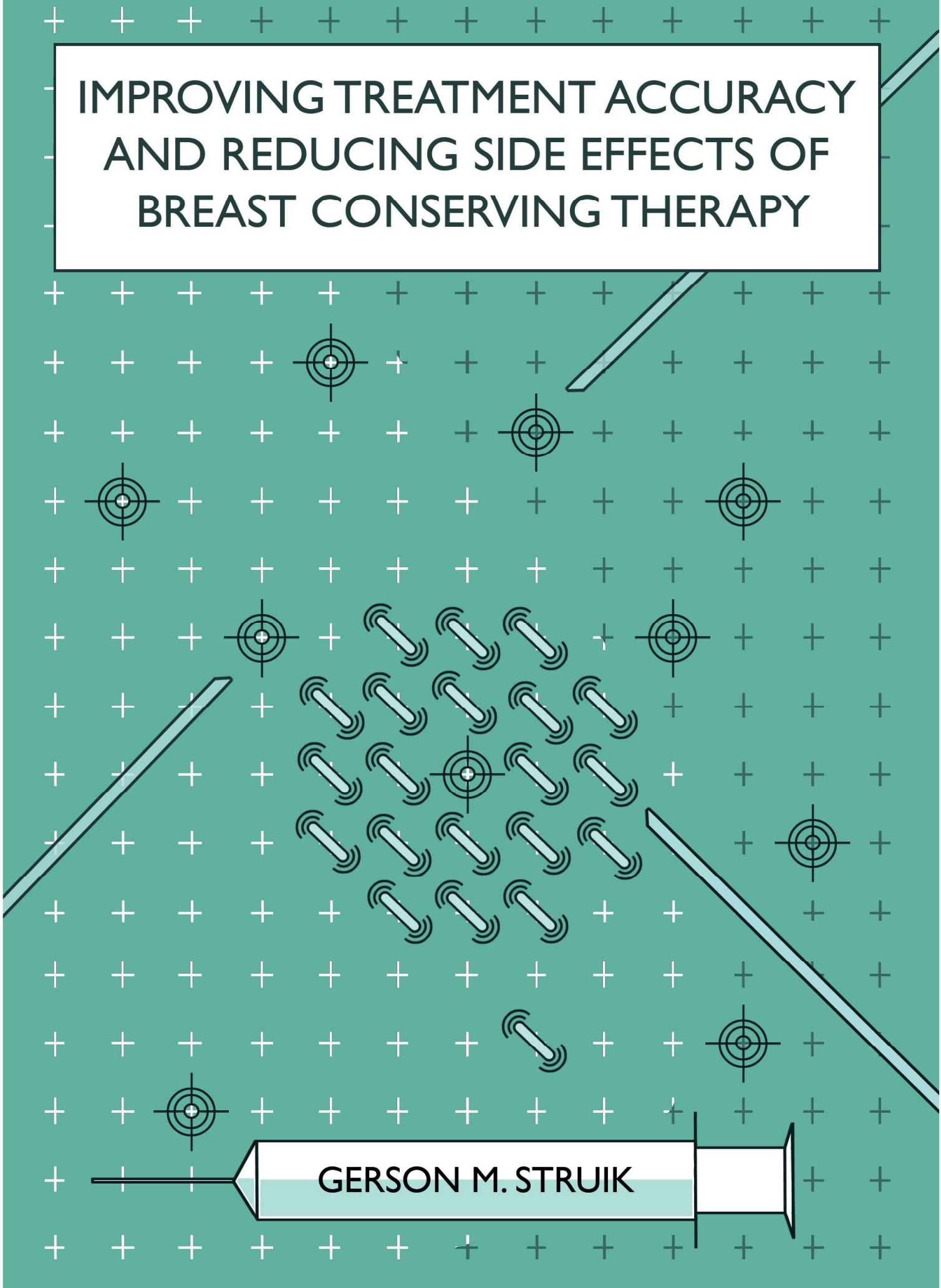
IMPROVING TREATMENT ACCURACY AND REDUCING SIDE EFFECTS OF BREAST CONSERVING THERAPY



GERSON M. STRUIK

Improving treatment accuracy and reducing side effects of breast conserving therapy to increase patient satisfaction in early stage breast cancer

Colofon

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Improving Treatment Accuracy and Reducing Side Effects of Breast Conserving Therapy

to increase patient satisfaction in early stage breast cancer

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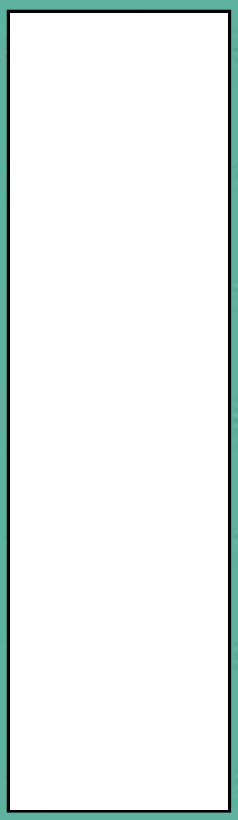
CHAPTER ONE



Introduction and outline

General introduction

Breast cancer is the most common malignancy among women in western countries; one out of eight women will develop one during their lifetime. In the Netherlands, nearly 15,000 new cases are diagnosed each year[1]. Breast cancer is the leading cause of cancer-related deaths and disability-adjusted life years (DALYs) among women globally[2]. As a result of screening mammography and improved imaging techniques, breast cancer is increasingly diagnosed at an early stage[3]. SEER data show that >60% of the patients are diagnosed at a localized stage, without extension to the regional nodes or distant metastasis[4].

For those early stage patients, breast conserving therapy, which includes wide local excision and radiotherapy with or without adjuvant systemic therapy, is equally effective as mastectomy in terms of local control, disease specific and overall survival[5, 6]. Oncological outcomes are excellent in early-stage breast cancer patients: the 5-year relative survival for those patients is 98.8%[4]. Furthermore, by preserving the breast, breast conserving therapy has cosmetic and functional benefits, which are directly related to patients' quality of life[7-10]. On the other hand, 5-year relative survival is much lower for patients with a cancer with loco-regional (stage 2-3) or distant spread (stage 4); 85.5% and 27.4% respectively in most recent SEER data[4].

Given the excellent oncological outcomes for early stage breast cancers, research in this group has shifted focus on improving patient outcomes regarding quality of life and cosmesis and reducing morbidity and treatment burden. Several possible strategies in the surgical and radiation treatment to do this are outlined in this introduction. This thesis subsequently describes interventions to improve treatment accuracy and reduce side effects of both the surgical and radiation treatment of early stage breast cancer patients.

Breast conserving surgery

Breast conserving surgery (BCS) aims at complete removal of the macroscopic tumor, while limiting the resected volume. Resecting smaller breast volume is associated with better cosmetic outcome[11-14]. Morbidity after breast conserving surgery includes surgical site infections (SSIs), re-operations and poor cosmesis.

Surgical strategies to reduce re-operation rate and improve cosmetic outcome are improved (pre-operative) tumor localization and oncoplastic surgical techniques. Tumor localization techniques are aiming at increased treatment accuracy and consequently reduced positive margin rates, while resecting similar or smaller volumes, which is associated with improved cosmesis. Conversely, oncoplastic techniques allow to remove larger volumes, while preserving good cosmesis and thereby reducing positive margin rates.

SSIs are associated with considerable morbidity and reduced quality of life for patients. SSIs lead to extended hospital stays, re-admissions and re-operations, poor cosmetic results, delay starting adjuvant treatment, and eventually additional costs[15-17]. SSIs might even result in increased occurrence

of local recurrences[18], however literature on this subject is scarce. Prevention of SSIs has recently gained attention as a strategy to improve patient outcomes.

Optimal tumor localization

In early stage breast cancer patients lesions are small and often non-palpable at time of diagnosis. Therefore, accurate pre-operative localization of these lesions is standard of care to guide the surgeon during surgery. Since the 1970s, wire guided localization (WGL) has been the gold standard[19, 20]. In WGL, a metal anchor wire is placed within or near the tumor, under radiologic guidance. Typically, the procedure takes place on the day of surgery. During surgery, the wire guides the surgeon, who removes the tissue around the hook at the tip of the wire. WGL has several disadvantages including: 1) risk of wire kinking, dislocation or transection; 2) patient distress and discomfort from the protruding wire; 3) injury associated with the hook wire; 4) interference with the surgical approach and 5) limitation in scheduling flexibility[20-22].

Alternative localization techniques have been developed to overcome the disadvantages of WGL. In radioactive seed localization (RSL), a 1 x 5 mm radioactive Iodine-125 seed is placed within or near the tumor under radiologic guidance. The radioactive seed can be placed days to weeks or even months (in case of neo-adjuvant chemotherapy) before the planned lumpectomy. Intraoperatively, a gamma probe is used to identify the seed and guide the surgical resection. Advantages of RSL are: 1) real-time three-dimensional guidance towards the lesion[23]; 2) logistic flexibility[24, 25]; and 3) higher patient satisfaction[26].

Comparisons of RSL to WGL are conflicting regarding positive margin rates. In 2015, a Cochrane review concluded that RSL could be offered as an equal alternative to WGL[20]. Since RSL offers a major logistic advantage[24, 25, 27] and significantly higher patient satisfaction[26] compared to WGL, recent studies recommended using RSL as an alternative to WGL. On the other hand, strict regulations on radiation safety make the use of RSL challenging. Consequently, the adoption of RSL is relatively low and WGL remains the preferred localization technique internationally. Recently, a new magnetic marker localization device (MaMaLoc) was developed[28]. It would provide the similar benefits over WGL as RSL, but without the challenges associated with radioactivity.

Oncoplastic surgical techniques

Oncoplastic surgical techniques are increasingly used[29] to further improve the cosmetic outcome of the surgical treatment[7, 29-31]. Those techniques involve at minimum a simple volume displacement (level I oncoplastic technique), with the breast parenchyma walls being approximated using stitches, to close the lumpectomy cavity[32]. For larger resections (level II oncoplastic technique), a mammoplasty technique is required. In principle, oncoplastic surgical techniques extend the possibilities for breast conservation for large or poorly limited cancers, with good oncological outcomes, low complication rates and good cosmetic results[30, 33, 34].

Prevention of surgical site infections

Surgery of the breast is regarded as a "clean" procedure, a term used to identify types of surgery with the lowest risk of bacterial contamination and likelihood to develop wound infections, as opposed to clean-contaminated, contaminated or dirty-infected surgical wounds[35, 36]. However, there is a relative high incidence of surgical site infections (SSIs), making it the most frequent surgical complication[37]. Previous studies on SSIs in women after breast cancer surgery showed incidences ranging between 3% and 19%[37-40]. This is much higher than the expected 3.4% infection rate associated with "clean" surgical techniques[41].

A meta-analysis by Xue in 2012[42] identified several significant risk factors for SSI after breast cancer surgery, but the type of wound dressings was not evaluated. The Cochrane Review of 2014[43] on the role of wound dressing in the prevention of SSIs revealed that in the current literature, there is no evidence that wound dressings could reduce the rate of SSIs nor that any particular wound dressing is superior to another in this regard. The studies included in this review were old and of low quality. As a result, the CDC guideline has no specific recommendation on the type of dressing or wearing time, except that primarily closed wounds should be sterile dressed for at least 24 to 48 hours[44]. High-quality research on the role of wound dressings in the prevention of SSIs is needed.

Optimal radiotherapy

Radiotherapy essentially provides a cosmetic and quality of life benefit over mastectomy[7], since oncological outcomes are equal in early stage breast cancer patients. Traditionally, radiotherapy is delivered to the whole breast in 16-23 fractions. Adjuvant radiotherapy results in a 50% reduction of local recurrence rates compared to omitting radiotherapy following breast conserving surgery, as shown by the Early Breast Cancer Trialists' Collaborative Group (EBCTG) meta-analysis by Darby et al.[45]. Young or high-risk patients are benefiting from a boost dose to the tumor bed after or during whole breast radiotherapy[46]. Radiotherapy results in a high treatment burden (3-5 weeks of daily treatments), considerable toxicity of mainly the skin, and risk of secondary malignancies.

To reduce overall treatment time and improve patient convenience, the concept of hypofractionation was introduced and tested in several randomized trials[47-49]. It was shown that hypofractionation (in 13-16 fractions) is equally effective as standard fractionation in terms of local control and late side effects. Other studies have investigated whether omitting radiotherapy would be possible for specific patient groups. However, a 3-5 times increased risk of local recurrences was found in the group without radiotherapy, in 3 different studies comparing lumpectomy with or without radiotherapy regardless of anti-hormonal therapy use[50-52].

Accelerated Partial Breast Irradiation (APBI)

Since local recurrences usually occur close to the primary tumor[53], the concept of accelerated partial breast irradiation (APBI) was introduced by Bethune in 1991[54]. APBI reduces the amount of breast tissue irradiated, enabling to deliver higher dose per fraction and hence treatment acceleration.

For well-selected patients, APBI has been tested and validated through several large randomized clinical trials, using either brachytherapy[55-58], external 3D conformal radiotherapy[59, 60], or intra-operative radiotherapy[61, 62].

Reducing skin toxicity

Brachytherapy has been the most evaluated APBI technique and recent advances beyond multicatheter implantation include balloon or strut brachytherapy as well as permanent breast seed implants[55, 63, 64]. Brachytherapy is generally well tolerated and reported long-term toxicities are acceptable. A lower incidence of low-grade acute skin toxicity for APBI, 21% versus 86% for whole breast radiotherapy ($p<0.001$) has been reported for the GEC-ESTRO trial[65]. Regarding late side effects at 5-years follow-up, lower rates of severe grade 2-3 skin, 6.9% versus 10.7%, and similar rates of subcutaneous side effects, 12.0% versus 9.7% for APBI compared to whole breast radiotherapy were found in this study[66].

Telangiectasia is a specific marker of radiation toxicity, with dose to the skin as main risk factor. Telangiectasia corresponds to the dilatation of an abnormal neo-vasculature in the skin following the destruction of normal capillaries by the radiation treatment, resulting in visible vessels. Although rates are lower than with whole breast irradiation, in breast brachytherapy 10 to 27% of the patients develop some grade of telangiectasia[55, 66, 67]. The majority of lesions are grade 1 ($< 1 cm^2$) in breast radiotherapy studies reporting on late skin toxicity[55, 68, 69]. The onset of telangiectasia is about from 6 months till 10 years after radiotherapy delivery[70], and telangiectasia rate peaks at 2 years with PBSI[55]. Although permanent in most cases, some authors report disappearing of the telangiectasia with longer follow-up[55]. Nevertheless, if present, telangiectasia can remind patients of their cancer similar to a surgical scar, and have a direct negative impact on the cosmetic outcomes[55, 69, 71].

Target definition

Following (oncoplastic) breast conserving surgery, the seroma is often limited in size, and becomes hardly visible on a CT-scan. Eventually this creates challenges for tumor bed delineation by a radiation oncologist at the time of adjuvant radiotherapy planning[72]. Accurate tumor bed delineation to target breast radiotherapy is particularly critical for accelerated partial breast irradiation (APBI) or when a boost dose is required. Inaccurate target definition carries the risk of a radiation geographical miss, which, in turn, might lead to an increased risk of local recurrence, especially for APBI. Furthermore, if the tumor bed delineation is enlarged due to uncertainties, there is an increased risk of toxicity[73-75]. Finally, if the target cannot be appropriately defined, some patients may be declined for patient-friendly APBI techniques[65, 76-79]. Traditionally, surgical clips are placed at the time of surgery to guide the tumor bed delineation. However, a recent study by den Hartogh shows that radiotherapy target definition using clips has poor inter-observer agreement in patients following oncoplastic surgery[72]. Thus, the attempt to improve surgical outcome by performing oncoplastic techniques

might impair radiotherapy treatment outcomes. Therefore, to increase treatment accuracy, it is crucial to improve target definition.

Secondary cancer risk

Long-term follow-up of large randomized trials comparing lumpectomy with or without adjuvant radiotherapy has shown that the benefit of radiotherapy is eclipsed by non-breast cancer mortality[80, 81]. The most common causes of non-breast cancer mortality include major cardiac events and secondary cancers[82-84]. Previously, in the 2011 EBCTCG meta-analysis, excess non-breast cancer mortality following breast radiotherapy was mainly attributed to cardiac mortality[45]. Darby et al. found a 0.5 to 0.7% risk of cardiac mortality before the age of 80 for a 50 year old node negative breast cancer patient treated with radiotherapy[82]. It is important to realize that fatal cardiac events occur much earlier than secondary cancer related mortality. This latency may explain why the meta-analysis by Darby et al., including trials with limited follow-up, did not fully capture the risk of secondary cancer mortality[82]. The published excess cardiac mortality rates stimulated widespread implementation of preventive techniques such as deep inspiration breath hold radiotherapy. Introducing new irradiation techniques may result in differences in the amount of dose to the whole body and thus to differences in the risk of radiation-induced secondary cancer[84, 85]. Any interventions on improving radiotherapy target definition and/or reducing radiotherapy (skin) toxicity will also alter the radiation dose to both tumor and healthy tissue. Scarce comparisons of secondary cancer risks for different techniques have been published[86-88].

Patients' perspective of treatment quality

With the excellent oncological outcomes in early stage breast cancer patients, patient reported outcome measures (PROMs) are increasingly important to indicate healthcare quality and compare different surgical and radiotherapeutic techniques[89-91]. The validated 22-item English Breast Cancer Treatment Outcome Scale (BCTOS) questionnaire is based on the comparison of the treated and untreated breast by the patient[92]. It is clearly structured, comprehensive and assesses the most important aspects of morbidity after BCT; including a cosmetic, functional and breast sensitivity subscale. Although it is widely used as a PROM in both breast conserving surgery and radiotherapy clinical trials[71, 93, 94], it has never been validated in a population after completing all BCT modalities. Also, a more concise version would further improve adoption. Uniformity in PROMs is essential for a good evaluation of treatment outcomes from a patients' perspective.

Rationale and outline of this thesis

The aim of this thesis was to evaluate innovative interventions to improve treatment accuracy and reduce side effects of both the surgical ánd radiation treatment of early stage breast cancer patients, thereby improving patient satisfaction and outcomes.

The first part of this thesis focuses on the surgical treatment. **Chapter 2** describes a novel technique of magnetic tumor localization that aims to combine the surgical and radiological advantages of a point source without the drawbacks of using radioactivity and its administrative and radio protective consequences. In **chapter 3** we describe the role of a silver-containing dressing in SSI reduction and its effect on patient satisfaction.

The second part of this thesis focuses on APBI and our work on skin toxicity reduction. **Chapter 4** shows the advantage of APBI with regards to secondary cancer risk, another incentive for APBI. **Chapter 5** describes the results of the Spacer Study. It provides a proof-of-principle of a subcutaneous spacer injection to protect the skin in breast brachytherapy. In **chapter 7** we describe a novel use of Gafchromic films to measure skin dose of permanent breast seed implants and the predictive value of this measured skin dose on acute skin toxicity. **Chapter 6** gives the rationale for the PBSI trial and summarizes the protocol of the ongoing randomized clinical trial testing the use of a skin spacer to reduce late skin toxicity of PBSI. In **chapter 8** our experience with the introduction of Permanent Breast Seed Implant, a form of APBI, in the Netherlands is described including the administrative and technical challenges involved.

The third part of this thesis describes the challenges in target definition for partial breast (and boost) radiotherapy and a novel intervention in which the surgeon provides the radiation oncologist with more information on the tumor bed location. In **chapter 9** we describe the Target-1 study: a radiopaque hydrogel was used during lumpectomy to improve tumor bed delineation for breast radiotherapy.

In **chapter 10** the psychometric evaluation of a Dutch translated shorter version of the BCTOS questionnaire is presented. This tool gives the patient the opportunity to rate differences between the treated and untreated breast. It covers cosmetic and functional outcome of both the surgical ánd radiation treatment.

At the end of this thesis, in **chapter 11**, we present our conclusions and the future prospects on each subject. A thesis summary is provided in **chapter 12.**

References

1. Netherlands Cancer Registry. Dutch cancer figures [Internet]. 2015 jan 1. Available from: http://www.cijfersoverkanker.nl/p=557b111870359.
2. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524-48.
3. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. *Lancet*. 2000;355(9217):1822.
4. SEER database. Cancer Stat Facts: Female Breast Cancer 2017 [Available from: https://seer.cancer.gov/statfacts/html/breast.html.]

5. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233-41.
6. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med*. 2002;347(16):1227-32.
7. Kim MK, Kim T, Moon HG, Jin US, Kim K, Kim J, et al. Effect of cosmetic outcome on quality of life after breast cancer surgery. *Eur J Surg Oncol*. 2015;41(3):426-32.
8. Sun Y, Kim SW, Heo CY, Kim D, Hwang Y, Yom CK, et al. Comparison of quality of life based on surgical technique in patients with breast cancer. *Jpn J Clin Oncol*. 2014;44(1):22-7.
9. Cipora E, Konieczny M, Karwat ID, Roczniak W, Babuska-Roczniak M. Surgical method of treatment and level of satisfaction with life among women diagnosed with breast cancer, according to time elapsed since performance of surgery. *Ann Agric Environ Med*. 2018;25(3):453-9.
10. Klassen AF, Pusic AL, Scott A, Klok J, Cano SJ. Satisfaction and quality of life in women who undergo breast surgery: a qualitative study. *BMC Womens Health*. 2009;9:11.
11. Cochrane RA, Valasiadou P, Wilson AR, Al-Ghazal SK, Macmillan RD. Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised. *Br J Surg*. 2003;90(12):1505-9.
12. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JH, Jager JJ, et al. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. *Radiother Oncol*. 2000;55(3):219-32.
13. Parvez E, Cornacchi SD, Hodgson N, Thoma A, Kong I, Foster G, et al. A cosmesis outcome substudy in a prospective, randomized trial comparing radioguided seed localization with standard wire localization for nonpalpable, invasive, and in situ breast carcinomas. *Am J Surg*. 2014;208(5):711-8.
14. Staradub VL, Rademaker AW, Morrow M. Factors influencing outcomes for breast conservation therapy of mammographically detected malignancies. *J Am Coll Surg*. 2003;196(4):518-24.
15. Olsen MA LM, Dietz JR, Brandt KE, Aft R, Matthews R, Mayfield J, Fraser VJ. Risk factors for surgical site infection after major breast operation. *Journal of American Ccollege of Surgeons*. 2008:326-35.
16. Reilly J TS, McIntosh J, Kean L. An economic analysis of surgical wound infection. *Journal of Hospital Infections*. 2001:245-9.
17. Avritscher EB, Cooksley CD, Rolston KV, Swint JM, Delclos GL, Franzini L, et al. Serious postoperative infections following resection of common solid tumors: outcomes, costs, and impact of hospital surgical volume. *Support Care Cancer*. 2014;22(2):527-35.
18. Indelicato D, Grobmyer SR, Newlin H, Morris CG, Haigh LS, Copeland EM, 3rd, et al. Association between operative closure type and acute infection, local recurrence, and disease surveillance in patients undergoing breast conserving therapy for early-stage breast cancer. *Surgery*. 2007;141(5):645-53.
19. Hall FM, Frank HA. Preoperative localization of nonpalpable breast lesions. *AJR Am J Roentgenol*. 1979;132(1):101-5.
20. Chan BK, Wiseberg-Firtell JA, Jois RH, Jensen K, Audisio RA. Localization techniques for guided surgical excision of non-palpable breast lesions. *Cochrane Database Syst Rev*. 2015(12):CD009206.
21. De Cicco C, Pizzamiglio M, Trifiro G, Luini A, Ferrari M, Prisco G, et al. Radioguided occult lesion localisation (ROLL) and surgical biopsy in breast cancer. Technical aspects. *Q J Nucl Med*. 2002;46(2):145-51.

