard treatment protocols. Until better identification tools are available to identify elderly low risk breast cancer patients who can be treated less intensively, one could consider to omit RT for these patients. Whether or not endocrine therapy should be part of treatment of these patients is still under debate; in this respect the reported side effects and the limited benefit in elderly patients should be taken into consideration.

**Future prospects**

One of the topics important in breast cancer treatment for elderly patients with low risk breast cancer is prevention of overtreatment. In the Netherlands the TOP (Tailored treatment in Older Patients) consortium has been established, aiming at more tailored treatment for older patients with breast cancer. The first trial of this consortium, the TOP-1 trial, was recently initiated, a trial in which all patients will not receive RT. Patients are eligible if they meet the following inclusion criteria: age ≥ 70 years, entry into the study within 3 months after breast conserving surgery, tumor < 1 cm for grade 1 or grade 2, tumor 1-2 cm for grade 1, tumor ER positive (>50%) and HER2 negative, negative sentinel node and surgical free margins. Exclusion criteria are bilateral breast cancer and indication for hormonal therapy. This multicenter, prospective study will register patients who will not be irradiated after breast conserving surgery. Primary endpoint of the study is LRR rate at 5 years, to answer the question whether RT can be safely omitted in elderly patients with very low risk of local recurrence. One of the secondary aims is relating biomarkers (tumor characteristics, including ER, PR, HER2 and Ki-67 status) and possibly genomic analyses to outcome. Two other ongoing trials (see clinicaltrial.gov, NCT02400190 IDEA
trial and NCT01791829 LUMINA trial) investigate omitting RT in elderly low risk patients who undergo adjuvant endocrine therapy. The IDEA trial also takes into account the Oncotype-DX recurrences score 40, and the LUMINA trial only includes luminal A subtype tumors. Combining traditional clinicopathological factors with additional factors, and (new) gene-expression profiles will lead to better guidance for breast cancer treatment in the near future.

The PAPBI trial has been completed, and the PAPBI-2 trial has recently started. This randomized phase III trial compares preoperative PBI with postoperative PBI. Also, it has been decided to include patients > 50 years old. Postoperative PBI treatment outside the context of a clinical trial is already possible for selected low risk patients 25, 26. In order to confirm our favorable results of preoperative PBI, this phase III PAPBI-2 trial was developed. The main objective is to assess the cosmetic outcome after treatment, and secondary endpoints are fibrosis, breast pain, local recurrence free survival, disease free survival, distant metastases free survival, overall survival and quality of live. An additional objective of the PAPBI-2 trial is to assess response of the tumor to RT. In the first PAPBI trial fresh frozen tumor material has been collected; and DNA/RNA is being isolated. We have performed gene expression profiling (using RNA-seq) in the pretreatment biopsy and in the tumor after RT. By comparing gene expression profiles of responders to RT with non-responders we will try to identify a gene expression profile that predicts RT response. Due to the relatively low number of pathological (complete) responders, identifying such a predictive gene expression profile is difficult. To increase the number of patients that can be analyzed, we will continue these gene expression profiling studies in the PAPBI-2 trial. We expect to develop additional genomic tools that will help predict local recurrence and that will lead to improving personalized local treatment of breast cancer in the coming years.

**Concluding remarks**

In conclusion, treatment outcome for elderly patients with low risk breast cancer is excellent, which leads to an increasing need for selection tools to identify patients who can be safely treated less intensively. Less intensive treatment of these patients will lead to less side effects and less inconvenience and therefore better care.
References