22. Cheang E, Ha R, Thornton CM, Mango VL. Innovations in image-guided preoperative breast lesion localization. *The British journal of radiology*. 2018;91(1085):20170740.
23. McGhan LJ, McKeever SC, Pockaj BA, Wasif N, Giurescu ME, Walton HA, et al. Radioactive seed localization for nonpalpable breast lesions: review of 1,000 consecutive procedures at a single institution. *Ann Surg Oncol*. 2011;18(11):3096-101.
24. Bloomquist EV, Ajkay N, Patil S, Collett AE, Frazier TG, Barrio AV. A Randomized Prospective Comparison of Patient-Assessed Satisfaction and Clinical Outcomes with Radioactive Seed Localization versus Wire Localization. *Breast J*. 2016;22(2):151-7.
25. Langhans L, Tvedskov TF, Klausen TL, Jensen MB, Talman ML, Vejborg I, et al. Radioactive Seed Localization or Wire-guided Localization of Nonpalpable Invasive and In Situ Breast Cancer: A Randomized, Multicenter, Open-label Trial. *Ann Surg*. 2017;266(1):29-35.
26. Ong JSL, Teh J, Saunders C, Bourke AG, Lizama C, Newton J, et al. Patient satisfaction with Radioguided Occult Lesion Localisation using iodine-125 seeds ('ROLLIS') versus conventional hookwire localisation. *Eur J Surg Oncol*. 2017;43(12):2261-9.
27. Lovrics PJ, Goldsmith CH, Hodgson N, McCready D, Gohla G, Boylan C, et al. A multicentered, randomized, controlled trial comparing radioguided seed localization to standard wire localization for nonpalpable, invasive and in situ breast carcinomas. *Ann Surg Oncol*. 2011;18(12):3407-14.
28. Schermers B, van der Hage JA, Loo CE, Vrancken Peeters M, Winter-Warnars HAO, van Duijnhoven F, et al. Feasibility of magnetic marker localisation for non-palpable breast cancer. *Breast*. 2017;33:50-6.
29. Driul L, Bernardi S, Bertozzi S, Schiavon M, Londero AP, Petri R. New surgical trends in breast cancer treatment: conservative interventions and oncoplastic breast surgery. *Minerva Ginecol*. 2013;65(3):289-96.
30. Clough KB, Kaufman GJ, Nos C, Buccimazza I, Sarfati IM. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. *Ann Surg Oncol*. 2010;17(5):1375-91.
31. Asgeirsson KS, Rasheed T, McCulley SJ, Macmillan RD. Oncological and cosmetic outcomes of oncoplastic breast conserving surgery. *Eur J Surg Oncol*. 2005;31(8):817-23.
32. Chatterjee A, Dayicioglu D, Khakpour N, Czerniecki BJ. Oncoplastic Surgery: Keeping It Simple With 5 Essential Volume Displacement Techniques for Breast Conservation in a Patient With Moderate- to Large-Sized Breasts. *Cancer Control*. 2017;24(4):1073274817729043.
33. Clough KB, Ihrai T, Oden S, Kaufman G, Massey E, Nos C. Oncoplastic surgery for breast cancer based on tumour location and a quadrant-per-quadrant atlas. *Br J Surg*. 2012;99(10):1389-95.
34. Clough KB, van la Parra RFD, Thygesen HH, Levy E, Russ E, Halabi NM, et al. Long-term Results After Oncoplastic Surgery for Breast Cancer: A 10-year Follow-up. *Ann Surg*. 2018;268(1):165-71.
35. Haley RW CD, Morgan WM, White JW, Emori TG, Hooton TM. Identifying patients at high risk of surgical wound infection. A simple multivariate index of patient susceptibility and wound contamination. *American Journal of Epidemiology*. 1985:206-15.
36. Surgical Site Infection (SSI) Event: Center for Disease Control. 2019 [updated jan 2019. Available from: http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf?agree=yes&next=Accept.]
37. El-Tamer MB WB, Schifftner T, Neumayer L, Khuri S, Henderson W. Morbidity and mortality following breast cancer surgery in women: national benchmarks for standards of care. *Annals of Surgery*. 2007:665-71.
38. Degnim AC, Throckmorton AD, Boostrom SY, Boughey JC, Holifield A, Baddour LM, et al. Surgical site infection after breast surgery: impact of 2010 CDC reporting guidelines. *Ann Surg Oncol*. 2012;19(13):4099-103.
39. Williams N, Sweetland H, Goyal S, Ivins N, Leaper DJ. Randomized trial of antimicrobial-coated sutures to prevent surgical site infection after breast cancer surgery. *Surg Infect (Larchmt)*. 2011;12(6):469-74.

40. Gulluoglu BM, Guler SA, Ugurlu MU, Culha G. Efficacy of prophylactic antibiotic administration for breast cancer surgery in overweight or obese patients: a randomized controlled trial. *Ann Surg*. 2013;257(1):37-43.
41. Vazquez-Aragon P L-GM, Cascales-Sanchez P,Villar-Canovas MT, Garcia-Olmo D. Nosocomial infection and related risk factors in a general surgery service: a prospective study. *Journal of Infection*. 2003:17-22.
42. Xue DQ, Qian C, Yang L, Wang XF. Risk factors for surgical site infections after breast surgery: a systematic review and meta-analysis. *Eur J Surg Oncol*. 2012;38(5):375-81.
43. Dumville JC GT,Walter CJ, Sharp CA, Page T. Dressings for the prevention of surgical site infection. *Cochrane Database of Systematic Reviews*. 2014.
44. Berríos-Torres SI, Umscheid CA, Bratzler DW, Leas B, Stone EC, Kelz RR, et al. Centers for Disease Control and Prevention Guideline for the Prevention of Surgical Site Infection, 2017. *JAMA Surgery*. 2017;152(8):784-91.
45. Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707-16.
46. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56.
47. Group ST, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008;371(9618):1098-107.
48. Group ST, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008;9(4):331-41.
49. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010;362(6):513-20.
50. Fyles AW, McCready DR, Manchul LA, Trudeau ME, Merante P, Pintilie M, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med. 2004;351(10):963-70.
51. Hughes KS, Schnaper LA, Bellon JR, Cirrincione CT, Berry DA, McCormick B, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. J Clin Oncol. 2013;31(19):2382-7.
52. Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabar L, Nordgren H, et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. J Clin Oncol. 1999;17(8):2326-33.
53. Fisher ER, Sass R, Fisher B, Gregorio R, Brown R, Wickerham L. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). II. Relation of local breast recurrence to multicentricity. Cancer. 1986;57(9):1717-24.
54. Bethune WA. Partial breast irradiation for early breast cancer. J Natl Med Assoc. 1991;83(9):768, 800, 8.
55. Pignol JP, Caudrelier JM, Crook J, McCann C, Truong P, Verkooijen HA. Report on the Clinical Outcomes of Permanent Breast Seed Implant for Early-Stage Breast Cancers. Int J Radiat Oncol Biol Phys. 2015;93(3):614-21.
56. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation

with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016;387(10015):229-38.

57. Vicini FA, Chen PY, Fraile M, Gustafson GS, Edmundson GK, Jaffray DA, et al. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. Int J Radiat Oncol Biol Phys. 1997;38(2):301-10.
58. White J, Winter K, Kuske RR, Bolton JS, Arthur DW, Scroggins T, et al. Long-Term Cancer Outcomes From Study NRG Oncology/RTOG 9517: A Phase 2 Study of Accelerated Partial Breast Irradiation With Multicatheter Brachytherapy After Lumpectomy for Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys. 2016;95(5):1460-5.
59. NSABP. Protocol B-39/RTOG 0413, A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer [Available from: http://www.nsabp.pitt.edu/B-39.asp.
60. Vicini F, Winter K, Straube W, Wong J, Pass H, Rabinovitch R, et al. A phase I/II trial to evaluate three-dimensional conformal radiation therapy confined to the region of the lumpectomy cavity for Stage I/II breast carcinoma: initial report of feasibility and reproducibility of Radiation Therapy Oncology Group (RTOG) Study 0319. Int J Radiat Oncol Biol Phys. 2005;63(5):1531-7.
61. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Saunders C, et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). Health Technol Assess. 2016;20(73):1-188.
62. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013;14(13):1269-77.
63. Gitt A, Bose-Ribeiro H, Nieder C, Kup PG, Hermani H, Buhler H, et al. Treatment Results of MammoSite Catheter in Combination with Whole-breast Irradiation. Anticancer Res. 2016;36(1):355-60.
64. Yashar C, Attai D, Butler E, Einck J, Finkelstein S, Han B, et al. Strut-based accelerated partial breast irradiation: Report of treatment results for 250 consecutive patients at 5 years from a multicenter retrospective study. Brachytherapy. 2016;15(6):780-7.
65. Ott OJ, Strnad V, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. GEC-ESTRO multicenter phase 3-trial: Accelerated partial breast irradiation with interstitial multicatheter brachytherapy versus external beam whole breast irradiation: Early toxicity and patient compliance. Radiother Oncol. 2016;120(1):119-23.
66. Polgar C, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(2):259-68.
67. Vargo JA, Verma V, Kim H, Kalash R, Heron DE, Johnson R, et al. Extended (5-year) outcomes of accelerated partial breast irradiation using MammoSite balloon brachytherapy: patterns of failure, patient selection, and dosimetric correlates for late toxicity. Int J Radiat Oncol Biol Phys. 2014;88(2):285-91.
68. Chen PY, Vicini FA, Benitez P, Kestin LL, Wallace M, Mitchell C, et al. Long-term cosmetic results and toxicity after accelerated partial-breast irradiation. Cancer. 2006;106(5):991-9.
69. Ott OJ, Lotter M, Fietkau R, Strnad V. Accelerated Partial-Breast Irradiation with Interstitial Implants. Strahlentherapie und Onkologie. 2009;185(3):170-6.

70. Archambeau JO, Pezner R, Wasserman T. Pathophysiology of irradiated skin and breast. Int J Radiat Oncol Biol Phys. 1995;31(5):1171-85.
71. Pignol JP, Truong P, Rakovitch E, Sattler MG, Whelan TJ, Olivotto IA. Ten years results of the Canadian breast intensity modulated radiation therapy (IMRT) randomized controlled trial. Radiother Oncol. 2016;121(3):414-9.
72. den Hartogh MD, van den Bongard HJ, Davidson MT, Kotte AN, Verkooijen HM, Philippens ME, et al. Full-thickness closure in breast-conserving surgery: the impact on radiotherapy target definition for boost and partial breast irradiation. A multimodality image evaluation. Ann Surg Oncol. 2014;21(12):3774-9.
73. Borger JH, Kemperman H, Smitt HS, Hart A, van Dongen J, Lebesque J, et al. Dose and volume effects on fibrosis after breast conservation therapy. Int J Radiat Oncol Biol Phys. 1994;30(5):1073-81.
74. den Hartogh MD, van Asselen B, Monninkhof EM, van den Bosch MA, van Vulpen M, van Diest PJ, et al. Excised and irradiated volumes in relation to the tumor size in breast-conserving therapy. Breast Cancer Res Treat. 2011;129(3):857-65.
75. Strnad V, Hannoun-Levi JM, Guinot JL, Lossl K, Kauer-Dorner D, Resch A, et al. Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost Partial Breast Irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery. Radiother Oncol. 2015;115(3):342-8.
76. NRG Oncology (2018). NSABP Clinical Trials OverviewProtocol B-39/RTOG 0413 [Available from: http://www.nsabp.pitt.edu/B-39.asp.
77. Major T, Gutierrez C, Guix B, van Limbergen E, Strnad V, Polgar C. Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. Radiother Oncol. 2016;118(1):199-204.
78. Pignol JP, Keller B, Rakovitch E, Sankreacha R, Easton H, Que W. First report of a permanent breast 103Pd seed implant as adjuvant radiation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2006;64(1):176-81.
79. Vicini F, Shah C, Tendulkar R, Wobb J, Arthur D, Khan A, et al. Accelerated partial breast irradiation: An update on published Level I evidence. Brachytherapy. 2016;15(5):607-15.
80. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087-106.
81. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol. 1994;12(3):447-53.
82. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987-98.
83. Grantzau T, Overgaard J. Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: A systematic review and meta-analysis of population-based studies including 522,739 patients. Radiother Oncol. 2016;121(3):402-13.
84. Xu XG, Bednarz B, Paganetti H. A review of dosimetry studies on external-beam radiation treatment with respect to second cancer induction. Phys Med Biol. 2008;53(13):R193-241.
85. Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys. 2006;65(1):1-7.

86. Donovan EM, James H, Bonora M, Yarnold JR, Evans PM. Second cancer incidence risk estimates using BEIR VII models for standard and complex external beam radiotherapy for early breast cancer. Med Phys. 2012;39(10):5814-24.
87. Han EY, Paudel N, Sung J, Yoon M, Chung WK, Kim DW. Estimation of the risk of secondary malignancy arising from whole-breast irradiation: comparison of five radiotherapy modalities, including TomoHDA. Oncotarget. 2016;7(16):22960-9.
88. Pignol JP, Keller BM, Ravi A. Doses to internal organs for various breast radiation techniques--implications on the risk of secondary cancers and cardiomyopathy. Radiat Oncol. 2011;6:5.
89. Hu ES, Pusic AL, Waljee JF, Kuhn L, Hawley ST, Wilkins E, et al. Patient-reported aesthetic satisfaction with breast reconstruction during the long-term survivorship Period. Plast Reconstr Surg. 2009;124(1):1-8.
90. Kanatas A, Velikova G, Roe B, Horgan K, Ghazali N, Shaw RJ, et al. Patient-reported outcomes in breast oncology: a review of validated outcome instruments. Tumori. 2012;98(6):678-88.
91. Ou KW, Yu JC, Ho MH, Chiu WK, Ou KL, Chen TM, et al. Oncological safety and outcomes of nipple-sparing mastectomy with breast reconstruction: a single-centered experience in Taiwan. Ann Plast Surg. 2015;74 Suppl 2:S127-31.
92. Stanton AL, Krishnan L, Collins CA. Form or function? Part 1. Subjective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. Cancer. 2001;91(12):2273-81.
93. Jethwa KR, Kahila MM, Mara KC, Harmsen WS, Routman DM, Pumper GM, et al. Patient-reported outcomes of catheter-based accelerated partial breast brachytherapy and whole breast irradiation, a single institution experience. Breast Cancer Res Treat. 2018;169(1):189-96.
94. Swanick CW, Lei X, Shaitelman SF, Schlembach PJ, Bloom ES, Fingeret MC, et al. Longitudinal analysis of patient-reported outcomes and cosmesis in a randomized trial of conventionally fractionated versus hypofractionated whole-breast irradiation. Cancer. 2016;122(18):2886-94.

CHAPTER THREE

3

A randomized controlled trial on the effect of a silver carboxymethylcellulose dressing on surgical site infections after breast cancer surgery

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Abstract

Introduction: The incidence of surgical site infections (SSIs) after breast cancer surgery is relatively high; ranging from 3 to 19%. The role of wound dressings in the prevention of SSI after breast cancer surgery is unclear. This study compares a silver carboxymethylcellulose dressing (AQUACEL Ag Surgical (Aquacel)) with standard wound dressing in SSI rate after breast cancer surgery.

Methods: A single-center randomized controlled trial among women ≥18 years, diagnosed with breast cancer, undergoing breast conserving or ablative surgery, was conducted in a combined in and outpatient setting. The intervention was the use of Aquacel, compared with standard gauze dressing. Primary outcome measure was SSI following CDC criteria.

Results: A total of 230 patients were analyzed: 106 in the Aquacel group and 124 controls. Seven patients (6.6%) developed SSI in the Aquacel group and 16 patients (12.9%) in the control group (RR 0.51 [95% Confidence Interval (CI): 0.22-1.20]; p=0.112). Unplanned exploratory subgroup analysis of breast conserving surgery patients, showed that SSI rate was lower in the Aquacel group than in controls: 1/56 (1.8%) vs. 7/65 (10.8%); RR 0.51 [95% Confidence Interval (CI): 0.22-1.20]; adjusted Odds Ratio (OR) 0.49 [0.19-1.25] p=0.135. The Aquacel group showed better patient satisfaction (median 8 vs. 7 on a Numerical Rating Scale, p=0.006), fewer dressing changes within 48 hours RR 0.21 [CI:0.11-0.40], adjusted OR 0.12 [0.05-0.27] p<0.001, fewer re-operations (0% vs. 3.2%, p=0.062), and lower mean wound-related treatment costs, both in a high (€265.42 (SD=908) vs. €470.65 (SD=1223) [p<0.001]) and low (€59.12 (SD=129) vs. €67.55 (SD=172) [p<0.001]) attributable costs of SSI model.

Conclusion: In this randomized controlled trial in women undergoing surgery for breast cancer, the use of AQUACEL Ag Surgical wound dressing did not significantly reduce the occurrence of SSIs compared to standard gauze dressing. The use of Aquacel resulted in significantly improved patient satisfaction and reduced wound-related costs.

Introduction

Background

Breast cancer is the most common malignancy among women in western countries, and one out of eight women will develop it during their lifetime. In the Netherlands, nearly 15,000 new cases are identified each year[1]. Breast cancer is the second cause of cancer-related deaths among women and the leading cause of disability-adjusted life years (DALYs) globally[2]. The majority of patients with breast cancer are treated surgically, amongst other treatment modalities. Although surgery of the breast is regarded as a clean procedure[3], a high incidence of surgical site infections (SSIs) is found, making it the most common complication[4]. Previous studies on SSIs in women after breast cancer surgery showed incidences ranging between 3% and 19%[4-7]. This is much higher than the expected 3.4% infection rate associated with clean surgical techniques[8].

SSIs are associated with considerable morbidity and reduced quality of life for patients. SSIs lead to extended hospital stays, re-admissions and re-operations, poor cosmetic results, delay in commencing adjuvant treatment, and they consequently result in additional costs and poorer outcomes[9-11]. Therefore, prevention of SSI has recently gained attention. A recent meta-analysis[12] identified several significant risk factors for SSI after breast cancer surgery, but the type of wound dressings was not evaluated in the included studies. A recent Cochrane Review[13] on the role of wound dressing in the prevention of SSIs revealed that in the current literature, there is no evidence that covering surgical wounds healing by primary intention with wound dressings reduces the rate of SSI, nor that any particular wound dressing is superior to another in this regard. Studies included in this review were mainly outdated and of poor quality. The authors concluded that decision-making should be based on dressing cost and the ability to deal with specific symptoms. High-quality research on the role of wound dressings in the prevention of SSIs is needed. As a result, the CDC guideline has no specific recommendation on the type of dressing or wearing time, except that primarily closed wounds should be sterile dressed for at least 24 to 48 hours[13, 14].

All sorts of wound dressings are available presently, containing different materials and using different application techniques. Characteristics of an ideal wound dressing are the ability to absorb and contain exudate without leakage, a lack of particulate contaminants left in the wound, thermal insulation, impermeability to water and bacteria, suitability with different skin closures (sutures, staples), avoidance of wound trauma on removal, little need for dressing change, provision of pain relief, cosmesis, comfort, and a positive effect on scar tissue formation[15, 16].

AQUACEL Ag Surgical (Aquacel) is a type of wound dressing that is thought to meet these characteristics more than others: in-vitro tests showed that the silver in the dressing inhibits aerobic, anaerobic, gram-negative, and gram-positive bacteria, as well as yeast and fungi within 30 minutes[17, 18]. The antibacterial activity lasts for 14 days[18] and it is occlusive. Several studies found that less changing of the dressing is needed. Furthermore, patient satisfaction was higher when a wound was treated with Aquacel[19, 20]. Despite Aquacel's favorable characteristics, a randomized comparative study of Aquacel with other wound dressings after breast cancer surgery has not yet been performed.

Objectives

Our aim in this study was to compare Aquacel with standard gauze wound dressing in the occurrence of SSI among women after breast cancer surgery. We hypothesize that Aquacel will reduce the occurrence of SSI in this particular group of patients.

Patients and Methods

Trial design

This study was a prospective, open label, randomized, single center active controlled clinical study with a two arm 1:1 parallel group design. It was designed to assess the effectiveness of Aquacel in reducing the risk of SSIs in women after breast cancer surgery. The trial was set to establish the superiority of Aquacel to standard wound care. It was performed in a large secondary teaching hospital (Franciscus Gasthuis, Rotterdam), in a combined inpatient and outpatient setting. The inclusion period was between June 2013 and May 2016, with the last patient completing the 90-day follow-up in August 2016. The study protocol (dossier nr. NL42892.101.12) was reviewed and approved by the Medical Ethics Committee: Toetsingscommissie Wetenschappelijk Onderzoek Rotterdam (TWOR). After approval of the protocol the following changes in the protocol were made: Extension of the randomization list to have the option to extend patient inclusion; addition of two exclusion criteria because of the anticipated differences of a priori SSI risk in neo-adjuvant chemotherapy and immediate reconstructive surgery; planning of an exploratory subgroup analysis of breast conserving surgery and mastectomy, for being clinically relevant. The study was conducted according to the principles of the Declaration of Helsinki (version 10, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

Participants

All women of age 18 years or above who were diagnosed with breast cancer, needing uni- or bilateral ablative or breast conserving surgery in our hospital, were considered eligible for inclusion in our study. Patients were only included after giving a written informed consent.

Patients were excluded if they had local inflammation or ulceration of the breast, previous breast surgery in the previous 3 months, use of antibiotics in the previous 2 weeks, neo-adjuvant chemotherapy, intended immediate reconstructive surgery, a known allergy for Aquacel or silver, and the inability to read or understand the Dutch language to give informed consent or fill out questionnaires.

Interventions (surgical procedures, wound management and follow-up)

Included patients underwent ablative or conservative breast surgery, with or without an axillary procedure. All procedures were performed or supervised by senior surgeons with a case load of more than 50 per year. All patients received a single dose of intravenous antibiotics as

recommended[21](cefazolin 1 gram, by hospital protocol) 1 hour before surgery. In accordance with the CDC guidelines, we considered bilateral procedures as two separate observations[22]. Drain management was performed according to the surgeon's preference.

After surgery, wounds were cleaned with normal saline and patients received their allocated wound care: standard wound dressing, consisting of an eight layer woven cotton gauze fixed with adhesive tape, or Aquacel. AQUACEL Ag Surgical is a hydrocolloid dressing with hydrofiber technology that delivers ionic silver when it comes in contact with the wound (e.g., exudate). The occlusive dressing protects the skin surrounding the wound, by moisture retention. The material is soft and pliable and can therefore be adjusted to the size of the wound[17, 18].

Both standard wound dressing and Aquacel were kept in place for 7 days by protocol, unless saturated by excessive exudate. Between the 7th and 10th days after surgery, follow-up was scheduled at the outpatient clinic. Unblinded, the wound(s) were inspected on signs of an infection following CDC criteria[14, 22] by the independent surgeon or attending physician and any clinical diagnosis of SSI was made. Patients, who were unblinded, filled out a questionnaire on patient satisfaction. Re-admissions/operations, the occurrence of SSI diagnosis after the clinical assessment, and the use of antibiotics were scored 30 days after surgery in two ways: a blinded review of patient's record by an independent physician and a telephone consult with the patient by an independent blinded nurse. Patient records were also checked for deep infections on the 90th postoperative day, by an independent blinded physician, to fulfil reporting guidelines[22].

Outcomes

The primary outcome of this study was the incidence (risk) of SSI. Secondary outcome measures were patient satisfaction, the re-admission and re-operation rate, antibiotic use within 30 days, the need for changing the dressing within the first 48 hours, wearing time of first applied dressing, and costs. For managerial purposes, we added a cost analysis. Aquacel costs €23.25 per dressing. Standard wound care costs €1.28 per dressing. Mean wound-related treatment costs were calculated with the following equation:

dressing price(1+proportion dressing change<48h)+ proportion SSI*attributable cost of SSI,* with attributable cost of SSI after breast surgery in a low (€510/$574[11]) and high(€3634/$4091[10]) cost model, based on the existing literature.

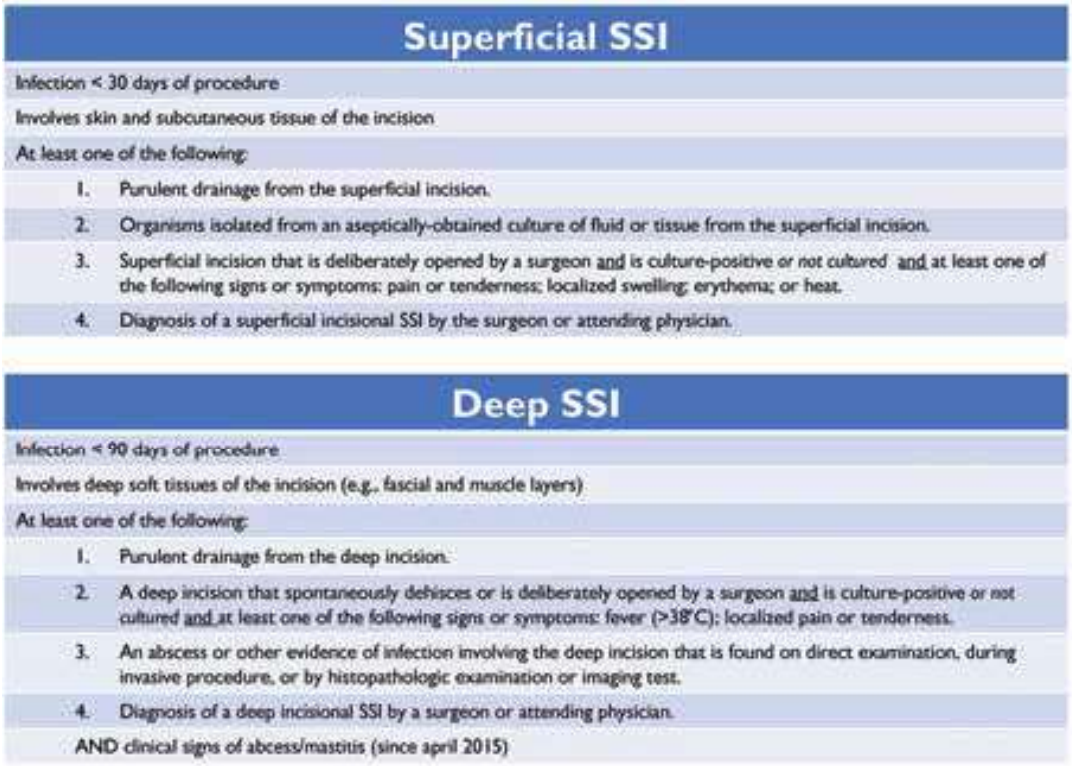
Assessment of SSI

SSI outcome was scored by a blinded and independent physician, using the CDC criteria following the reporting instructions after breast procedures: 30 days follow-up for superficial incisional SSI, and 90 days for a deep incisional SSI [14, 22] (Fig. 1). Final scoring was based on the information captured from 1) the unblinded clinical observation recorded during the follow-up visit at day 7-10 after surgery, 2) the blinded review of patients record and telephone consult on day 30 after surgery, and 3) the blinded review of patients record after completing 90 day follow-up.

Patient satisfaction

Overall satisfaction regarding the wound dressing was scored by the patient on a 10-point numerical rating scale (NRS) from 0 (complete dissatisfaction) to 10 (complete satisfaction), on days 7-10 after the procedure. The 10-point NRS is commonly used in similar studies[23-28] and was externally validated to other patient surveys in the study by Keurentjes[29] who found correlations of 0.52 and 0.64, which can be interpreted as moderate to substantial correlation according to the Landis and Koch guidelines[30].

Figure 1 CDC criteria for an SSI[14, 22], a Diagnosis of 'cellulitis' alone does not meet criterion 4 since 2010, but this change underestimates the infection rate and is not recommended to be used by Degnim[5].



Superficial SSI
Infection < 30 days of procedure
Involves skin and subcutaneous tissue of the incision
At least one of the following:
1. Purulent drainage from the superficial incision.
2. Organisms isolated from an aseptically-obtained culture of fluid or tissue from the superficial incision.
3. Superficial incision that is deliberately opened by a surgeon and is culture-positive or not cultured and at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat.
4. Diagnosis of a superficial incisional SSI by the surgeon or attending physician.

Deep SSI
Infection < 90 days of procedure
Involves deep soft tissues of the incision (e.g., fascial and muscle layers)
At least one of the following:
1. Purulent drainage from the deep incision.
2. A deep incision that spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not cultured and at least one of the following signs or symptoms: fever (>38°C); localized pain or tenderness.
3. An abscess or other evidence of infection involving the deep incision that is found on direct examination, during invasive procedure, or by histopathologic examination or imaging test.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.
AND clinical signs of abcess/mastitis (since april 2015)

Sample size

A 10% (12.5% to 2.5%) absolute reduction of occurrence of wound infection was considered to be clinically relevant. To reject the null hypothesis (risk of SSI is equal between the wound dressing strategies) with an accepted type I error of 5% (two-sided) and type 2 error of 20%, at least 106 patients per treatment arm would be required (randomization ratio 1:1) (www.sealedenveloppe.com, Chi^2-test). No interim analysis was planned.

Randomization (sequence generation, allocation, implementation) and blinding

A randomization list for up to 400 patients with an allocation ratio of 1:1 was computer generated (www.sealedenveloppe.com) with stratification by age > 60 years of age, smoking, diabetes, use of

corticosteroids, and the type of operation (lumpectomy vs mastectomy). The independent nurse created 400 instead of 212 numbers, under supervision of the study supervisor to compensate for and anticipate on the possibility to extend patient inclusion, any unplanned exploratory subgroup analysis and to guarantee a sufficient number of study numbers in each stratum. Patients were enrolled by physicians and group assignment was performed by the independent nurse. Allocation was performed on the day of surgery; for concealed allocation, the operation department was informed by the independent nurse just before applying the dressing. Surgeons were blinded for treatment allocation during surgery until the moment of applying the dressing, not during follow-up. Patients could not be blinded because of the nature of the intervention.

Statistical methods

Statistical analysis was performed according to the intention-to-treat principle. Because protocol compliance was high, per-protocol analysis was avoided. As bilateral cases only occurred in two patients, adjusted statistics through repeated measurements analysis were not performed. Efforts were made to minimize missing data, by recalling patients not attending follow-up. If complete follow-up data were missing, patients were excluded from the analysis. Otherwise, patients were analyzed only on available data. Differences in the baseline characteristics and the primary and secondary outcome measures between the allocated study groups were compared with the chi-squared test for nominal/ordinal variables (e.g. proportions of SSI, re-operations, early dressing change), the independent Student's t-test for continuous variables with normal distributions (age), and the nonparametric Mann-Whitney U test for continuous variables with skewed distributions (e.g. operation duration, patient satisfaction, mean costs). Differences in outcome measures between groups were estimated using a logistic regression analysis (enter analysis) with the respective outcome measure as dependent variable and randomization factors and type of wound dressing as independent variables. Adjusted odds ratios with 95%CIs and p-values are reported. Differences in wearing time of the first dressing between groups were estimated using Cox regression analysis with dressing change as event, randomization factors as covariables and wearing time as time to event. Associations between the potential risk factors and the presence of SSI were quantified in terms of odds ratios (ORs with 95%CIs) and tested using binary multiple logistic regression analysis. Risk factors with a p-value <0.1 in univariate analysis were included in the logistic regression model (enter analysis). An unplanned exploratory subgroup analysis, as well as an unplanned effect modifier analysis was performed to detect differences in the primary outcome measure between breast conserving and ablative surgery, because of its high clinical relevance. Effect modification was modelled as an interaction effect of mode of breast surgery (lumpectomy vs. mastectomy) x allocated wound dressing (Aquacel vs. standard). A p-value < 0.05 (two-sided) was considered to be significant. Statistical analyses were performed using IBM-SPSS version 24 (IBM Corporation, Armonk, New York, USA).

Results

Participant flow

A total of 295 patients underwent breast cancer surgery in our hospital, of which 59 patients were excluded. Fig. 2 shows the study profile: 236 patients were randomized, 107 patients to the Aquacel group and 129 patients to the control group. Total loss to follow-up was 6/236 (2.5%), these patients were excluded from the analysis. Based on the available data in the medical records of these patients, no SSI occurred in these patients. Protocol compliance was 227/230 (98.7%). Finally, 230 patients were analyzed on a intention-to-treat basis. There were no missing data in the primary outcome and secondary outcome measures (except dressing change), from which we conclude that analysis of available data only is not likely to have caused bias in the results.

Figure 2 Patient flowchart (CONSORT)

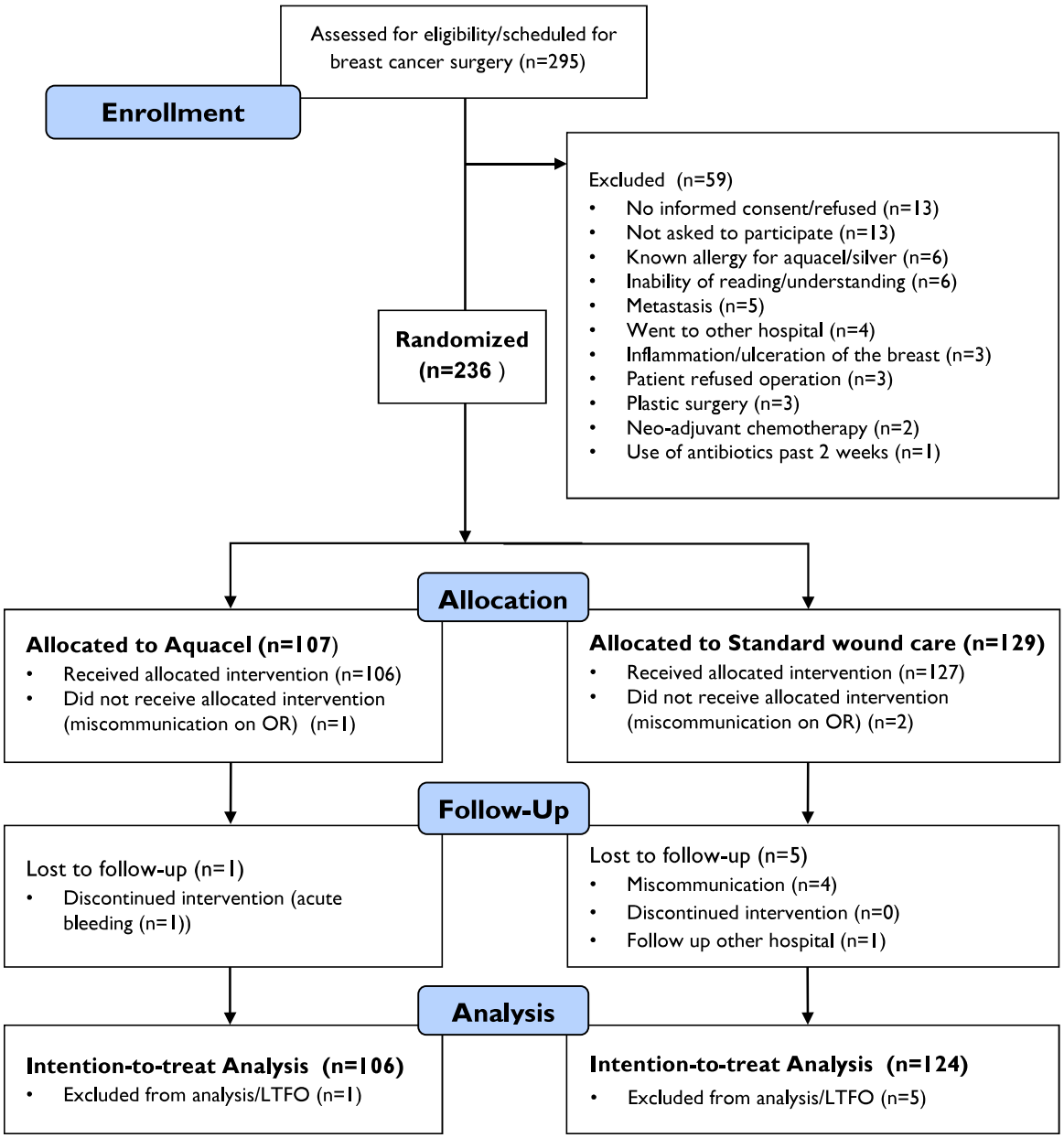


Table 1 Shows the baseline characteristics of patients. As expected, there were no differences between the groups.

	Aquacel (n=106)	Control group (n=124)
Mean age, years(SD)	59 (12)	60 (13)
BMI >30	26/106 (24.5%)	29/124 (23.4%)
Diabetes	5/106 (4.7%)	6/124 (4.8%)
Current smoker	15/106 (14.2%)	19/124 (15.3%)
Corticosteroid use	1/106 (0.9%)	2/124 (1.6%)
ASA classification		
1	46/106 (43.4%)	47/124 (37.9%)
2	50/106 (47.2%)	68/124 (54.8%)
3	10/106 (9.4%)	9/124 (7.3%)
Positive *S.aureus* nasal culture	11/65 (16.9%)	16/83 (19.3%)
Type of surgery		
Lumpectomy + SLNB	52/106 (49.1%)	61/124 (49.2%)
Mastectomy +SLNB	35/106 (33.0%)	39/124 (31.5%)
Mastectomy+ALND	14/106 (13.2%)	20/124 (16.1%)
Lumpectomy + ALND	2/106 (1.9%)	3/124 (2.4%)
Lumpectomy	2/106 (1.9%)	1/124 (0.8%)
Mastectomy	1/106 (0.9%)	
Operation time, median in min (range)	78 (25-224)	73 (35-293)
Wounddrain	49/106 (46.2%)	54/124 (43.5%)
Drainage time in days, median (range)	2 (1-21)	2 (1-13)
Clinical stage (TNM)		
I	58/106 (54.7%)	65/124 (52.4%)
II	34/106 (32.1%)	45/124 (36.3%)
II	14/106 (13.2%)	14/124 (11.3%)

SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection,

Outcomes and estimation

Table 2 displays the outcome measures between the groups. A total of 7 patients (6.6%) developed an SSI in the Aquacel group, and 16 patients (12.9%) developed an SSI in the control group (RR 0.51 [95% Confidence Interval (CI): 0.22-1.20]; adjusted Odds Ratio (OR) 0.49 [0.19-1.25] p=0.135). The majority of SSIs were superficial in both groups. In the Aquacel group, only one patient (0.9%) had a deep SSI, compared to four patients (3.2%) in the control group (RR 0.29 [CI: 0.03-2.58], adjusted OR 0.28 [0.03-2.54] p=0.257).

Furthermore, the Aquacel group scored significantly better than controls on patient satisfaction (median score of 8 vs. 7 [p=0.006] and need for changing the dressing within the first 48 hours (9.6%, vs. 45.9% [RR 0.21 (CI: 0.11-0.40), adjusted OR 0.12 [0.05-0.27] p<0.001). For the outcome

measure dressing change, a sensitivity analysis was performed showing an observed difference between the allocated groups of 9/94 (9.6%) and 45/98 (45.9%); a minimal estimated difference of 21/106 (19.8%) Aquacel vs 45/124 (36.3%) control; and a maximal estimated difference of 9/106 (8.5%) vs 71/124 (57.3%).

For the whole group lowering the need for early changing of the dressing was associated with higher patient satisfaction (median score of 8 in the 'no early change' vs. 7 in the 'early change' group; p=0.003.A non-significant reduction in re-operation rate was found (0% vs. 3.2%, p=0.062). Of the 23 patients with an SSI in this study, 15 had a positive bacterial culture result. Among these patients, *Staphylococcus aureus* and *Pseudomonas aeruginosa* were found most frequently, in 10/15 cases (67%) and in 3/15 cases (20%), respectively. Other culture results can be found in Table 3.

Table 2. Outcome measures and comparison between the groups

	Aquacel (n=106)	**Control (n=124)**	**RR [CI]**	**Adjusted OR [CI]**	**p-value[a]**
SSI					
Total	**7/106 (6.6%)**	**16/124 (12.9%)**	**0.51 [0.22-1.20]**	**0.49 [0.19-1.25]**	**0.135**
Superficial	6/106 (5.7%)	12/124 (9.7%)	0.59 [0.23-1.51]	0.58 [0.21-1.64]	0.306
Deep	1/106 (0.9%)	4/124 (3.2%)	0.29 [0.03-2.58]	0.28 [0.03-2.54]	0.257
Patient Satisfaction	**8 (1-10)**	**7 (0-10)**	**n.a.**	**n.a.**	**0.006[b]**
Re-admissions	7/106 (6.6%)	4/124 (3.2%)	2.05 [0.62-6.80]	2.21 [0.61-7.93]	0.225
Re-operations	**0/106 (0%)**	**4/124 (3.2%)**	**n.a.**	**n.a.**	**0.062**
Antibiotics use	12/106 (11.3%)	14/124 (11.3%)	1.00 [0.49-2.07]	1.04 [0.45-2.39]	0.934
Dressing change<48h	**9/94 (9.6%)**	**45/98 (45.9%)**	**0.21 [0.11-0.40]**	**0.12 [0.05-0.27]**	**<0.001**
Wearing time first dressing	**7 (1-7)**	**3 (0-7)**	**n.a.**	**0.42 [0.31-0.57]**	**<0.001[c]**

[a]*p*-values were calculated using the logistic regression model, unless stated otherwise,[b] Mann Whitney U test, [c]Cox regression model

Table 3. Microbiological culture results of SSI cases

Micro-organism	Overall (n=15) [a]	Aquacel (n=6) [a]	Control (n=9) [a]
Staphylococcus aureus	**10/15 (66.7%)**	**4/6 (66.7%)**	**6/9 (66.7%)**
Pseudomonas aeruginosa	**3/15 (20.0%)**	1/6 (16.7%)	**2/9 (22.2%)**
Serratia marcescens	2/15 (13.3%)	1/6 (16.7%)	1/9 (11.1%)
β-hemolytic Streptococcus group B	1/15 (6.7%)		1/9 (11.1%)
β-hemolytic Streptococcus group A	1/15 (6.7%)	1/6 (16.7%)	
Haemophilus parainfluenzae	1/15 (6.7%)		1/9 (11.1%)
Citrobacter freundii	1/15 (6.7%)	1/6 (16.7%)	
Enterobacter aerogenes	1/15 (6.7%)		1/9 (11.1%)
Acinetobacter baumannii	1/15 (6.7%)		1/9 (11.1%)

[a]% do not add to 100%. One SSI patient may have two or more microorganisms as the causative agent.

Ancillary analyses

Logistic regression analysis

The following potential risk factors for SSI were analyzed: Age > 60 years, BMI > 30, presence of diabetes mellitus, current smoking, corticosteroid use, positive *s.aureus* nasal culture, ASA class (2 or more), use of post-operative drain, prolonged drainage time (≥ 3 days), operation time, histological diagnosis, high clinical TNM stage (3 or more), dressing change within the first 48 hours, type of surgery (lump yes/no), any axillary procedure yes/no (no was only 3 patients) and ALND vs no ALND Univariate analysis identified the following potential risk factors for SSI (p>0.1): use of post-operative drain (p=0.016), prolonged drainage time (≥ 3 days) (p=0.002), operation time (p=0.050), high clinical TNM stage (3 or more) (p=0.015), dressing change within the first 48 hours (p=0.036), any axillary procedure (p=0.013)Of these risk factors, prolonged drainage time (≥ 3 days) (adjusted OR 5.722 [1.406-23.297] p=0.015)) and dressing change within the first 48 hours (adjusted OR 2.979 [1.022-8.685] p=0.046) were found to be independent risk factors for SSIs in a logistic regression analysis.

Subgroup and effect modifier analysis

Unplanned exploratory subgroup analysis of type of surgery was performed. In the subgroup of breast conserving surgery, the SSI rate was lower in the Aquacel group than in controls: 1/56 (1.8%) vs. 7/65 (10.8%), RR 0.17 [CI: 0.03-0.99], adjusted OR 0.15 [0.02-1.31] p=0.087. This would result in a number needed to treat (NNT) of 11.1 [CI 5.8-145.4] patients to prevent one SSI in this subgroup. Patient satisfaction was significantly higher in the Aquacel group (median score 8 vs. 7, p=0.003) and the need for changing the dressing within the first 48 hours was lower (6.1% vs. 37.3%, p<0.001). The large reduction of SSI risk was not found in the group of

patients undergoing mastectomy: 6/50 (12%) vs. 9/59 (15.3%); RR 0.89 [CI: 0.56-1.40], adjusted OR 0.77 [0.25-2.35] p=0.647.
Effect modifier analysis showed that the interaction breast conserving surgery*Aquacel resulted in an adjusted OR 0.13 [0.02-1.14] p=0.065, suggesting a trend that the use of Aquacel wound dressing is more effective in reducing SSIs when applied to patients who received breast conserving therapy.

Costs

Mean wound-related treatment costs were significantly lower in the Aquacel group than in the controls, both in the high (€265.42 (SD=908) vs. €470.65 (SD=1223) [p<0.001]) and low (€59.12 (SD=129) vs. €67.55 (SD=172) [p<0.001]) attributable costs of the SSI model.

Harms

There were no important harms or unintended effects in both groups.

Discussion

We found an SSI risk of 6.6% for the Aquacel group and 12.9% for the control group. The SSI rate in the control group is comparable to previous studies in the recent literature using CDC criteria for definition of SSI[5-7]. The incidence of SSI after breast cancer surgery is high, and although breast surgery is regarded as a clean surgical procedure, SSI is a relatively common complication. In our study we found that the use of AQUACEL AG Surgical dressing approximately reduces 50% of the incidence of SSI compared with standard dressing in women after surgery for breast cancer (RR 0.51), although we were not able to detect a significant difference. Exploring the effect in the subgroup of patients undergoing breast conserving surgery showed a relative reduction of 83% (RR 0.17) that was also not significant. Furthermore, with Aquacel, the need to change dressings within the first 48 hours was significantly lower, as was the need for re-operation (though not as significantly). Patient satisfaction was higher and the mean costs were lower with Aquacel, both significantly. Overall, Aquacel improves patient satisfaction and reduces dressing changes, but did not significantly reduce SSI risk in this particular patient group.

Strengths and limitations

To our knowledge, this is the first well-designed RCT that shows a substantial reduction in SSI after breast cancer surgery using a certain type of wound dressing. Major strengths of this study, apart from its randomized design, are the inclusion of all types of breast cancer surgery, the use of very strict criteria for SSI (CDC) as the primary outcome, complete (90 days) follow-up, very few patients being lost to follow-up, and high protocol compliance.
One study weakness is the fact that during follow-up, patients and surgeons or attending physicians were not blinded when assessing satisfaction and infectious signs. This could potentially lead

to optimistic satisfaction scoring by the patient for the new therapy, resulting in an incorrect significant difference. The lack of blinding by the physicians during follow-up could potentially lead to underreporting the clinical diagnosis of infection in the interventional group. However, scoring of the outcome measure SSI itself was done by a blinded physician, not involved in the surgical procedures or follow-up clinical observations. Furthermore, we aimed to minimize the risk of bias in outcome assessment by the physician and nurse by using very strict criteria for both clinical observation scoring and SSI outcome scoring (CDC). A second weakness is that although the SSI rate in the control group was estimated quite accurate, detecting a 10% absolute reduction starting from 12.5% was rather ambitious. The definition of a minimal clinically relevant reduction was extensively debated in our study group at the time of protocol development. Eventually we opted for a 10% absolute reduction. It is a rather conservative estimate in the sense that every surgeon will support that a 10% absolute reduction is clinically meaningful. The disadvantage of this conservative approach is that the study is likely to overlook smaller, but maybe also clinically relevant, risk reductions. Our study showed a relative risk reduction of approximately 50%. A total of 694 patients would have been needed to demonstrate a significant reduction of this size. A third limitation is that the large randomization list resulted in a slight skewness of treatment allocation. However, comparison of baseline characteristics showed that treatment groups were comparable and the randomization was not subverted. Lastly, SSI can result in a delay in adjuvant treatment and consequently an impaired oncological outcome[24, 31]. However, we did not specifically analyze the impact of this delay.

Interpretation and generalizability

Generalization of our findings should be done with caution, as we acknowledge the fact that there is a lack of clear evidence about the value of dressings in surgical practice, and some surgeons use glue or no dressings[32], as opposed to the simple dressing which we have used as control intervention.

Interpretation of SSI reduction rates should be balanced against the nature of the intervention, the setting and the related morbidity, quality of life and costs. There is no guideline providing any strict recommendation on how this interpretation can be achieved. In recent years it has been increasingly recommended by several authors[33-36] to also judge the clinical relevance of study findings. In our study, there is no disadvantage/harm for patients through the intervention and there is proven benefit in terms of patient satisfaction and costs. Therefore, given the fact that our study is underpowered for the detection of a minimal clinically meaningful difference, i.e. 5%, we consider the rather large effect size of SSI reduction in our study to be relevant.

The discrepancy in treatment effect found by the exploratory subgroup analysis between breast conserving surgery and ablative surgery might be explained by the fact that other factors than the type of wound dressing contribute more to the development of SSI in ablative surgery: compromised vascularization of skin and subcutaneous tissue by extensive dissection, seroma and hematoma formation, and prolonged drainage time[4, 12, 37]. It seems that with the importance of these factors, the

type of wound dressing plays a negligible or modest role in reducing the risk of infection after breast ablative surgery. Research in that patient group should focus on reducing these specific risk factors. As expected, using Aquacel lowered the need for changing the dressing. Early change of the dressing (within the first 48 hours after surgery) was shown to be an independent risk factor for SSI occurrence in this study. This could be an explanation of the reduction in SSI occurrence in the Aquacel group, besides the antibacterial effect of the silver. Recommendation of the CDC to sterile dress primarily closed wounds for at least 24-48 hours could be extended to not change the dressing in the first 48 hours, as early change of the dressing was shown to be an independent risk factor for SSI in our study. Furthermore, lowering the need for early changing of the dressing was associated with an improvement in patient satisfaction of more than 5%, which in literature on quality of life and utility is considered to be a relevant difference[38, 39].

Our findings are highly relevant for healthcare providers, with significant differences in favor of the Aquacel group on two of the recently proposed outcome measures to assess wound management by Elliot[32]: patient satisfaction with the dressing and dressing removal Based on our exploratory subgroup analysis, the treatment effect of silver containing dressings on SSI rates might be different between breast conserving surgery and mastectomy. Our results stimulate early drain removal and discourage the early change of dressings. Furthermore, reduced costs and improved patient satisfaction are very relevant in healthcare nowadays. Finally, our study confirms the findings of studies in orthopedic surgery that found that Aquacel reduced the occurrence of SSI[20, 40].

In summary, clinicians should be aware of the difference in risk factors for SSI between breast conserving and ablative surgery and the role of Aquacel dressings in improving patient satisfaction, reducing dressing changes and possibly reducing SSI after breast cancer surgery.

Conclusion

In this randomized controlled trial in women undergoing surgery for breast cancer, the use of AQUACEL Ag Surgical wound dressing did not significantly reduce the occurrence of SSIs compared to standard gauze dressing. The use of Aquacel resulted in significantly improved patient satisfaction, reduced dressing changes and reduced wound-related costs.

References

1. Netherlands Cancer Registry. Dutch cancer figures [Internet]. 2015 jan 1. Available from: http://www.cijfersoverkanker.nl/p=557b111870359.
2. Global Burden of Disease Cancer C, Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, et al. The Global Burden of Cancer 2013. JAMA Oncol. 2015;1(4):505-27.
3. Haley RW CD, Morgan WM, White JW, Emori TG, Hooton TM. Identifying patients at high risk of surgical wound infection. A simple multivariate index of patient susceptibility and wound contamination. American Journal of Epidemiology. 1985:206-15.

4. El-Tamer MB WB, Schifftner T, Neumayer L, Khuri S, Henderson W. Morbidity and mortality following breast cancer surgery in women: national benchmarks for standards of care. Annals of Surgery. 2007:665-71.
5. Degnim AC, Throckmorton AD, Boostrom SY, Boughey JC, Holifield A, Baddour LM, et al. Surgical site infection after breast surgery: impact of 2010 CDC reporting guidelines. Ann Surg Oncol. 2012;19(13):4099-103.
6. Gulluoglu BM, Guler SA, Ugurlu MU, Culha G. Efficacy of prophylactic antibiotic administration for breast cancer surgery in overweight or obese patients: a randomized controlled trial. Ann Surg. 2013;257(1):37-43.
7. Williams N, Sweetland H, Goyal S, Ivins N, Leaper DJ. Randomized trial of antimicrobial-coated sutures to prevent surgical site infection after breast cancer surgery. Surg Infect (Larchmt). 2011;12(6):469-74.
8. Vazquez-Aragon P L-GM, Cascales-Sanchez P,Villar-Canovas MT, Garcia-Olmo D. Nosocomial infection and related risk factors in a general surgery service: a prospective study. Journal of Infection. 2003:17-22.
9. Avritscher EB, Cooksley CD, Rolston KV, Swint JM, Delclos GL, Franzini L, et al. Serious postoperative infections following resection of common solid tumors: outcomes, costs, and impact of hospital surgical volume. Support Care Cancer. 2014;22(2):527-35.
10. Olsen MA LM, Dietz JR, Brandt KE, Aft R, Matthews R, Mayfield J, Fraser VJ. Risk factors for surgical site infection after major breast operation. Journal of American Ccollege of Surgeons. 2008:326-35.
11. Reilly J TS, McIntosh J, Kean L. An economic analysis of surgical wound infection. Journal of Hospital Infections. 2001:245-9.
12. Xue DQ, Qian C, Yang L, Wang XF. Risk factors for surgical site infections after breast surgery: a systematic review and meta-analysis. Eur J Surg Oncol. 2012;38(5):375-81.
13. Dumville JC GT, Walter CJ, Sharp CA, Page T. Dressings for the prevention of surgical site infection. Cochrane Database of Systematic Reviews. 2014.
14. Mangram AJ HT, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. American Journal of Infection Control. 1999:97-132.
15. BNF. British National Formulary. Appendix 8: Wound management products and elastic hosiery2010.
16. NICE. NICE clinical guideline 74. Surgical site infection: Prevention and treatment of surgical site infection [Internet]. 2008. Available from: https://www.nice.org.uk/guidance/cg74.
17. Bowler P. Microbicidal properties of a silver-containing hydrofiber dressing against a variety of burn wound pathogens. . J Burn Care Rehabil 2004:192–6.
18. Barnea Y, Weiss J, Gur E. A review of the applications of the hydrofiber dressing with silver (Aquacel Ag) in wound care. Ther Clin Risk Manag. 2010;6:21-7.
19. Clarke JV, Deakin AH, Dillon JM, Emmerson S, Kinninmonth AW. A prospective clinical audit of a new dressing design for lower limb arthroplasty wounds. J Wound Care. 2009;18(1):5-8, 10-1.
20. Springer BD, Beaver WB, Griffin WL, Mason JB, Odum SM. Role of Surgical Dressings in Total Joint Arthroplasty: A Randomized Controlled Trial. Am J Orthop (Belle Mead NJ). 2015;44(9):415-20.
21. Jones DJ, Bunn F, Bell-Syer SV. Prophylactic antibiotics to prevent surgical site infection after breast cancer surgery. Cochrane Database Syst Rev. 2014(3):CD005360.
22. Prevention Centers for Disease Control and. Surgical Site Infection (SSI) Event. Guidelines and procedures for monitoring SSI. 2016 [cited 2016 31 May]. Available from: http://www.cdc.gov/nhsn/PDFs/pscManual/9pscSSIcurrent.pdf.
23. Berry DP, Bale S, Harding KG. Dressings for treating cavity wounds. J Wound Care. 1996;5(1):10-7.

24. Cannavo M, Fairbrother G, Owen D, Ingle J, Lumley T. A comparison of dressings in the management of surgical abdominal wounds. J Wound Care. 1998;7(2):57-62.
25. Langlois J, Zaoui A, Ozil C, Courpied JP, Anract P, Hamadouche M. Randomized controlled trial of conventional versus modern surgical dressings following primary total hip and knee replacement. Int Orthop. 2015;39(7):1315-9.
26. Specht K, Kjaersgaard-Andersen P, Kehlet H, Wedderkopp N, Pedersen BD. High patient satisfaction in 445 patients who underwent fast-track hip or knee replacement. Acta orthopaedica. 2015;86(6):702-7.
27. van Berckel MM, Bosma NH, Hageman MG, Ring D, Vranceanu AM. The Correlation Between a Numerical Rating Scale of Patient Satisfaction With Current Management of an Upper Extremity Disorder and a General Measure of Satisfaction With the Medical Visit. Hand (New York, NY). 2017;12(2):202-6.
28. Viciano V, Castera JE, Medrano J, Aguilo J, Torro J, Botella MG, et al. Effect of hydrocolloid dressings on healing by second intention after excision of pilonidal sinus. Eur J Surg. 2000;166(3):229-32.
29. Keurentjes JC. Patient acceptable symptom states after total hip or knee replacement at mid-term follow-up: Thresholds of the Oxford hip and knee scores. 2014;3(1):7-13.
30. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
31. Tsoutsou PG, Belkacemi Y, Gligorov J, Kuten A, Boussen H, Bese N, et al. Optimal sequence of implied modalities in the adjuvant setting of breast cancer treatment: an update on issues to consider. Oncologist. 2010;15(11):1169-78.
32. Elliott D, Bluebelle Study G. Developing outcome measures assessing wound management and patient experience: a mixed methods study. BMJ Open. 2017;7(11):e016155.
33. Allan GM, Finley CR, McCormack J, Kumar V, Kwong S, Braschi E, et al. Are potentially clinically meaningful benefits misinterpreted in cardiovascular randomized trials? A systematic examination of statistical significance, clinical significance, and authors' conclusions. BMC Med. 2017;15(1):58.
34. Grocott HP. Understanding the Significance of Aerosolized Vasodilator Use in Pulmonary Hypertension: What Is Numerically, Statistically, and Clinically Meaningful? Anesth Analg. 2017;125(6):2167.
35. Hung M, Bounsanga J, Voss MW. Interpretation of correlations in clinical research. Postgrad Med. 2017;129(8):902-6.
36. Mellis C. Lies, damned lies and statistics: Clinical importance versus statistical significance in research. Paediatr Respir Rev. 2018;25:88-93.
37. Mukesh MB, Barnett G, Cumming J, Wilkinson JS, Moody AM, Wilson C, et al. Association of breast tumour bed seroma with post-operative complications and late normal tissue toxicity: results from the Cambridge Breast IMRT trial. Eur J Surg Oncol. 2012;38(10):918-24.
38. Horsman J, Furlong W, Feeny D, Torrance G. The Health Utilities Index (HUI): concepts, measurement properties and applications. Health and quality of life outcomes. 2003;1:54.
39. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2005;14(6):1523-32.
40. Cai J, Karam JA, Parvizi J, Smith EB, Sharkey PF. Aquacel surgical dressing reduces the rate of acute PJI following total joint arthroplasty: a case-control study. J Arthroplasty. 2014;29(6):1098-100.

CHAPTER FOUR

4

Long-term risks of secondary cancer for various whole and partial breast irradiation techniques

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Abstract

Introduction: For early stage breast cancer patients, non-breast cancer mortality including secondary cancers and cardiac events can overshadow the benefit of adjuvant radiotherapy. This study evaluates the excess risk of secondary cancer for various breast radiotherapy techniques including accelerated partial breast irradiation (APBI).

Methods: Secondary cancers Lifetime Attributable Risks (LAR) were calculated using a modified BEIR-VII formalism to account for the specific survival of breast cancer patients. Those survivals were extracted from the SEER database. Doses scattered to various organs were measured into a Rando phantom with custom-made breast phantoms. Treatments delivered typical doses of brachytherapy APBI (34 Gy in 10 fractions), external beam APBI (38.5 Gy in 10 fractions) using 3D-conformal, Cyberknife stereotactic (CK), or VMAT, as well as whole breast irradiation (WBI) delivering 42.5 Gy in 16 fractions.

Results: WBI resulted in the highest total LAR, with 4.3% excess risk of secondary cancer for a patient treated at age 50 years. Lung cancers accounted for 75–97% of secondary malignancies. For a typical early stage patient irradiated at 50, the excess risks of secondary lung cancer were 1.1% for multicatheter HDR, between 2.2% and 2.5% for 3D-CRT or CK, 3.5% for VMAT APBI, and 3.8% for WBI.

Conclusion: APBI reduces the risk of secondary cancer 2–4 fold compared to WBI. These techniques are well suited for long-living early stage breast cancer patients. HDR brachytherapy and 3D-conformal APBI achieve mean lung doses between 1 and 1.5 Gy, which could serve as reference.

Introduction

Today breast cancer is frequently diagnosed at an early stage and has an excellent prognosis. SEER data show that 60% of the patients are diagnosed at a localized stage, without extension to the regional nodes, and the 5-year cancer specific survival for those patients is 98.9%[1]. Standard treatment includes limited surgery followed by whole breast irradiation (WBI). Long-term follow-up of large randomized trials comparing lumpectomy with or without adjuvant radiotherapy has shown that the benefit of radiotherapy is eclipsed by non-breast cancer mortality[2, 3]. The most common causes of non-breast cancer mortality include major cardiac events and secondary cancers[4-6]. To reduce cardiac toxicity, the radiation oncology community has massively adopted preventive measures like breath-hold[7, 8]. The issue of secondary cancer has not yet led to changes regarding the breast irradiation technique.

Accelerated partial breast irradiation (APBI) has been recently proposed for selected patients with favorable characteristics, and results of the few randomized trials suggest non-inferiority in local control compared to WBI[9-12]. Introducing new irradiation techniques may result in differences in the amount of dose to the whole body and thus to differences in the risk of radiation-induced secondary cancer[6, 13]. Scarce comparisons of secondary cancer risks for different techniques have been published[14-16]. They focused either exclusively on whole breast radiotherapy techniques or evaluated the scatter dose theoretically using Monte Carlo simulation. Currently there is no thorough comparison between whole breast radiotherapy and APBI.

The aim of this study is to evaluate the risk of secondary cancer of whole breast radiotherapy and several APBI techniques, using a modified BEIR VII formalism accounting for the specific survival of a breast cancer population, and experimentally measure the scatter dose to various organs for these breast radiotherapy techniques.

Materials and Methods

Calculation of lifetime attributable risks (LARs)

LARs were calculated using the BEIR VII formalism[17]. This model includes empirical and in vitro data to calculate secondary cancer risks for specific organs depending on sex, age at exposure and attained age. For the esophagus, we used the organ specific parameters from the study by Berrington de Gonzalez[18]. We selected age at exposure of 40 years and older, since this age corresponds to the lower threshold of the "cautionary group" of the ASTRO guidelines and the "intermediate-risk group" of the GEC-ESTRO guidelines[19-21]. We used the probability of survival for the general population from the U.S. Decennial Life Tables for 1999–2001[22]. We corrected the probability of survival for breast cancer patients using the probability of survival after localized breast cancer from the SEER database[23]. The SEER database provides survival data up to 40 years after diagnosis. For the period after this, we extrapolated the linear trend in the survival probability. We used the baseline cancer risks for the general population from the SEER database[24]. To put the risks into perspective, we calculated the lifetime Relative Risk (RR) of secondary cancer per organ.

Radiotherapy planning and phantom treatments

Measurements of the scatter dose for various breast radiotherapy techniques were performed using a Rando-Alderson phantom (Radiology Support Devices, Inc., Long Beach, CA, USA) with custom-made tissue equivalent breast phantoms adapted from Ruschin et al.[25]. Five surgical clips were inserted in the upper outer quadrant of the right breast at typical places found on patients treated in our institutions, and creating a virtual seroma of about 3 cm in diameter.

Planning CT-scans of the realistic breast phantom were made according to our institutional protocol. The whole breast clinical target volume (CTV) was delineated up to the chest wall and excluded the first 5 mm below the surface. The whole breast CTV expanded by a 5 mm margin and limited 5 mm under the surface corresponded to the PTV for WBI. The tumor bed was delineated using the surgical clips. It was expanded with a margin of 15 mm to create the CTV for the APBI treatments following the NSABP B-39/RTOG 0413 protocol[26] . The planning target volume (PTV) margin was 10 mm for the external beam APBI techniques and zero mm for the HDR techniques[26].

Whole breast radiotherapy used a hypofractionated regimen of 42.5 Gy in 16 fractions mixing 6 and 10 MV tangent beams. Beam angles were optimized to limit the contralateral breast and lung dose. Dynamic wedges were used to improve the dose distribution and the treatment was delivered using an Elekta Synergy S linear accelerator.

The technique described by Baglan et al. was used to plan the 3D-conformal (3D-CRT) APBI treatment[27]. The prescribed dose was 38.5 Gy in 10 fractions. The plan fulfilled the dose constraints of the NSABP B-39/RTOG 0413 protocol[26]. VMAT APBI was delivered using a single 6 MV arc ranging from 190°to 20°The plan was optimized for breast conformality, minimizing the heart and lung dose according to the NSABP B-39/RTOG 0413 constraints[26]. The prescribed dose was 38.5 Gy in 10 fractions. Cyberknife plans were created in Multiplan version 5.3.0 (Accuray Inc., Sunnyvale, USA) with an inverse plan optimization. Plans used either the Iris (CK-Iris) or the MLC (CK-MLC) collimators. Beams were not allowed to enter through the contralateral breast or heart. The prescribed dose, margins and dose constraints applied were identical to the other external beam APBI techniques.

For HDR multicatheter APBI, 8 catheters were inserted in the breast phantom in 2 planes using a free hand implantation technique. A post-implant CT-scan was acquired, and the images were transferred to the Oncentra brachytherapy dose planning system version 4.5.1 (Elekta). The prescribed dose was 34 Gy in 10 fractions. Dwell times were optimized to ensure that coverage and dose homogeneity were optimized following the constraints of the NSABP B-39 protocol[26]. To mimic a balloon for HDR balloon-based APBI, a single catheter was inserted in the breast phantom. On the planning CT-scan, a sphere of 3.5 cm diameter was delineated around the catheter to represent the balloon. A dose of 34 Gy in 10 fractions was delivered to a point 1 cm away from the balloon surface. The plan also satisfied the constraints from the NSABP B-39/RTOG 0413 protocol for balloon-based HDR[26]. Both HDR APBI techniques were delivered using a 192-Ir Flexitron Remote Afterloading system (Elekta).

Dose measurement

Dose was measured in the lungs, contralateral breast, thyroid, esophagus, colon, ovaries and the uterus. Those organs were chosen because of elevated risks of radiation-induced cancers reported in these organs[5, 28-30]. Doses were measured using 34 ThermoLuminescent dosimeters (TLDs) distributed uniformly over the organs and Gafchromic film for the lungs (Ashland Advanced Materials, Bridgewater, USA). The LiF 700 powder TLDs were read out using the Pitman 654 TLD-reader and annealed with the Pitman 622/B annealing facility using a standard of 400 °C for 1.5 h and 80 °C for 16 h, with subsequent natural cooling down to room temperature. TLDs were calibrated for doses of 1 cGy to 10 Gy. Gafchromic EBT3 films were used next to TLDs to measure the scatter dose in the lungs in the presence of steep dose gradients. The films were analyzed after 24 h storage in the dark at room temperature using the dose-density curve for each batch of films. For each technique a single dose of 10–12 Gy was delivered to the PTV, to ensure that the TLDs and films received a dose within its accuracy range. Measured doses were rescaled to the total dose that would be delivered per technique. Mean organ doses were calculated weighing the dose from each TLD or film for the percentage of the organ it represented. Each measurement was repeated 3 times.

Results

The mean organ doses per technique are shown in Table 1. The lungs had the highest mean doses, ranging from 50 to 200 cGy depending on the breast radiotherapy technique. The mean doses to the other organs varied a lot, but they generally remained well below 70 cGy. The only exception was the esophagus which received more than 100 cGy with the 3D-CRT APBI. The mean doses to the ovaries and uterus were very low, ranging from 1 to 8 cGy. Comparing the various techniques, whole breast radiotherapy delivered the highest doses overall. Conversely, all APBI techniques resulted in lower doses to the lungs and contralateral breast. The two Cyberknife techniques showed a slightly higher dose to the abdominal organs compared to other APBI techniques, which is due to the non-coplanar technique.

Table 1: Mean dose per organ for the various breast radiotherapy techniques in cGy.

	WBI	3D-APBI	VMAT	Multicath HDR	Balloon HDR	CK-Iris	CK-MLC
Thyroid	17.6	10.4	1.6	15.5	20.6	9.0	14.3
Breast	45.5	6.6	14.9	17.4	24.2	18.8	30.2
Lung	202.1	114.6	182.1	58.4	93.7	129.5	132.6
Esophagus	33.0	116.3	48.4	41.8	63.5	40.5	25.8
Colon	21.8	3.7	0.5	12.4	19.6	59.0	32.7
Ovary	3.3	1.3	0.6	2.5	3.5	7.7	8.1
Uterus	2.6	1.1	0.5	1.8	2.4	5.6	6.0

WBI: Whole Breast Irradiation, 3D-APBI: 3D conformal Accelerated Partial Breast Irradiation, VMAT: Volumetric Modulated Arc partial breast radiotherapy, Multicath HDR: Multicatheter High Dose Rate brachytherapy, Balloon HDR: Balloon-based High Dose Rate brachytherapy, CK-Iris: Cyberknife stereotactic partial breast irradiation with Iris collimator, CK-MLC: Cyberknife stereotactic partial breast irradiation with multileaf collimator.

Table 2 shows the LARs for the individual organs and the total LARs per technique for ages at exposure of 40, 50, 60 and 80 years using the BEIR VII formalism. The results are presented graphically in Fig. 1 for age at exposure of 50 years, which corresponds to the ASTRO "suitable group" and the GEC-ESTRO "low-risk group"[19-21]. As the secondary cancer risks are proportional to the mean organ doses, the comparison of the various techniques in terms of LAR yields the same findings as the comparison of the various techniques in terms of dose since the technique with the highest organ doses results in the highest LARs. The LAR values are highly variable between the organs. The lungs carry the highest LAR, with a 3.8% lifetime risk of a secondary lung malignancy for whole breast radiotherapy at age 50 years. In our calculations, lung tumors accounted for 75–97% of all secondary cancers. Conversely the LARs for the uterus were lower than 1/1000th of the LARs of the lungs.

Table 2: Lifetime Attributable Risks for various breast radiotherapy techniques for a woman exposed at age 40, 50, 60 and 80 years, excess cases per 100,000 exposed persons.

		WBI	3D-APBI	VMAT	Multicath HDR	Balloon HDR	CK-Iris	CK-MLC
40	Thyroid	43	25	13	38	50	22	35
	Breast	521	76	512	199	277	215	346
	Lung	3687	2091	3322	1065	1709	2362	2419
	Esophagus	20	71	37	26	39	25	16
	Colon	148	25	31	84	133	402	223
	Ovary	7	3	4	5	7	16	17
	Uterus	3	1	2	2	3	6	6
	Total	**4429**	**2292**	**3578**	**1419**	**2219**	**3048**	**3061**
50	Thyroid	13	8	4	12	16	7	11
	Breast	283	41	278	108	151	117	188
	Lung	3847	2181	3466	1112	1784	2465	2524
	Esophagus	20	71	36	25	39	25	16
	Colon	142	24	30	81	127	383	212
	Ovary	6	2	3	5	7	14	15
	Uterus	3	1	1	2	2	5	6
	Total	**4314**	**2328**	**3634**	**1344**	**2124**	**3016**	**2972**
60	Thyroid	4	2	1	3	4	2	3
	Breast	132	19	130	51	70	55	88
	Lung	3668	2080	3305	1060	1700	2350	2406
	Esophagus	17	62	32	22	34	21	14
	Colon	124	21	26	71	112	336	186
	Ovary	5	2	2	4	5	11	12
	Uterus	2	1	1	1	2	4	4
	Total	**3952**	**2186**	**3410**	**1211**	**1927**	**2779**	**2713**
80	Thyroid	0	0	0	0	0	0	0
	Breast	16	2	16	6	9	7	11
	Lung	1580	896	1424	457	733	1012	1037
	Esophagus	6	21	11	8	12	7	5
	Colon	47	8	10	27	43	128	71
	Ovary	1	1	1	1	1	3	3
	Uterus	0	0	0	0	0	1	1
	Total	**1652**	**928**	**1451**	**499**	**797**	**1159**	**1128**

WBI Whole Breast Irradiation, 3D-APBI 3D conformal accelerated partial breast radiotherapy, VMAT Volumetric Modulated Arc partial breast radiotherapy, Multicath HDR Multicatheter High Dose rate brachytherapy, Balloon HDR Balloon-based High Dose Rate brachytherapy, CK-Iris Cyberknife with Iris collimator, CK-MLC Cyberknife with multileaf collimator.

We calculated the RRs for women exposed at age 40, 50, 60 and 80 years as compared to non-irradiated breast cancer patients of the same age (Table 3). Selecting a threshold of 50% RR increase as being clinically significant, only the WBI and the VMAT technique are significantly increasing the risk of secondary lung cancer, which remains dominant in absolute numbers. Selecting a threshold of 10% as being clinically significant, there was an increased risk of lung cancer for all techniques at all ages. At this 10% threshold, there was also an increased risk of esophagus cancers, but the absolute numbers remain small. The risks of secondary malignancies of the thyroid, contralateral breast, ovaries and uterus were close to the baseline risks and may not be detectable in population-based studies.

Figure 1. Lifetime attributable risk of secondary cancer per organ for the various breast radiotherapy techniques. Number of cases per 100,000 persons receiving adjuvant breast radiotherapy at age 50 years.

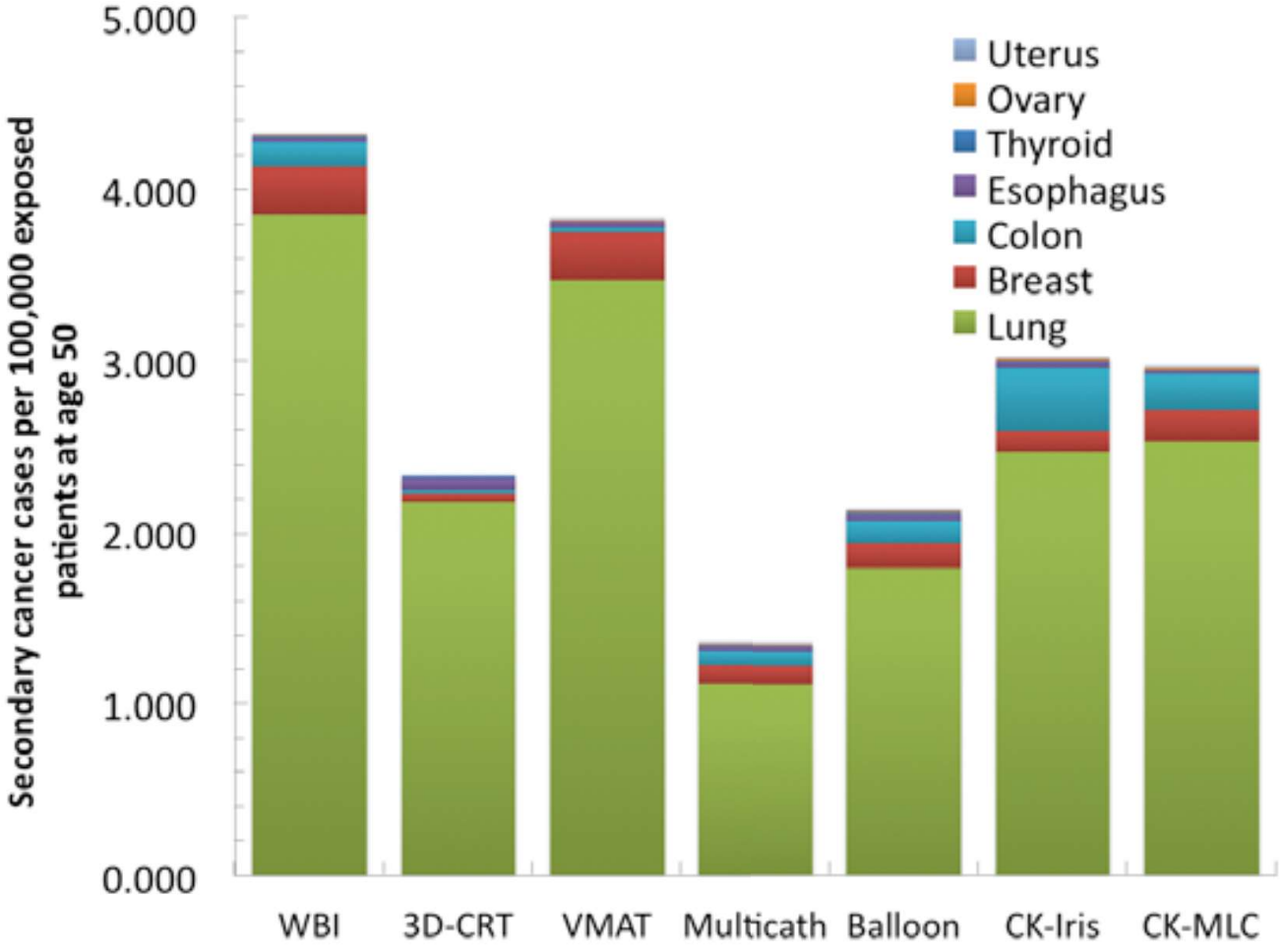


Table 3: Relative risks per organ for various breast radiotherapy techniques for a woman exposed at age 40, 50, 60 and 80 years, as compared to a non-irradiated localized breast cancer patient. Relative risks larger than 1.5 are shown in bold.

		WBI	3D-APBI	VMAT	Multicath HDR	Balloon HDR	CK-Iris	CK-MLC
40	Thyroid	1.046	1.027	1.014	1.040	1.054	1.023	1.037
	Breast	1.050	1.007	1.049	1.019	1.026	1.021	1.033
	Lung	**1.753**	1.427	**1.678**	1.217	1.349	1.482	1.494
	Esophagus	1.114	1.401	1.205	1.144	1.219	1.140	1.089
	Colon	1.040	1.007	1.008	1.023	1.036	1.108	1.060
	Ovary	1.007	1.003	1.003	1.005	1.007	1.015	1.016
	Uterus	1.001	1.001	1.001	1.001	1.001	1.003	1.003
50	Thyroid	1.018	1.011	1.005	1.016	1.021	1.009	1.015
	Breast	1.028	1.004	1.028	1.011	1.015	1.012	1.019
	Lung	**1.724**	1.410	**1.652**	1.209	1.336	1.464	1.475
	Esophagus	1.104	1.366	1.188	1.132	1.200	1.128	1.081
	Colon	1.036	1.006	1.008	1.020	1.032	1.097	1.054
	Ovary	1.006	1.002	1.003	1.004	1.006	1.014	1.014
	Uterus	1.001	1.000	1.001	1.001	1.001	1.003	1.003
60	Thyroid	1.007	1.004	1.002	1.006	1.008	1.004	1.006
	Breast	1.015	1.002	1.015	1.006	1.008	1.006	1.010
	Lung	**1.679**	1.385	**1.612**	1.196	1.315	1.435	1.446
	Esophagus	1.090	1.316	1.162	1.114	1.173	1.110	1.070
	Colon	1.032	1.005	1.007	1.018	1.029	1.086	1.048
	Ovary	1.005	1.002	1.003	1.004	1.005	1.012	1.013
	Uterus	1.001	1.000	1.001	1.001	1.001	1.002	1.002
80	Thyroid	1.000	1.000	1.000	1.000	1.001	1.000	1.000
	Breast	1.005	1.001	1.004	1.002	1.002	1.002	1.003
	Lung	**1.598**	1.339	**1.539**	1.173	1.277	1.383	1.392
	Esophagus	1.048	1.169	1.087	1.061	1.092	1.059	1.038
	Colon	1.017	1.003	1.004	1.010	1.015	1.046	1.025
	Ovary	1.003	1.001	1.002	1.002	1.003	1.007	1.007
	Uterus	1.001	1.000	1.000	1.000	1.001	1.001	1.001

WBI Whole Breast Irradiation, 3D-APBI 3D conformal accelerated partial breast radiotherapy, VMAT Volumetric Modulated Arc partial breast radiotherapy, Multicath HDR Multicatheter High Dose rate brachytherapy, Balloon HDR Balloon-based High Dose Rate brachytherapy, CK-Iris Cyberknife with Iris collimator, CK-MLC Cyberknife with multileaf collimator.

Discussion

Our study shows that all APBI techniques produce less scatter dose compared to whole breast radiotherapy, which translates into a lower secondary cancer risk. The use of APBI could eventually halve the lifetime secondary cancer risk. In our calculations, the lifetime risks are high, up to 4.3% for a woman treated at 50 years old. This strongly supports the generalization of partial breast irradiation as standard for early stage breast cancers or DCIS instead of whole breast radiotherapy.

Importantly our study also shows that the vast majority, between 75 and 97%, of the calculated secondary cancers involve the lungs. We calculated an absolute lifetime excess risk of lung cancer of 3.7% for patients treated with whole breast radiotherapy at age 60 years. The SEER database shows that the lifetime risk of lung cancer for a 60-year old female from the general population is 5.75% and the lifetime risk of dying from lung cancer is 4.66%[31]. This means that about 80% of lung cancer patients will die from their disease. Translated to our result, this means that whole breast radiotherapy could result in a 2.9% excess mortality due to secondary lung cancer.

One limitation of the present study is the use of a single phantom with average size breasts. Different patient geometries, for example larger breast volumes, may increase or decrease the mean lung dose for respectively brachytherapy or WBI[32]. However, those variations are relatively limited compared to the differences in techniques we tested. Also, the goal of this study was precisely to compare those techniques one with each other, which means we had to keep the patient's characteristics strictly identical between techniques, which is ideally performed using a phantom study.

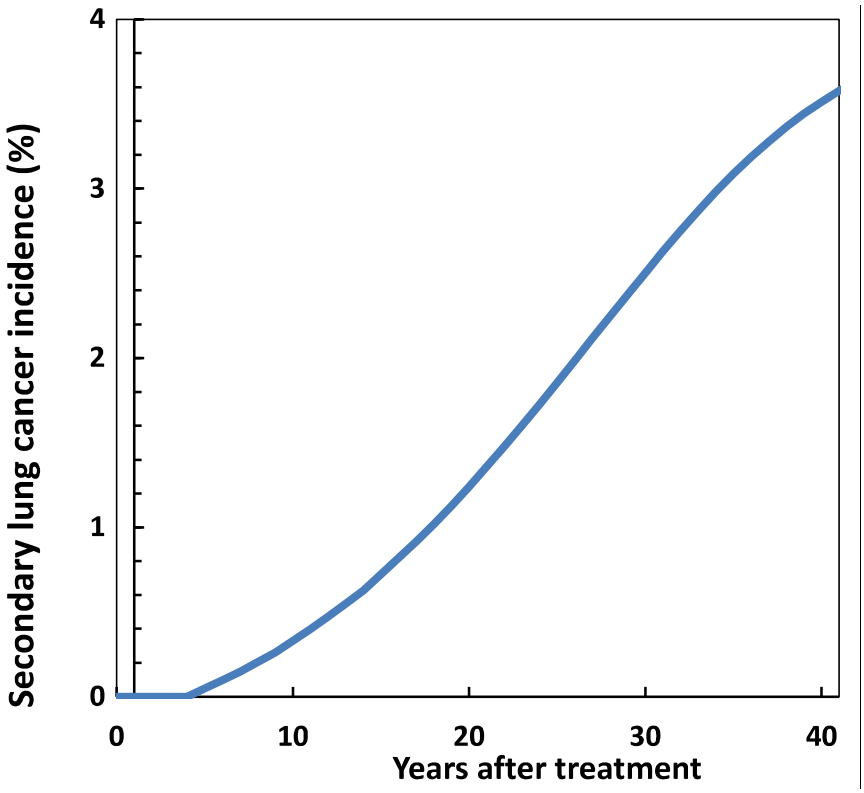
Another limitation of the present study is the use of the BEIR-VII model for higher doses than intended in the report, where low doses were defined up to 0.1 Gy. Also, this model assumes a proportionality relationship that is not seen at doses above 3 or 4 Gy where a saturation effect has been demonstrated with a plateau between 10 and 20 Gy[33]. Also, our predictions for lung cancer compare well with other studies. We calculated a lung cancer RR of 1.68 for patients receiving whole breast radiotherapy at age 60 years. This number is in good agreement with a meta-analysis of patients treated with whole breast radiotherapy between 1935 and 2007 at a median age of 56 years where the standardized incidence ratio for lung cancer after 15 years was 1.91[5]. The mean lung doses were not reported in this meta-analysis, but they were likely higher compared to our phantom study as modern radiation machines have a reduced scatter dose compared to older ones. For example, we used a virtual wedge technique while patients treated between 1935 and 2007 in the Grantzau cohort had probably much more often treatment with physical wedges which generate a much higher scatter dose[32]. Similarly, in the 2017 EBCTCG meta-analysis, which included 40,781 patients treated between 1972 and 1997 in randomized trials comparing the use of adjuvant radiotherapy or not, the RR of lung cancer at 10 years or more after irradiation was 2.1[34]. This meta-analysis emphasized the large increased risk, about 10 times higher, for smokers versus nonsmokers to develop secondary lung cancer applying the increased incidence probability to a population of non-smokers from the American Cancer Society Cancer Prevention Study II[35] and a population of smokers from the Million Women Study in the United Kingdom[36].

The calculated lifetime risk of secondary lung cancer mortality is high and is in the same order of magnitude as the survival benefit of radiotherapy. In the 2011 EBCTCG meta-analysis node negative patients had a 3.3% reduction of breast cancer related mortality at 15 years[37]. On the

other hand Darby et al. calculated that a 50-year old woman would have a risk of death from ischemic heart disease of 0.5% before the age of 80 for a patient without pre-existing cardiac risk factors, and of 0.7% in case of one or more additional risk factors[4]. Such excess in cardiac mortality has encouraged the widespread implementation of preventive techniques, including as deep inspiration breath-hold. Our calculations showed an absolute increase in lung cancer mortality before age 80 of 2.4% for a 50-year old woman treated with WBI, which is about 4 times as high as the reported cardiac mortality. The excess of lung cancer mortality has not yet encouraged clinicians to actively adopt measures reducing the mean lung dose. It is noteworthy that cardiac events occur much earlier than secondary cancers. In the Darby study 44% of cardiac events occurred in the first 10 years after treatment[4]. The risk of secondary lung cancer is increased after a latency period of at least 5 years, and continued to increase up to 15 years[5]. In our calculations, 93% of all secondary lung cancers occurred after 10 years (Fig. 2). This latency may explain why earlier meta-analysis including trails with limited follow-up primarily stressed the cardiac morbidity and did not fully capture the risk of lung cancer mortality. With this in mind, and in the context of the improved outcomes of early stage breast cancer, it is important to select radiotherapy techniques generating the lowest scatter dose possible. In this study the lowest mean lung dose was obtained using brachytherapy or 3D-conformal radiotherapy, both leading to doses between 1 and 1.5 Gy. Following the ALARA (As Low As Reasonably Achievable) principle[38], it is reasonable to recommend keeping the mean lung dose below this achievable level. For patients with more aggressive disease requiring loco-regional radiotherapy and whohave a poorer prognosis, a higher value for the constraint on the mean lung dose may be acceptable, especially when regional nodes must be treated.

In conclusion, the present study finds an excess of lung cancer mortality due to irradiation that appears larger than the excess of cardiac mortality for early stage breast cancer patients having a very long survival. This risk can be greatly reduced using partial breast irradiation techniques minimizing the mean dose to the lung in addition to smoking prevention.

Figure 2: Time occurrence of secondary lung cancers for a person exposed at age 50.



References

1. SEER database. Cancer Stat Facts: Female Breast Cancer 2017 [Available from: https://seer.cancer.gov/statfacts/html/breast.html.
2. Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087-106.
3. Cuzick J, Stewart H, Rutqvist L, Houghton J, Edwards R, Redmond C, et al. Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy. J Clin Oncol. 1994;12(3):447-53.
4. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Bronnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013;368(11):987-98.
5. Grantzau T, Overgaard J. Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer:A systematic review and meta-analysis of population-based studies including 522,739 patients. Radiother Oncol. 2016;121(3):402-13.
6. Xu XG, Bednarz B, Paganetti H. A review of dosimetry studies on external-beam radiation treatment with respect to second cancer induction. Phys Med Biol. 2008;53(13):R193-241.
7. Offersen B, Hojris I, Overgaard M. Radiation-induced heart morbidity after adjuvant radiotherapy of early breast cancer - Is it still an issue? Radiother Oncol. 2011;100(2):157-9.
8. Vikstrom J, Hjelstuen MH, Mjaaland I, Dybvik KI. Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold with audio-visual guidance, without compromising target coverage. Acta Oncol. 2011;50(1):42-50.

9. Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer. 2015;51(4):451-63.
10. Polgar C, Fodor J, Major T, Sulyok Z, Kasler M. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. Radiother Oncol. 2013;108(2):197-202.
11. Rodriguez N, Sanz X, Dengra J, Foro P, Membrive I, Reig A, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys. 2013;87(5):1051-7.
12. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016;387(10015):229-38.
13. Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys. 2006;65(1):1-7.
14. Donovan EM, James H, Bonora M, Yarnold JR, Evans PM. Second cancer incidence risk estimates using BEIR VII models for standard and complex external beam radiotherapy for early breast cancer. Med Phys. 2012;39(10):5814-24.
15. Han EY, Paudel N, Sung J, Yoon M, Chung WK, Kim DW. Estimation of the risk of secondary malignancy arising from whole-breast irradiation: comparison of five radiotherapy modalities, including TomoHDA. Oncotarget. 2016;7(16):22960-9.
16. Pignol JP, Keller BM, Ravi A. Doses to internal organs for various breast radiation techniques--implications on the risk of secondary cancers and cardiomyopathy. Radiat Oncol. 2011;6:5.
17. Council NR. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. . National Academies Press; 2006.
18. Berrington de Gonzalez A, Iulian Apostoaei A, Veiga LH, Rajaraman P, Thomas BA, Owen Hoffman F, et al. RadRAT: a radiation risk assessment tool for lifetime cancer risk projection. J Radiol Prot. 2012;32(3):205-22.
19. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol. 2017;7(2):73-9.
20. Polgar C, Van Limbergen E, Potter R, Kovacs G, Polo A, Lyczek J, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). Radiother Oncol. 2010;94(3):264-73.
21. Smith BD, Arthur DW, Buchholz TA, Haffty BG, Hahn CA, Hardenbergh PH, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys. 2009;74(4):987-1001.
22. CDC. Decennial Life Tables for 1999–2001, United States Life Tables. In: Table02.xls., editor. 2008.
23. SEER*Stat Database: Incidence – SEER 18 Regs Research Data+ Hurricane Katrina Impacted Louisiana Cases, Nov 2015 Sub (1973-2013varying) – Linked To County Attributes - Total U.S., 1969–2014 Counties, National Cancer Institute, DCCPS, Surveillance Research Program [Internet]. 2016. Available from: http://www.seer.cancer.gov

24. Surveillance E, and End Results (SEER) Program. SEER*Stat Database: Incidence – SEER 18 Regs Research Data+ Hurricane Katrina Impacted Louisiana Cases, Nov 2016 Sub (2000–2014) <Katrina/Rita Population Adjustment> – Linked To County Attributes – Total U. S., 1969–2015 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, . 2017.
25. Ruschin M, Davidson SR, Phounsy W, Yoo TS, Chin L, Pignol JP, et al. Technical Note: Multipurpose CT, ultrasound, and MRI breast phantom for use in radiotherapy and minimally invasive interventions. Med Phys. 2016;43(5):2508.
26. NSABP. Protocol B-39/RTOG 0413, A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer [Available from: http://www.nsabp.pitt.edu/B-39.asp.
27. Baglan KL, Sharpe MB, Jaffray D, Frazier RC, Fayad J, Kestin LL, et al. Accelerated partial breast irradiation using 3D conformal radiation therapy (3D-CRT). Int J Radiat Oncol Biol Phys. 2003;55(2):302-11.
28. Marcu LG, Santos A, Bezak E. Risk of second primary cancer after breast cancer treatment. Eur J Cancer Care (Engl). 2014;23(1):51-64.
29. Mellemkjaer L, Friis S, Olsen JH, Scelo G, Hemminki K, Tracey E, et al. Risk of second cancer among women with breast cancer. Int J Cancer. 2006;118(9):2285-92.
30. Raymond JS, Hogue CJ. Multiple primary tumours in women following breast cancer, 1973-2000. Br J Cancer. 2006;94(11):1745-50.
31. Program. NCISEaER. Table 15.20 Cancer of the Lung and Bronchus (Invasive). 2014 [Available from: https://seer.cancer.gov/csr/1975_2014/browse_csr.php?sectionSEL=4&pageSEL=sect_04_table.17.html.
32. Woo TC, Pignol JP, Rakovitch E, Vu T, Hicks D, O'Brien P, et al. Body radiation exposure in breast cancer radiotherapy: impact of breast IMRT and virtual wedge compensation techniques. Int J Radiat Oncol Biol Phys. 2006;65(1):52-8.
33. Schneider U, Sumila M, Robotka J. Site-specific dose-response relationships for cancer induction from the combined Japanese A-bomb and Hodgkin cohorts for doses relevant to radiotherapy. Theor Biol Med Model. 2011;8:27.
34. Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. J Clin Oncol. 2017;35(15):1641-9.
35. Thun MJ, Henley SJ, Burns D, Jemal A, Shanks TG, Calle EE. Lung cancer death rates in lifelong nonsmokers. J Natl Cancer Inst. 2006;98(10):691-9.
36. Pirie K, Peto R, Reeves GK, Green J, Beral V, Million Women Study C. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. Lancet. 2013; 381(9861):133-41.
37. Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707-16.
38. Prasad KN, Cole WC, Haase GM. Radiation protection in humans: extending the concept of as low as reasonably achievable (ALARA) from dose to biological damage. The British journal of radiology. 2004;77(914):97-9.

CHAPTER FIVE

5

Subcutaneous spacer injection to reduce skin toxicity in breast brachytherapy: a pilot study on mastectomy specimens

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Brachytherapy. 2019;18(2):204-10.

Abstract

Introduction: Accelerated partial breast irradiation (APBI) is a treatment option for selected early stage breast cancer patients. Some APBI techniques lead to skin toxicity with the skin dose as main risk factor. Biodegradable spacers are effective and safe in prostate brachytherapy to protect the rectum. We hypothesize that a subcutaneous spacer injection reduces the skin dose in breast brachytherapy.

Material and Methods: Ultrasound-guided spacer injections, either hyaluronic acid (HA) or iodined polyethylene glycol (PEG), were performed on fresh mastectomy specimens. Success was defined as a spacer thickness of ≥5mm in the high-dose skin area. Usability was scored using the System Usability Scale (SUS). Pre- and post-injection CT-scans were used to generate low dose rate (LDR) seed brachytherapy treatment plans after defining a clinical target volume (CTV). Maximum dose to small skin volumes (D0.2cc) and existence of hotspots (isodose ≥90% on 1 cm2 of skin) were calculated as skin toxicity indicators.

Results: We collected 22 mastectomy specimens; half had HA and half had PEG injection. Intervention success was 100% for HA and 90.9% for PEG (p=NS). Hydrodissection was feasible in 81.8% with HA and 63.6% with PEG. Median SUS score was 97.5 for HA and 82.5 for PEG ($p<0.001$). Mean D0.2cc was 80.8Gy without spacer and 53.7Gy with spacer ($p<0.001$). Skin hotspots were present in 40.9% without spacer but none with spacer ($p<0.001$).

Conclusion: A spacer injection in mastectomy specimens is feasible. An extra 5mm space is always achieved, thereby potentially reducing the skin dose dramatically in LDR seed breast brachytherapy.

Introduction

Breast cancer is increasingly diagnosed at an early stage, and for that stage[1, 2], breast conserving therapy, which includes wide local excision and radiotherapy, is equivalent to mastectomy in terms of local control and overall survival[3, 4]. These oncological outcomes are excellent in early-stage breast cancer patients[1]. Hence, radiotherapy essentially has a cosmetic and quality of life benefit[5]. Since local recurrences usually occur close to the primary tumor[6], the concept of accelerated partial breast irradiation (APBI) was introduced[7] to reduce the amount of breast tissue irradiated and enable faster treatment. For well-selected patients, APBI has been tested and validated through large randomized clinical trials, using either brachytherapy[8-11], external 3D conformal radiotherapy[12, 13], intensity-modulated radiotherapy[14, 15] or intra-operative radiotherapy[4, 16].

Brachytherapy techniques also involve balloon or strut multicatheter brachytherapy[17, 18], with the applicator being placed in the surgical cavity by the breast surgeon at the time of or shortly after the wide local excision.

Brachytherapy is generally well tolerated, with reported long-term grade ≥ 2 skin toxicity (telangiectasia) ranging from 3.2% to 9% in interstitial brachytherapy[8, 9, 19, 20] and ranging from 8.9% to 15% grade ≥ 2 telangiectasia for applicator based brachytherapy[20, 21]. Nevertheless, ≥ grade 1 long-term skin toxicity (telangiectasia) of breast brachytherapy, if reported, ranges from 10.1%[19], 22.4%[8] up to 27%[21]. Various authors recommend keeping a distance of 5 mm between the planning target volume (PTV) and the skin[22, 23] and limiting the maximum skin dose to 70%[9]. However, such constraints occasionally cannot be satisfied, resulting in an increased risk of skin toxicity. This has a negative impact on patients quality of life[24]. A simple solution could be a spacer material injected subcutaneously to move the skin out of the high-dose region[25]. Recently, biocompatible and degradable gel materials have been proposed as spacers to prevent rectum toxicity in prostate cancer, using either polyethylene glycol (PEG), hyaluronic acid or collagen[26]. However, to the best of our knowledge, spacers have never been tested in breast cancer patients before.

In this work, we hypothesize that a space can be reliably created with the injection of a spacer between the breast skin and the radiation target, and that this would result in a reduction of skin dose. To best mimic breast tissue characteristics, we have used fresh mastectomy specimens as a realistic phantom and a low dose rate (LDR) seed brachytherapy planning technique used in our center to calculate the skin dose.

Materials and Methods

Patients

Anonymized mastectomy specimens of patients referred to the Department of Surgery, Franciscus Gasthuis and Vlietland (Rotterdam, the Netherlands) between September 2016 and January 2017 were used for this study. The protocol (nr. T2016-34) was reviewed by the TWOR regional medical research ethics committee (MREC). Ethical clearance for this study was granted; the study was not subject to the Medical Research Involving Human Subjects Act. Mastectomy specimens collected

prospectively were used for the study unless the patient refused the use of tissue, or the patient had inflammatory breast cancer or skin infiltration.

Spacer injection and imaging procedures

After mastectomy, the fixation in formalin was deferred, and the specimen was sent to the radiology department for a CT-scan. Images of 1 mm thickness and 1 mm spacing were acquired at 120 kVp. After imaging, the spacer was injected subcutaneously in a radial fashion in a predefined 20 mm radius skin area using an 18 G or 21 G needle under ultrasound (US) guidance (Fig. 1).

Figure 1: Delineation of the injected area (1a), and spacer injection under ultrasound guidance (1b)

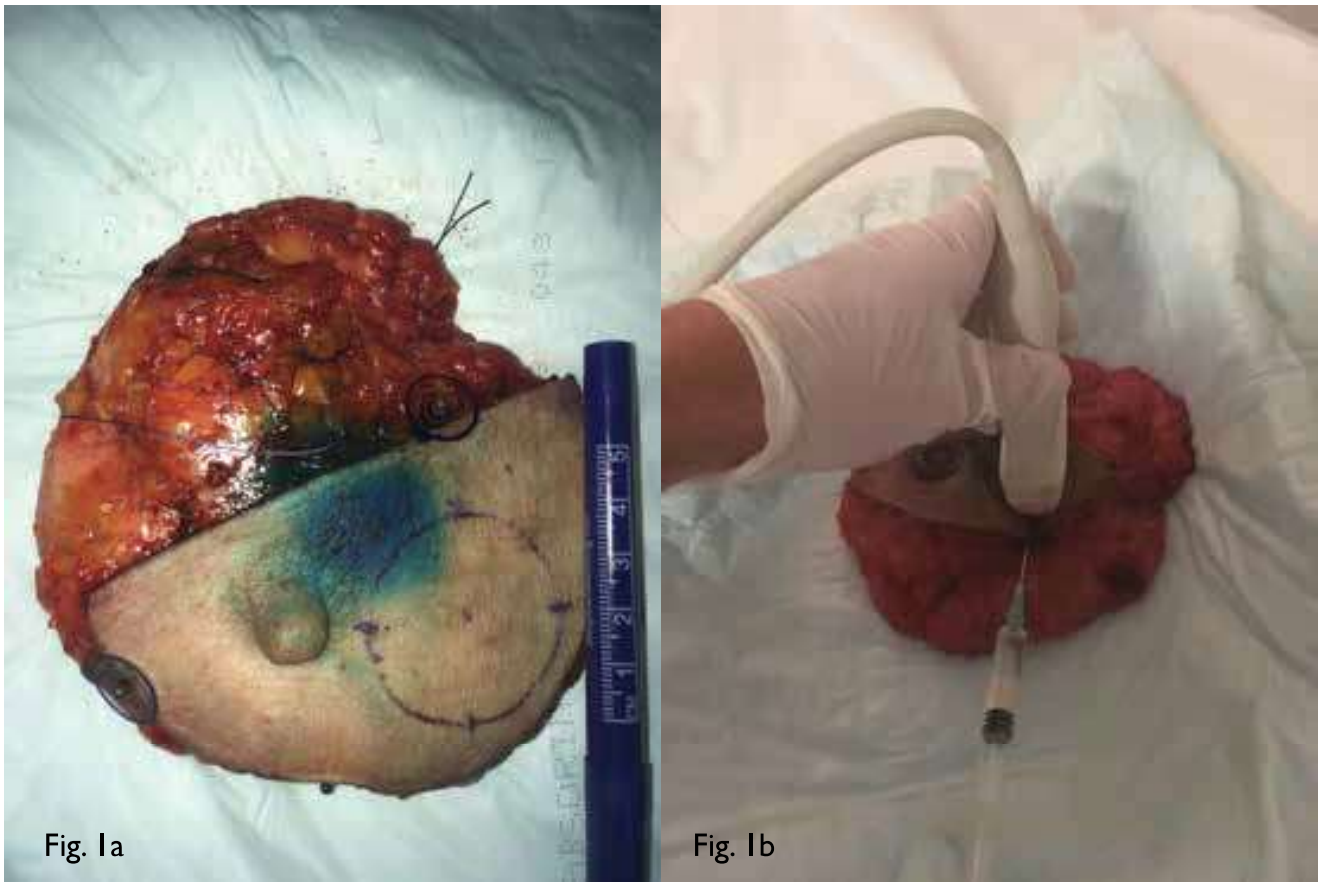
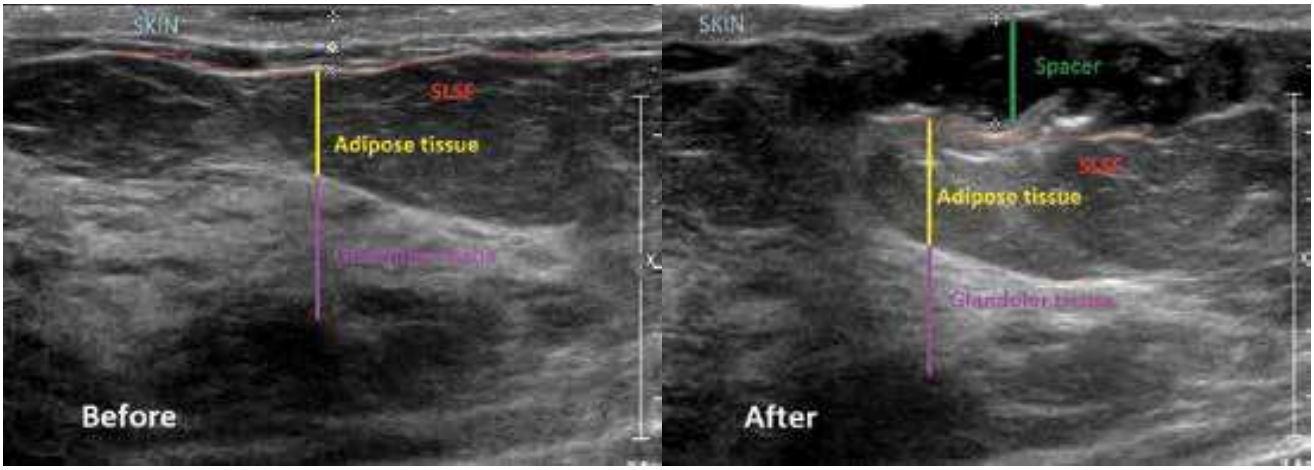


Fig. 1a Fig. 1b

This target skin area was simulated as the potential high-dose skin area. A maximum of 12 ml spacer product was injected using a hydrodissection technique; creating a plane between the breast skin and the superficial layer of the superficial fascia (SLSF), or directly below the skin if no SLSF was clearly identified (Fig. 2).

Figure 2: Ultrasound images before and after hyaluronic acid spacer injection.



The injection was finished once the goal of creating a spacer volume of 5 mm thickness covering the full target skin area, as measured by US, was achieved. Two products were tested alternatively, hyaluronic acid (Barrigel™, Palette Life Sciences, Santa Barbara, CA) and iodined PEG (TraceIT©, Augmenix Inc, Bedford, MA). Once completed, the thickness of the spacer volume was measured with ultrasound at the center and four cardinal sides within 5 mm of the injection boundaries. After injection, a second CT-scan was made for brachytherapy planning purpose.

Spacer injection and imaging outcome measures

Success of the intervention was defined as a spacer thickness equal or superior to 5 mm extending onto all the predefined skin area. The spacer thicknesses were compared between US and CT and also, over time, assessed with US 4 hours after injection. The ease of use of the spacer product was scored evaluating the feasibility of hydrodissection (yes/no), US and CT visibility (poor, moderate, good, excellent), and the convenience of the injection using the System Usability Scale (0-100 score)[27]. The mastectomy specimen were fixed in formalin after completing all study procedures.

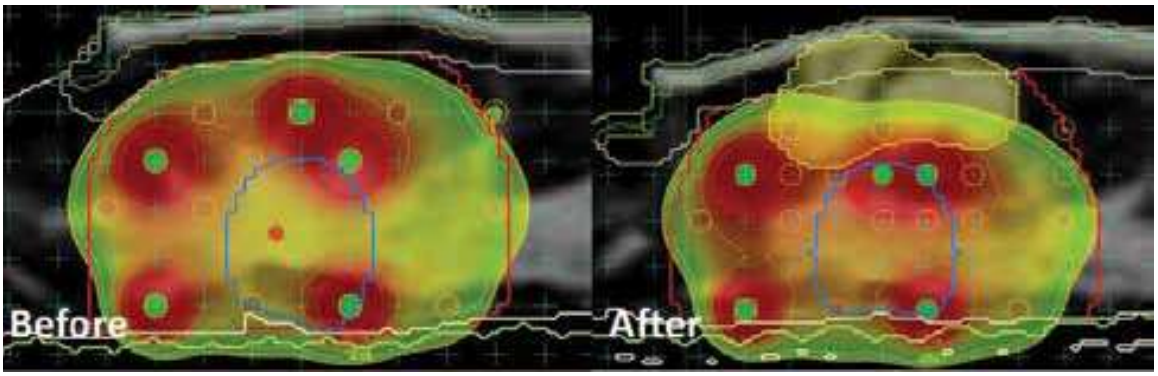
Dosimetry

The CT-images were transferred to the MIM Symphony (version 6.6) LDR seed brachytherapy treatment planning system (MIM Software Inc, Cleveland, OH). More details on this form of interstitial brachytherapy are described elsewhere[28]. Treatment plans were made for both the pre- and post-injection CT-scans of the same breast specimen. Since the clinical target volume (CTV), which usually corresponds to the post-lumpectomy seroma, was not visible, a virtual CTV was created instead. Anatomical breast tissue landmarks, including the nipple, visible blood vessels and fibroglandular tissue, were carefully identified and the virtual CTV was created from an expansion of a point contour. Using the landmarks as point contour enabled an accurate transfer of the CTV contour from the pre- to the post-injection CT. Consistent with the LDR breast seed brachytherapy literature[29, 30], the median virtual CTV volume was 8.1 cc (interquartile range [6.1-8.5]), and the

distance between CTV isocenter and the skin ranged between 14 and 35 mm on the pre-injection CT. Similar CTVs and skin distances were used for the hyaluronic acid and PEG injected specimen. Skin layers (external surface and its inner ring of 2 mm thickness) and a virtual chest wall were contoured. Virtual PTVs were created expanding the virtual CTV by 12.5 mm limited to the chest wall and either 5 mm below the skin surface or to the spacer volume.

Plans were initially performed on the pre-injection CT-images, and the seed placement configuration was imported and matched manually in the post-injection CT-scan using the anatomical landmarks. Since the spacer shapes were not even (Fig. 3), only a couple of seeds were eventually located inside the spacer volume on the post-injection CT scan. So to best mimic the post-injection situation, only the seeds located inside the spacer were shifted down until located in the underlying breast tissue. This realized a worst case scenario for the creation of dose distribution hotspots. Dose calculation was done according to the TG-43 protocols[31, 32]. A dose of 90 Gy was prescribed to the minimal peripheral dose that was set to cover the PTV. The PTV volumes receiving at least 100% or 200% of the prescribed dose (V_{100} and V_{200}) were calculated as quality assurance for all treatment plans. Maximum dose to a small skin volume of 2 mm thickness over 1 cm^2 ($D_{0.2cc}$)[25, 33] and the presence of a hotspot (isodose ≥90%[30]) on 1 cm^2 of the skin were calculated as indicators of skin toxicity.

Figure 3: Dose distribution on CT images before and after spacer injection. The spacer is identified with a yellow line and induces the shift of seeds inside the target volume.



Statistics

The sample size calculation used the primary outcome measure accepting at least two third of success in the spacer injection. With a sample size of 20, an expected success rate of 0.9 would have a 95% confidence interval of 0.68 to 0.99. We collected two extra specimens to anticipate for any loss to follow-up imaging.

The injection success rate was compared between products using the Fisher exact test. Spacer thicknesses and usability were compared using the Mann Whitney-U test. Correlation between CT and US measurements of central spacer thickness were analyzed with Pearson's (r) correlation coefficient[34]. Agreement between methods was assessed using a Bland-Altman analysis for both

products. To detect differences between pre- and post-injection, the McNemar's test was used to compare the proportion of cases with a 1 cm^2 skin hotspot ≥ 90%. The Wilcoxon signed ranks test or a paired T-test, depending on the skewness of the data distributions (Shapiro-Wilk test), was used to compare the V_{100}, V_{200} and $D_{0.2cc}$. A two-sided p-value below 0.05 was considered a statistically significant difference.

Results

We collected a total of 22 mastectomy specimens in 21 patients with no loss to follow-up. Hyaluronic acid was used in 11 specimens and PEG in the other 11 specimens. The SLSF was clearly identified on ultrasound in 13 out of 22 specimens (59.1%).

The injection success rate was similarly high for both products: a spacer thickness equal or superior to 5 mm was achieved in 100% (11/11, 95%CI: 0.72-1.00) with hyaluronic acid and 90.9% (10/11, 95%CI: 0.59-1.00, p=NS) with PEG. In one early case, the spacer thickness for PEG was 4.0 mm at the border instead of 5 mm. The median injected volumes were 8 ml (inter-quartile range [6 - 9.5 ml]) for hyaluronic acid and 7 ml (inter-quartile range [6 - 8 ml]) for PEG. Hydrodissection of a plane between the skin and the SLSF was feasible in 81.8% (95%CI: 0.48-0.98) with hyaluronic acid and 63.6% (95%CI: 0.31-0.89) with PEG. As anticipated in regard to the product characteristics, ultrasound visibility was good with hyaluronic acid but poor to moderate with PEG, while CT visibility was excellent with PEG and good but poorer with hyaluronic acid. Median spacer thickness was similar in both groups, 7.9 mm with hyaluronic acid and 7.8 mm with PEG (p=NS). Spacer shapes appeared slightly flatter and more homogeneous with hyaluronic acid and with a slight median spacer thickness growth over 4 hours of 4.2% (inter-quartile range [-4.2 – 16.2%]) centrally. A slight spacer shrinkage was noticed with PEG, with a median spacer thickness being 10.7% smaller after 4 hours (inter-quartile range [4.3 – 17.9%]) centrally. However, the difficulty to identify the spacer thickness with PEG using ultrasound may make this conclusion unreliable. The median System Usability Scale score was 97.5 (inter-quartile range [95.0-97.5]) for hyaluronic acid and 82.5 (inter-quartile range [72.5-87.5]) for PEG (p<0.001). Correlation between CT and US measurements of central spacer thickness was very high with hyaluronic acid (r=0.927, adjusted R^2=0.845, p<0.001), and high with PEG (r=0.842, adjusted R2=0.673, p=0.002). A small mean difference was found for hyaluronic acid (+0.4 mm) and PEG (+0.7 mm) when measured with CT rather than with US. Overall agreement interval for both products (mean±1.96SD) between methods was [-2.83-1.77 mm].

The mean V_{100} was 95.9% (SD=1.1%) without spacer and 94.9% (SD=2.2%) with spacer. Mimicking the situation that the spacer is injected after the seeds implant, we assume that the spacer volume changes both the PTV geometry and implanted volume geometry equally and does not result in a large difference in PTV coverage. Therefore, the comparable V_{100} percentages before and after spacer injection suggest that the transfer of the virtual CTV and seeds was relatively accurate. Mean V_{200} was 22.5% (SD=2.6%) without spacer and increased to 27.9% (SD=5.8%) with spacer (p=0.001), which was expected, as the most superficial seeds were shifted inside the PTV.

The mean $D_{0.2cc}$ skin dose was 80.8 Gy (SD=13.4 Gy) without spacer and 53.7 Gy (SD=11.2 Gy) with spacer (p<0.001), meaning an absolute reduction in $D_{0.2cc}$ of 27.1 Gy and a relative reduction of 33.5% (SD=8.4%). A skin hotspot ≥90% was present in 9/22 (40.9%, 95%CI: 0.21-0.64) specimens without spacer and 0/22 (0%, 95%CI: 0-0.28) specimens with spacer (p<0.001) (table 1).

Table 1: Dosimetry results for various metrics calculated with and without spacer

Outcome measure	Without spacer n=11	With spacer n=11	p-value
Mean $D_{0.2cc}$ (±SD)	80.8 Gy (±13.4)	53.7 Gy (±11.2)	p<0.001
Skin hotspot ≥90% present (%)	9/22 (40.9%)	0/22 (0%)	p<0.001
Mean PTV V_{100} (±SD)	95.9% (±1.1%)	94.9% (±2.2%)	p = NS
Mean PTV V_{200} (±SD)	22.5% (±2.6%)	27.9% (±5.8%)	p=0.001

SD = standard deviation; $D_{0.2cc}$ = maximum dose to a skin volume of 2cc; Gy = Gray; PTV = planning target volume

A comparison of skin measures between both products is shown in table 2. The use of hyaluronic acid led to a marginally higher skin dose reduction than that of PEG on all measures. In no case was the 90% isodose crossing the 2mm skin contour larger than 1 cm^2 for any spacer product. In regard to the volume of the 2mm skin contour receiving more than 90% of the prescribed dose (V_{90}), the relative reduction was slightly larger for hyaluronic acid.

Table 2: Improvement of dosimetry metrics linked to skin toxicity depending on the type of spacer.

Outcome measure	Hyaluronic acid n=11	PEG n=11
Mean D0.2cc with spacer (±SD)	49.8Gy (7.6)	57.6Gy (13.1)
D0.2cc reduction with spacer (±SD)	36.0% (11.1)	30.6% (8.6)
Skin hotspot ≥90% present (%)	0 (0)	0 (0)
Relative skin V90% reduction with spacer (±SD)	99.2% (28.4)	90.1% (37.4)

SD = standard deviation; $D_{0.2cc}$ = maximum dose to a skin volume of 2cc; PEG = polyethylene glycol; Gy = Gray; skin $V_{90\%}$ = volume of 2mm skin contour receiving at least 90% of prescribed dose

Discussion

This study is the first to investigate the possible use of a subcutaneous spacer injection to reduce the risk of skin toxicity with breast brachytherapy. We found a high success rate of the intervention, and each time a stable spacer volume was created under ultrasound guidance in real human breast specimens. This suggests that the spacer technique would also be technically feasible in breast cancer patients. Compared to PEG, hyaluronic acid has a better ultrasound visibility, which eventually improves the quality of the spacer injection. Additionally, being more liquid, hyaluronic

acid better allows the hydrodissection of a plane between the SLSF and the skin. This enables a more homogeneous injection of the spacer, whereas PEG leads to more irregular clusters of the spacer. We believe that these advantages explain the higher System Usability Scale score at 97.5 for hyaluronic acid compared to 82.5 for PEG ($p<0.001$).

In the present study, a spacer thickness of more than 5 mm always significantly reduced the skin dose. This means that a 1 cm^2 area of the skin would never receive more than 90% of the prescribed dose, a metric that is significantly correlated with a higher risk of long term skin toxicity[30]. Compared to prostate studies, the use of a spacer for breast brachytherapy appears to be more effective in reducing a high dose to the nearby critical structure, which is the skin. In a review by Mok[26] on the use of prostate spacers, the mean relative V_{90} reduction was 84% with hyaluronic acid and 46% to 61% with PEG, whereas our results show a mean relative V_{90} reduction at 90% with PEG and 99% with hyaluronic acid (Table 2).

There was a very strong correlation of the spacer thickness between US and CT measurements ($p < 0.001$) and good agreement between methods. This suggests that when a 5 mm space is created by the injection (under US guidance), a similar value will be found for planning done on CT-images.

There are some limitations doing a dosimetry study using mastectomy specimens compared to a breast in place. We aimed to create a setting as close as possible to the real breast anatomy:

- The intervention was done immediately post-surgery without the specimen being fixed into formalin, to keep tissue consistence and hydration close to living breast tissue.
- We used full mastectomy instead of partial mastectomy specimens, so we could perform the intervention at a selected location with enough tissue to avoid breast deformation under the skin impacting on the quality of spacer.

However, while the spacer partly pushed the skin away, it also expanded the breast volume laterally and inferiorly, possibly explained by the absence of a thoracic wall. Therefore, the full effect of a spacer injection may not have been completely evaluated. We adopted a conservative approach shifting only the sources that were found inside the spacer on the post-injection CT. Since only the superficial sources and not the deeper sources were shifted, a higher dose to the skin and the creation of larger hotspots in the implanted area was generated. Despite this, the injection of a spacer systematically resulted in a large reduction of the skin dose. Our findings (high feasibility and potential large skin dose reduction) already stimulated the conduction of a clinical trial. Another potential limitation of our study is that with both the use of a virtual CTV and the presence of spacer, we could not use deformable image registration (DIR) to identify the CTV on the post-injection CT-scan, as recommended by Hilts et al[35].

Our study specifically evaluated LDR seed brachytherapy as an APBI technique. Therefore, our dosimetric findings cannot be generalized to single balloon or strut based breast brachytherapy techniques since the dose fall-off is much less abrupt in those techniques[17, 18]. On the other hand, similar results are anticipated for external beam radiotherapy including stereotactic body

radiotherapy (SBRT)[36] or 3D-CRT[37] and multicatheter brachytherapy[38] since steep dose gradients are also achieved around the target volume with these techniques.

In a clinical setting, the procedure would be realized as follows: first perform the seed implant and afterwards the spacer injection. This allows for the most accurate seed placement. Furthermore, once the dose reduction effect of the spacer is confirmed in a clinical trial, patients at risk of skin toxicity could be detected using in vivo skin dose measurements. This would allow to only inject a spacer in patients with a high skin dose, that benefit from a spacer being injected.

Conclusion

A biodegradable spacer injected between the radiation source and the skin in human mastectomy specimens is technically feasible and leads to a high rate of success using either hyaluronic acid or PEG. With those products, an extra 5 mm space is always achieved, thereby reducing the skin dose dramatically in a simulated LDR seed breast brachytherapy planning. Although this is a proof-of-concept, the impact on dose distribution including skin dose and clinical outcomes should still be confirmed in a randomized clinical trial.

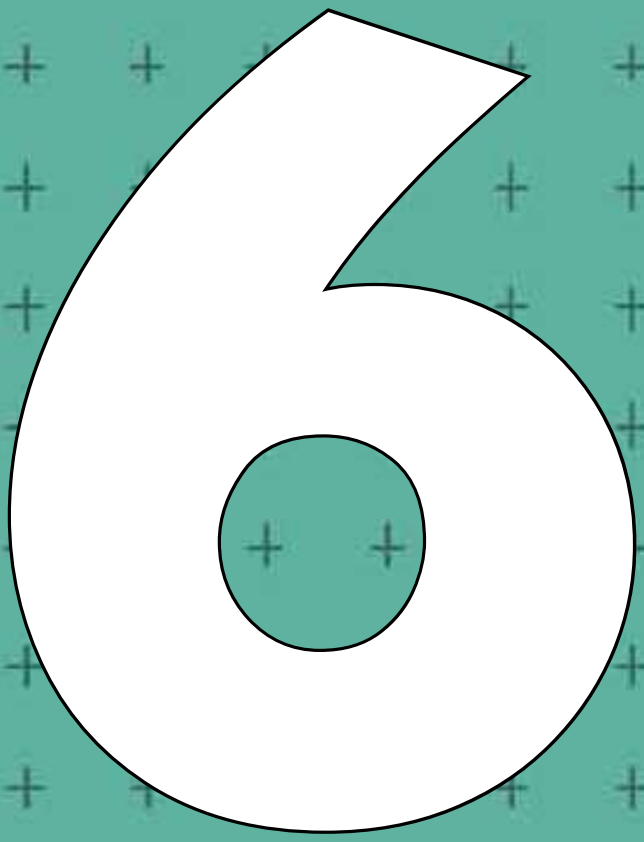
References

1. SEER database. Cancer Stat Facts: Female Breast Cancer 2017 [Available from: https://seer.cancer.gov/statfacts/html/breast.html.
2. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. Lancet. 2000;355(9217):1822.
3. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233-41.
4. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013;14(13):1269-77.
5. Kim MK, Kim T, Moon HG, Jin US, Kim K, Kim J, et al. Effect of cosmetic outcome on quality of life after breast cancer surgery. Eur J Surg Oncol. 2015;41(3):426-32.
6. Fisher ER, Sass R, Fisher B, Gregorio R, Brown R, Wickerham L. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). II. Relation of local breast recurrence to multicentricity. Cancer. 1986;57(9):1717-24.
7. Bethune WA. Partial breast irradiation for early breast cancer. J Natl Med Assoc. 1991;83(9):768, 800, 8.
8. Pignol JP, Caudrelier JM, Crook J, McCann C, Truong P, Verkooijen HA. Report on the Clinical Outcomes of Permanent Breast Seed Implant for Early-Stage Breast Cancers. Int J Radiat Oncol Biol Phys. 2015;93(3):614-21.
9. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016;387(10015):229-38.

10. Vicini FA, Chen PY, Fraile M, Gustafson GS, Edmundson GK, Jaffray DA, et al. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. Int J Radiat Oncol Biol Phys. 1997;38(2):301-10.
11. White J, Winter K, Kuske RR, Bolton JS, Arthur DW, Scroggins T, et al. Long-Term Cancer Outcomes From Study NRG Oncology/RTOG 9517: A Phase 2 Study of Accelerated Partial Breast Irradiation With Multicatheter Brachytherapy After Lumpectomy for Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys. 2016;95(5):1460-5.
12. NSABP. Protocol B-39/RTOG 0413, A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer [Available from: http://www.nsabp.pitt.edu/B-39.asp.
13. Vicini F, Winter K, Straube W, Wong J, Pass H, Rabinovitch R, et al. A phase I/II trial to evaluate three-dimensional conformal radiation therapy confined to the region of the lumpectomy cavity for Stage I/II breast carcinoma: initial report of feasibility and reproducibility of Radiation Therapy Oncology Group (RTOG) Study 0319. Int J Radiat Oncol Biol Phys. 2005;63(5):1531-7.
14. Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer. 2015;51(4):451-63.
15. Pignol JP, Truong P, Rakovitch E, Sattler MG, Whelan TJ, Olivotto IA. Ten years results of the Canadian breast intensity modulated radiation therapy (IMRT) randomized controlled trial. Radiother Oncol. 2016;121(3):414-9.
16. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Saunders C, et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). Health Technol Assess. 2016;20(73):1-188.
17. Gitt A, Bose-Ribeiro H, Nieder C, Kup PG, Hermani H, Buhler H, et al. Treatment Results of MammoSite Catheter in Combination with Whole-breast Irradiation. Anticancer Res. 2016;36(1):355-60.
18. Yashar C, Attai D, Butler E, Einck J, Finkelstein S, Han B, et al. Strut-based accelerated partial breast irradiation: Report of treatment results for 250 consecutive patients at 5 years from a multicenter retrospective study. Brachytherapy. 2016;15(6):780-7.
19. Polgar C, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(2):259-68.
20. Wobb JL, Shah C, Jawad MS, Wallace M, Dilworth JT, Grills IS, et al. Comparison of chronic toxicities between brachytherapy-based accelerated partial breast irradiation and whole breast irradiation using intensity modulated radiotherapy. Breast. 2015;24(6):739-44.
21. Vargo JA, Verma V, Kim H, Kalash R, Heron DE, Johnson R, et al. Extended (5-year) outcomes of accelerated partial breast irradiation using MammoSite balloon brachytherapy: patterns of failure, patient selection, and dosimetric correlates for late toxicity. Int J Radiat Oncol Biol Phys. 2014;88(2):285-91.
22. Wazer DE, Kaufman S, Cuttino L, DiPetrillo T, Arthur DW. Accelerated partial breast irradiation: an analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. Int J Radiat Oncol Biol Phys. 2006;64(2):489-95.

23. Strnad V, Ott O, Potter R, Hildebrandt G, Hammer J, Resch A, et al. Interstitial brachytherapy alone after breast conserving surgery: interim results of a German-Austrian multicenter phase II trial. Brachytherapy. 2004;3(3):115-9.
24. Johansen J, Overgaard J, Rose C, Engelholm SA, Gadeberg CC, Kjaer M, et al. Cosmetic outcome and breast morbidity in breast-conserving treatment--results from the Danish DBCG-82TM national randomized trial in breast cancer. Acta Oncol. 2002;41(4):369-80.
25. Mashouf S, Fleury E, Lai P, Merino T, Lechtman E, Kiss A, et al. Clinical Significance of Accounting for Tissue Heterogeneity in Permanent Breast Seed Implant Brachytherapy Planning. Int J Radiat Oncol Biol Phys. 2016;94(4):816-23.
26. Mok G, Benz E, Vallee JP, Miralbell R, Zilli T. Optimization of radiation therapy techniques for prostate cancer with prostate-rectum spacers: a systematic review. Int J Radiat Oncol Biol Phys. 2014;90(2):278-88.
27. Brooke J. SUS - A quick and dirty usability scale. In: P. W. Jordan BT, B. A. Weerdmeester, A. L. McClelland, editor. Usability evaluation in industry. London: Taylor and Francis; 1996. p. 189-94.
28. Pignol JP, Keller B, Rakovitch E, Sankreacha R, Easton H, Que W. First report of a permanent breast 103Pd seed implant as adjuvant radiation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2006;64(1):176-81.
29. Pignol JP, Rakovitch E, Keller BM, Sankreacha R, Chartier C. Tolerance and acceptance results of a palladium-103 permanent breast seed implant Phase I/II study. Int J Radiat Oncol Biol Phys. 2009;73(5):1482-8.
30. Keller BM, Ravi A, Sankreacha R, Pignol JP. Permanent breast seed implant dosimetry quality assurance. Int J Radiat Oncol Biol Phys. 2012;83(1):84-92.
31. Monroe JI, Williamson JF. Monte Carlo-aided dosimetry of the theragenics TheraSeed model 200 103Pd interstitial brachytherapy seed. Med Phys. 2002;29(4):609-21.
32. Rivard MJ, Coursey BM, DeWerd LA, Hanson WF, Huq MS, Ibbott GS, et al. Update of AAPM Task Group No. 43 Report: A revised AAPM protocol for brachytherapy dose calculations. Med Phys. 2004;31(3):633-74.
33. Hilts M, Halperin H, Morton D, Batchelar D, Bachand F, Chowdhury R, et al. Skin dose in breast brachytherapy: Defining a robust metric. Brachytherapy. 2015;14(6):970-8.
34. Hinkle DE, Wiersma W, Jurs SG. Applied statistics for the behavioral sciences. 5th ed. Boston: Houghton Mifflin; 2003. xxi, 756 p. p.
35. Hilts M, Batchelar D, Rose J, Crook J. Deformable image registration for defining the postimplant seroma in permanent breast seed implant brachytherapy. Brachytherapy. 2015;14(3):409-18.
36. Obayomi-Davies O, Kole TP, Oppong B, Rudra S, Makariou EV, Campbell LD, et al. Stereotactic Accelerated Partial Breast Irradiation for Early-Stage Breast Cancer: Rationale, Feasibility, and Early Experience Using the CyberKnife Radiosurgery Delivery Platform. Front Oncol. 2016;6:129.
37. Weed DW, Edmundson GK, Vicini FA, Chen PY, Martinez AA. Accelerated partial breast irradiation: A dosimetric comparison of three different techniques. Brachytherapy. 2005;4(2):121-9.
38. Major T, Stelczer G, Pesznyak C, Meszaros N, Polgar C. Multicatheter interstitial brachytherapy versus intensity modulated external beam therapy for accelerated partial breast irradiation: A comparative treatment planning study with respect to dosimetry of organs at risk. Radiother Oncol. 2017;122(1):17-23.

CHAPTER SIX



A randomized controlled trial testing a hyaluronic acid spacer injection for skin toxicity reduction of brachytherapy accelerated partial breast irradiation (APBI): a study protocol

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Abstract

Introduction: Accelerated partial breast irradiation (APBI) is a treatment option for selected early stage breast cancer patients. Some APBI techniques lead to skin toxicity with the skin dose as main risk factor. We hypothesize that a spacer injected between the skin and target volume reduces the skin dose and subsequent toxicity in Permanent Breast Seed Implant (PBSI) patients.

Methods: In this parallel group randomized controlled single-center trial, the effect of a subcutaneous spacer injection on skin toxicity among patients treated with PBSI is tested. Eligibility for participation is derived from international guidelines for suitable patients for partial breast radiotherapy, e.g. women ≥ 50 years of age with a histologically proven non lobular breast carcinoma and/or DCIS, tumor size≤ 3cm, node negative and PBSI technically feasible. Among exclusion criteria are neo-adjuvant chemotherapy, lymphovascular invasion and allergy for hyaluronic acid. For the patients allocated to receive spacer, after the PBSI procedure, 4-10 cc of biodegradable hyaluronic acid (Barrigel™, Palette Life Sciences, Santa Barbara, CA or Restylane SubQ®, Galderma Benelux, Breda, the Netherlands) is injected directly under the skin using ultrasound guidance to create an extra 0,5-1 cm space between the treatment volume and the skin. The primary outcome is the rate of telangiectasia at 2 years, blindly assessed using Bentzen's 4-point scale. Secondary outcomes include: local recurrence, disease-free and overall survival rates, adverse events (pain, redness, skin/ subcutaneous induration, radiation dermatitis, pigmentation, surgical site infection), skin dose, cosmetic and functional results and health related quality of life.
A Fisher Exact test will be used to test differences between groups on the primary outcome. Previous studies found 22.4% telangiectasia at 2 years. We expect the use of a spacer could occurrence of telangiectasia to 7.7%. A sample size of 230 patients will allow for a 10% lost to follow-up rate.

Discussion: In this study, the effect of a subcutaneous spacer injection on the skin dose, late skin toxicity and cosmetic outcome is tested in patients treated with PBSI in the setting of breast conserving therapy. Our results will be relevant for most forms of breast brachytherapy as well as robotic radiosurgery, as skin spacers could protect the skin with these other techniques.

Introduction

Breast cancer is increasingly diagnosed at an early stage[1, 2], and for that stage, breast conserving therapy, which includes wide local excision and radiotherapy, is equivalent to mastectomy in terms of local control and overall survival[3, 4]. These oncological outcomes are excellent in early-stage breast cancer patients[1]. Hence, radiotherapy essentially provides a cosmetic and quality of life benefit over mastectomy[5]. Since local recurrences usually occur close to the primary tumor[6], the concept of accelerated partial breast irradiation (APBI) was introduced[7] to both reduce the amount of breast tissue irradiated and enable faster treatment. For well-selected patients, APBI has been tested and validated through large randomized clinical trials, using either brachytherapy[8-11], external 3D conformal radiotherapy[12, 13], or intra-operative radiotherapy[14, 15].

Brachytherapy has been the most evaluated technique and recent advances beyond multicatheter implantation include balloon or strut brachytherapy as well as permanent breast seed implants[16, 17]. Brachytherapy is generally well tolerated and reported long-term toxicities are acceptable. A lower incidence of low-grade acute skin toxicity for APBI, 21% versus 86% for whole breast radiotherapy ($p<0.001$) has been reported for the GEC-ESTRO trial[18]. Regarding late side effects at 5-years follow-up, lower rates of severe grade 2-3 skin, 6.9% versus 10.7%, and similar rates of subcutaneous side effects, 12.0% versus 9.7% were found in this study[19]. On the other hand, in a retrospective analysis of 1,034 breast patients treated at The Ohio State University including 31% treated with a balloon applicator, Wobb reported more seroma grade 2 or higher (14.4% versus 2.9%, $p<0.001$), more painful fat necrosis (10.2% versus 3.6%, $p<0.001$), and more telangiectasia grade 2 or higher (12.3% versus 2.1%, $p<0.001$) for APBI compared to whole breast radiotherapy[20]. Among those permanent side effects, increased painful seroma is almost exclusively due to balloon applicator, fat-necrosis can be due to multiple factors, while telangiectasia is almost exclusively due to an excess of dose to the skin. This makes telangiectasia a specific marker of radiation toxicity[21, 22]. Telangiectasia corresponds to the dilation of an abnormal neo-vasculature in the skin following the destruction of normal capillaries by the radiation treatment, resulting in visible vessels[23]. Although rates are lower than with whole breast irradiation, in breast brachytherapy 10-27%[9, 19, 24] of the patients develop some grade of telangiectasia. The majority of lesions are grade 1 ($< 1 cm^2$) in breast radiotherapy studies reporting on late skin toxicity[9, 25, 26]. The onset of telangiectasia is from 6 months till 10 years after radiotherapy delivery[23], however rates of telangiectasia peak at 2 years with PBSI . Although permanent in most cases, some authors report disappearing of the telangiectasia with longer follow-up[9, 27]. Nevertheless, if present, telangiectasia can remind patients of their cancer similar to a surgical scar, and have a direct negative impact on the cosmetic outcomes[9, 26].

Several authors recommend keeping a distance of at least 5 mm between the planning target volume (PTV) and the skin[28, 29] and limiting the maximum skin dose to 70%[8]. However, such constraints are not always achievable. A simple solution would be the use of a spacer material injected subcutaneously to move the skin out of the high dose region[21].

In this manuscript we report the protocol of a randomized controlled trial investigating the clinical benefit of a subcutaneous spacer injection on the skin dose, late skin toxicity and cosmetic outcome in patients treated with LDR seed brachytherapy. For this study the breast skin is considered as a critical structure for the radiotherapy and the clinical outcomes are measured using a breakdown of traditional skin toxicity scales in order to specifically capture the toxicity that is specific to radiotherapy[9, 21, 23, 30].

Methods

Aim and design

We propose a parallel group randomized controlled trial comparing the occurrence of telangiectasia at 2 years in PBSI patients with or without a subcutaneous spacer injection. Allocation ratio is 1:1 and the trial is designed to test the superiority of the intervention. The primary hypothesis for the trial assumes that an injected hyaluronic acid spacer will reduce skin dose of PBSI and eventually the rate of telangiectasia at 2 years, compared to patients undergoing PBSI without spacer. As the intervention is applied when the patient is sedated a placebo injection as comparator was deemed unnecessary. The methods section is described according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist (see additional file 1).

Eligible patients will be recruited at hospitals referring patients after breast conserving surgery for adjuvant radiotherapy at the Erasmus MC Cancer Institute, a large University hospital in Rotterdam, where the PBSI technique can be performed in the Netherlands.

Eligibility and exclusion criteria

Eligibility criteria were derived from international guidelines[31, 32] for suitable patients for partial breast radiotherapy. Eligible patients are females aged 50 years or older with a confirmed histological diagnosis of invasive ductal carcinoma (IDC), and/or papillary, tubular, cribriform or medullar carcinoma and/or ductal carcinoma in situ (DCIS), after breast conserving surgery with axillary node dissection (with a minimum of 6 nodes sampled) or sentinel lymph node biopsy. The maximum dominant tumor size is 3 cm and the tumor must be excised with negative surgical margins at ink for invasive carcinoma and over or equal to 2 mm for DCIS, or have a negative re-excision. The PBSI should be deemed technically feasible based on the seroma location, visibility and size performing an ultra-sound, and the total implanted volume should be less than 150 cc. Patient should have signed an informed consent.

Ineligible patients include those with lymphovascular invasion, lobular features on histology (pure or mixed) or sarcoma histology, triple negative tumors, extensive in situ carcinoma, multicentric disease (in more than one quadrant or separated by 2 cm or more), bilateral breast cancer, recurrent breast cancer, Paget's disease of the nipple, metastases or active other cancer (defined by any malignancy in<5 year, excluding any cured non-melanoma skin cancer or cervical cancer),

neo-adjuvant chemotherapy, known allergy for hyaluronic acid, active auto immune disorder with severe vasculitis component, uncontrolled and complicated diabetes insulin-dependent, pregnancy, cosmetic breast implants, psychiatric or addictive disorder that would preclude attending follow-up, post-operative wound infection or abscess following Centers for Disease Control and prevention (CDC) criteria.

Interventions

The permanent seed implant procedure includes a CT-simulation done positioning the patient similarly to for external beam breast radiotherapy. The Clinical Target Volume (CTV) corresponds to the seroma with 1 cm margin, limited to the fascia pectoralis and 5 mm below the skin, and the Planned Target Volume (PTV) is an additional expansion of 0.5 cm with the same skin and chest wall limits. A pre-implant plan is generated using the MIM Symphony® software (MIM Software Inc., Cleveland OH) to order stranded ^{103}Pd seeds of 2.5U activity.

For the procedure, anesthesia includes NSAID for 2 days, light sedation with Propofol, and local freezing. Patients are positioned on a breast board, with the arm abducted similarly to the CT simulation. The breast skin is sterilized and the patient draped. The PTV projection perpendicular to the fiducial needle axis is outlined on the skin surface and verified using ultrasound. A PBSI template (Concure Oncology, Seattle, WA) is attached to the fiducial needle and immobilized using a modified medical articulated arm (Fisso, Medtec Baitella Alt, Switzerland). The preloaded needles containing ^{103}Pd strands are then inserted under US guidance[33]. In patients allocated to receive spacer, an amount of 4-10 cc of biodegradable Hyaluronic Acid (Barrigel™, Palette Life Sciences, Santa Barbara, CA or Restylane SubQ®, Galderma Benelux, Breda, the Netherlands) is injected directly under the skin under ultrasound guidance covering the PTV projection aiming to create an extra 0,5-1 cm space between the treatment volume and the skin. If the skin is judged not to be at risk in all projection quadrants, it could be decided to only inject the area at risk. The injected skin quadrants will be reported specifically. All radiation oncologists involved in this study are trained to perform the intervention and the injection procedure and reporting instructions are incorporated in trial protocols. The hyaluronic acid spacer is expected to be fully degraded after 3-9 months.

Outcomes

The primary endpoint of this trial is the occurrence of telangiectasia at 2 years after PBSI. Assessment is performed by a blinded physician, following the Bentzen's four points scale which is included in the LENT/SOMA questionnaire[34, 35]. This scale is defined as: 'none', grade I – 'less than 1 cm^2', grade II – '1 to 4 cm^2' and grade III – 'over 4 cm^2'. Patients will also be blinded for the allocated treatment. The secondary outcomes include the local recurrence rate at 5 and 10 years, the disease free and overall survival rates at 5 years, as well as brachytherapy and spacer injection adverse events according to commonly used NCI Common Toxicity Criteria for Adverse Events (CTCAE v 4.03) scale for acute side effects[36], practically occurring within 3 months of the

brachytherapy, and the Radiation Therapy Oncology Group (RTOG)/ European Organisation for Research and Treatment of Cancer (EORTC) scoring systems for late side effects[37], practically occurring after 3 months. The symptoms include the experience of pain, skin redness, pigmentation, induration, dermatitis, subcutaneous induration, and the occurrence of infection at the site of spacer injection. Additionally, patients reported outcome measures (PROMs) include the cosmetic result with the breast cancer treatment outcome scale (BCTOS) questionnaire[38], using a validated Dutch version which will shortly be published by our group and the health-related Quality of Life using the Dutch version EORTC QLQ-C30 and BR23 questionnaires, version 3[39]. Ipsilateral breast recurrence must be proven getting a copy of the biopsy or the salvage surgery pathology report. Dosimetry outcomes include the PTV volumes receiving at least 100% or 200% of the prescribed dose (V_{100} and V_{200}) as quality assurance for all treatment plans and maximum dose to a small skin volume of 2 mm thickness over 1 cm^2 ($D_{0.2cc}$)[21, 40] and the presence of a hotspot (isodose ≥90%)[41] on 1 cm^2 of the skin as indicators of skin toxicity risk.

Outcomes are collected before the PBSI implantation as baseline, at the end of the procedure, and at 2, 6 months and every year, up to 5 years, during follow-up visit at the cancer center. If a patient does not show-up at a follow-up appointment she will be called, and/or her family doctor contacted. Reason for no-show will be recorded in order to ensure exhaustive capture of survival, recurrence and/or adverse events. Overall and disease-specific survival will be assessed until 10 years through GBA (Population registry, Gemeentelijke Basis Administratie) and/or general practitioners. A summary of the timing of questionnaires is detailed in figure 1.

Sample size

Previous studies found 22.4% telangiectasia at 2 years[9]. We expect the use of a spacer could reduce the skin dose to 50%[21] and the occurrence of any telangiectasia (≥ grade 1) to 7.7%[42]. To test this reduction, (e.g. the superiority of the intervention) 105 (Fisher Exact test) patients per treatment arm would be needed ($a=0.05$, $\beta=0.20$). A sample size of 230 patients will allow for a 10% lost to follow-up rate.

Figure 1. Schedule of enrolment, interventions, and assessments in this study

	STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation**					**Close-out**
TIMEPOINT	$-t_1$	*0*	*2 month*	*6 month*	*1 year*	*2 year*	*3-5 year*	*10 year*
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							

	STUDY PERIOD							
	Enrolment	**Allocation**	**Post-allocation**					**Close-out**
TIMEPOINT	$-t_1$	*0*	*2 month*	*6 month*	*1 year*	*2 year*	*3-5 year*	*10 year*
Technical feasibility screening (US/CT)	X							
Allocation		X						
INTERVENTIONS:								
arm A: PBSI without spacer		X						
arm B: PBSI with spacer		X						
ASSESSMENTS:								
Patient and tumor characteristics	X	X						
Baseline clinical assessment	X							
Pre-implant QA		X						
PBSI+spacer procedure data		X						
Post-implant QA			X					
Primary outcome assessment						X		
Adverse events/ side effects			X	X	X	X	X	
Survival and recurrence			X	X	X	X	X	X
Questionnaires								
BCTOS	X		X		X	X		
EORTC QLQ-C30	X			X	X	X	X	
EORTC QLQ-/BR23	X			X	X			
EQ-5D	X				X	X	X	

Recruitment

The Erasmus MC- Cancer Institute is treating approximately 1000 patients with adjuvant breast radiotherapy every year. Given the inclusion criteria it is expected approximately 20% of these patients are eligible for PBSI. On top of this, referrals from outside the area are also expected specifically for PBSI. This makes it very likely that the required sample size could be recruited in 3 years.

Treatment allocation and blinding

After written informed consent and final eligibility check, the radiation oncologist will enroll the patient and randomization will be performed by the department's independent trial manager. Patients will be randomly allocated to one of the treatment arms (spacer injection or no spacer injection) in a 1:1 allocation ratio, applying a variable block size randomization (block sizes 2, 4 and 6). This concealed allocation will be computer generated using the online randomization tool ALEA.

Patients will be blinded for the allocated treatment, as the spacer injection is performed under sedation. However, in some cases the patient might see or feel the effect of spacer injection afterwards. The treating radiation oncologist will be blinded during treatment planning and during the implant of the palladium seeds and be unblinded after the implant to inject the spacer or not using a telephone call with the departments trial manager.

Investigators will be blinded for allocated treatment during assessment of primary endpoint by performing this assessment in a separate visit in which the physician is not accessing patient's medical file. Unblinding will be performed if a patient is going (un)planned off-study. Also in case of medical emergencies possibly caused by the use of the spacer unblinding will be performed. In these cases, patient's allocated treatment can be unblinded by checking the medical record of the implantation or by contacting the trial management.

Data management

Secure collection of data is performed. Data entry will be performed using a predefined case report form (CRF) (additional file 2) with accompanied data entry protocol. This provides instructions units to be used, missing data handling and range checks.

Statistical methods

All statistical tests will be two-sided and p-value of less than 0.05 is considered to be significant. Statistical analyses will be performed using IBM-SPSS version 24 (IBM Corporation, Armonk, New York, USA). Data will be analyzed following intention-to-treat and per protocol. Missing data will be handled using multiple imputation. Descriptive statistics will be used for all outcome measures.

A Fisher Exact or Chi-squared test will be performed to test the reduction in the rate of telangiectasia in the study groups at 2 years follow-up, i.e. to test the hypothesis that the rates of telangiectasia in both study groups are equal (superiority study).

Local-recurrence free survival, overall and disease-specific survival rates at 5 and 10 years will be estimated using the Kaplan-Meier method. The local recurrence rate will be reported at 5 years and 10 years. A Fisher Exact or Chi-squared test will be performed to test the difference in proportions (6 months, 1 and 2 years cumulative rate of side effects, skin dose > 90% over at least 1cm^2 at post-planning) between groups. (Skin) dosimetry data, will be compared using a Mann-Whitney U test or an unpaired Student's t-test depending of distribution of data. To study the effect of spacer on cosmesis (BCTOS questionnaire) and Quality of Life (EORTC-QLQ-C30/BR23 and EQ5-D questionnaire) over time, a repeated measurements analysis will be performed (linear mixed model, covariance structure: unstructured) with independent variables time, allocated group and interaction effects between time and allocated group.

Discussion

For early stage breast cancer patients, that have outstanding survival outcomes[3, 4], the role of radiotherapy is essentially cosmetic[5]. The skin is a critical structure in breast radiotherapy, with skin dose as main risk factor[21, 22]. In this study we test an intervention to reduce cosmetic impairment by aiming to prevent long-term skin toxicity.

Telangiectasia are a specific marker of radiation toxicity[21, 22]. Although rates are lower than with whole breast irradiation, in breast brachytherapy 10-27%[9, 19, 24] of the patients develop some grade of telangiectasia. Rates of telangiectasia normally peak at 2 years till it stabilizes. Most of the lesions are permanent resulting in decreased quality of life[9]. Other skin toxicity scales (pigmentation, induration, fibrosis) are less specific for capturing radiation induced side effects[21].

Among our secondary outcomes are standard oncological outcomes. Based on our pre-clinical study we do not expect the spacer to influence the oncological effectivity of PBSI[43]. This work in mastectomy specimens showed excellent feasibility of creating an extra 5mm space directly below the skin using a biodegradable spacer. This space is not part of the PTV in LDR seed brachytherapy as the CTV expansion is limited to 5mm below the skin by protocol[33]. The spacer partly lifted the skin, but also moved the breast tissue inferior and laterally. However, with the seeds already in place, we expect that any change in PTV geometry will be similar in the treated volume containing the seeds. This hypothesis was supported by the excellent and comparable PTV coverage ($V_{100\%}$) pre and post-injection in the pre-clinical study[43]. However, this finding should be confirmed in a clinical setting.

Other secondary outcomes are brachytherapy and spacer injection adverse events according to commonly used NCI CTCAE and RTOG/EORTC scoring systems for late side effects. Where our main hypothesis is that the spacer increases distance and reduces skin dose and telangiectasia, this will allow for analyzing the effect on other less radiotherapy specific symptoms like pain, skin redness, pigmentation, induration, dermatitis, subcutaneous induration, and the occurrence of infection at the site of spacer injection. Although hyaluronic acid is widely used as a dermal filler, the application as a skin spacer in patient treated with breast radiotherapy is a new concept and

any unexpected side effects will be captured. Skin dose outcomes will potentially lead to updated skin dose constraints in treatment planning. Also, it could distinguish radiotherapy induced toxicity from other causes (f.e. intervention related toxicity). PROMs assess the effect of the skin spacer on cosmesis, function and quality of life. Furthermore, by using internationally recognized PROMs a better comparison with other radiotherapy techniques is possible.

This clinical trial was designed because it is unknown if the dosimetric benefit of the spacer, that was found in our pre-clinical study[43], translates in a real patient benefit. An example of a clinical trial that could not demonstrate that a dosimetric benefit translates into better patient outcomes, is the breast intensity modulated radiation therapy (IMRT) trial. In this trial, the improved radiation dose distribution and reduced moist desquamation using IMRT, compared to standard wedge RT, did not result in reduced long-term side effects like chronic breast pain[42].

Our primary analysis will be done following the intention-to-treat principle: the effect of skin spacer on telangiectasia rate at 2 years. However, a per-protocol analysis will allow for a better definition of a successful skin spacer as the skin spacer injection protocol (>5mm in PTV skin projection area) is not definite and the trial could be hypothesis generating.

A drawback of our study is that we are not able to secure a full double-blind design. Patients might be aware of an injected spacer as it could be palpable under the skin. For physicians it might be possible to remember the allocated treatment after being unblinded during the PBSI procedure. However, with the assessment of the primary outcome at 2 year follow-up this memory effect is not likely to cause any bias. Also, the type of outcome measure (telangiectasia using Bentzen's 4 -point scale) allows for an objective, reproducible assessment. Furthermore, this a single center study and our findings should be confirmed in a multicenter setting. Lastly, with only patients undergoing PBSI in this study, generalization of our findings to other APBI techniques should be done with caution. However, theoretically, this principle would hold for any APBI technique with a rapid dose fall off.

In this trial we investigate the effect of a subcutaneous spacer injection on the skin dose, late skin toxicity and cosmetic outcome in patients treated with PBSI in the setting of breast conserving therapy. Our results will be relevant for most forms of breast brachytherapy as well as robotic radiosurgery, as skin spacers could be used to protect the skin with these other techniques.

References

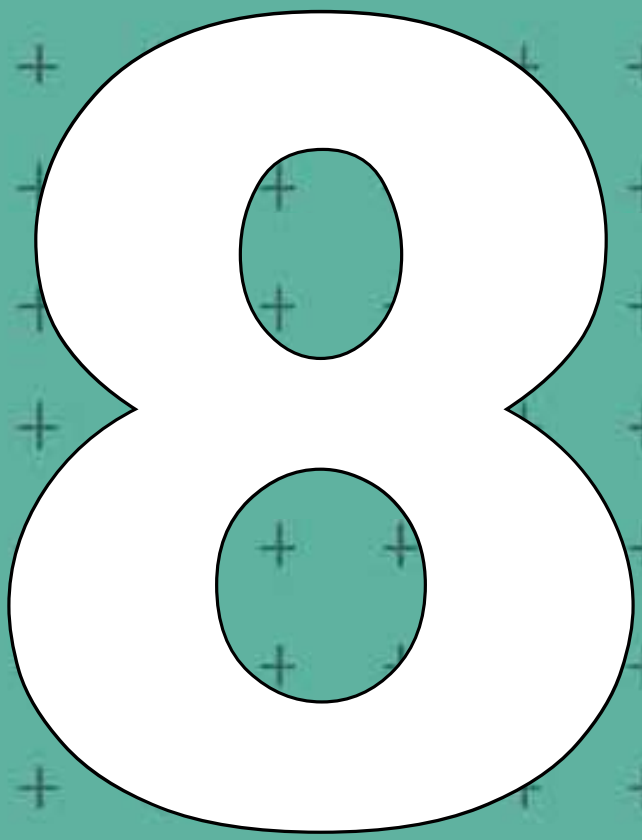
1. SEER database. Cancer Stat Facts: Female Breast Cancer 2017 [Available from: https://seer.cancer.gov/statfacts/html/breast.html.
2. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. Lancet. 2000;355(9217):1822.
3. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233-41.

4. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227-32.
5. Kim MK, Kim T, Moon HG, Jin US, Kim K, Kim J, et al. Effect of cosmetic outcome on quality of life after breast cancer surgery. Eur J Surg Oncol. 2015;41(3):426-32.
6. Fisher ER, Sass R, Fisher B, Gregorio R, Brown R, Wickerham L. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). II. Relation of local breast recurrence to multicentricity. Cancer. 1986;57(9):1717-24.
7. Bethune WA. Partial breast irradiation for early breast cancer. J Natl Med Assoc. 1991;83(9):768, 800, 8.
8. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016;387(10015):229-38.
9. Pignol JP, Caudrelier JM, Crook J, McCann C, Truong P, Verkooijen HA. Report on the Clinical Outcomes of Permanent Breast Seed Implant for Early-Stage Breast Cancers. Int J Radiat Oncol Biol Phys. 2015;93(3):614-21.
10. Vicini FA, Chen PY, Fraile M, Gustafson GS, Edmundson GK, Jaffray DA, et al. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. Int J Radiat Oncol Biol Phys. 1997;38(2):301-10.
11. White J, Winter K, Kuske RR, Bolton JS, Arthur DW, Scroggins T, et al. Long-Term Cancer Outcomes From Study NRG Oncology/RTOG 9517: A Phase 2 Study of Accelerated Partial Breast Irradiation With Multicatheter Brachytherapy After Lumpectomy for Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys. 2016;95(5):1460-5.
12. NSABP. Protocol B-39/RTOG 0413, A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer [Available from: http://www.nsabp.pitt.edu/B-39.asp.
13. Vicini F, Winter K, Straube W, Wong J, Pass H, Rabinovitch R, et al. A phase I/II trial to evaluate three-dimensional conformal radiation therapy confined to the region of the lumpectomy cavity for Stage I/II breast carcinoma: initial report of feasibility and reproducibility of Radiation Therapy Oncology Group (RTOG) Study 0319. Int J Radiat Oncol Biol Phys. 2005;63(5):1531-7.
14. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Saunders C, et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). Health Technol Assess. 2016;20(73):1-188.
15. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013;14(13):1269-77.
16. Gitt A, Bose-Ribeiro H, Nieder C, Kup PG, Hermani H, Buhler H, et al. Treatment Results of MammoSite Catheter in Combination with Whole-breast Irradiation. Anticancer Res. 2016;36(1):355-60.
17. Yashar C, Attai D, Butler E, Einck J, Finkelstein S, Han B, et al. Strut-based accelerated partial breast irradiation: Report of treatment results for 250 consecutive patients at 5 years from a multicenter retrospective study. Brachytherapy. 2016;15(6):780-7.

18. Ott OJ, Strnad V, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. GEC-ESTRO multicenter phase 3-trial: Accelerated partial breast irradiation with interstitial multicatheter brachytherapy versus external beam whole breast irradiation: Early toxicity and patient compliance. Radiother Oncol. 2016;120(1):119-23.
19. Polgar C, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(2):259-68.
20. Wobb JL, Shah C, Jawad MS, Wallace M, Dilworth JT, Grills IS, et al. Comparison of chronic toxicities between brachytherapy-based accelerated partial breast irradiation and whole breast irradiation using intensity modulated radiotherapy. Breast. 2015;24(6):739-44.
21. Mashouf S, Fleury E, Lai P, Merino T, Lechtman E, Kiss A, et al. Clinical Significance of Accounting for Tissue Heterogeneity in Permanent Breast Seed Implant Brachytherapy Planning. Int J Radiat Oncol Biol Phys. 2016;94(4):816-23.
22. Cuttino LW, Heffernan J, Vera R, Rosu M, Ramakrishnan VR, Arthur DW. Association between maximal skin dose and breast brachytherapy outcome: a proposal for more rigorous dosimetric constraints. Int J Radiat Oncol Biol Phys. 2011;81(3):e173-7.
23. Archambeau JO, Pezner R, Wasserman T. Pathophysiology of irradiated skin and breast. Int J Radiat Oncol Biol Phys. 1995;31(5):1171-85.
24. Vargo JA, Verma V, Kim H, Kalash R, Heron DE, Johnson R, et al. Extended (5-year) outcomes of accelerated partial breast irradiation using MammoSite balloon brachytherapy: patterns of failure, patient selection, and dosimetric correlates for late toxicity. Int J Radiat Oncol Biol Phys. 2014;88(2):285-91.
25. Chen PY, Vicini FA, Benitez P, Kestin LL, Wallace M, Mitchell C, et al. Long-term cosmetic results and toxicity after accelerated partial-breast irradiation. Cancer. 2006;106(5):991-9.
26. Ott OJ, Lotter M, Fietkau R, Strnad V. Accelerated Partial-Breast Irradiation with Interstitial Implants. Strahlentherapie und Onkologie. 2009;185(3):170-6.
27. Lilla C, Ambrosone CB, Kropp S, Helmbold I, Schmezer P, von Fournier D, et al. Predictive factors for late normal tissue complications following radiotherapy for breast cancer. Breast Cancer Res Treat. 2007;106(1):143-50.
28. Strnad V, Ott O, Potter R, Hildebrandt G, Hammer J, Resch A, et al. Interstitial brachytherapy alone after breast conserving surgery: interim results of a German-Austrian multicenter phase II trial. Brachytherapy. 2004;3(3):115-9.
29. Wazer DE, Kaufman S, Cuttino L, DiPetrillo T, Arthur DW. Accelerated partial breast irradiation: an analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. Int J Radiat Oncol Biol Phys. 2006;64(2):489-95.
30. Pignol JP, Rakovitch E, Keller BM, Sankreacha R, Chartier C. Tolerance and acceptance results of a palladium-103 permanent breast seed implant Phase I/II study. Int J Radiat Oncol Biol Phys. 2009;73(5):1482-8.
31. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol. 2017;7(2):73-9.

32. Polgar C, Van Limbergen E, Potter R, Kovacs G, Polo A, Lyczek J, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). Radiother Oncol. 2010;94(3):264-73.
33. Pignol JP, Keller B, Rakovitch E, Sankreacha R, Easton H, Que W. First report of a permanent breast 103Pd seed implant as adjuvant radiation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2006;64(1):176-81.
34. Hoeller U, Tribius S, Kuhlmey A, Grader K, Fehlauer F, Alberti W. Increasing the rate of late toxicity by changing the score? A comparison of RTOG/EORTC and LENT/SOMA scores. Int J Radiat Oncol Biol Phys. 2003;55(4):1013-8.
35. Bentzen SM, Overgaard M. Relationship between early and late normal-tissue injury after postmastectomy radiotherapy. Radiother Oncol. 1991;20(3):159-65.
36. CTCAE 4.03 quick reference [Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
37. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6.
38. Stanton AL, Krishnan L, Collins CA. Form or function? Part 1. Subjective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. Cancer. 2001;91(12):2273-81.
39. Sprangers MA, Groenvold M, Arraras JI, Franklin J, te Velde A, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. J Clin Oncol. 1996;14(10):2756-68.
40. Hilts M, Halperin H, Morton D, Batchelar D, Bachand F, Chowdhury R, et al. Skin dose in breast brachytherapy: Defining a robust metric. Brachytherapy. 2015;14(6):970-8.
41. Keller BM, Ravi A, Sankreacha R, Pignol JP. Permanent breast seed implant dosimetry quality assurance. Int J Radiat Oncol Biol Phys. 2012;83(1):84-92.
42. Pignol JP, Truong P, Rakovitch E, Sattler MG, Whelan TJ, Olivotto IA. Ten years results of the Canadian breast intensity modulated radiation therapy (IMRT) randomized controlled trial. Radiother Oncol. 2016;121(3):414-9.
43. Struik GM, Pignol JP, Kolkman-Deurloo IK, Godart J, Verduijn GM, Koppert LB, et al. Subcutaneous spacer injection to reduce skin toxicity in breast brachytherapy: A pilot study on mastectomy specimens. Brachytherapy. 2019;18(2):204-10.

CHAPTER EIGHT



Introducing Permanent Breast Seed Implants in Europe: the Rotterdam Experience

Gerson M. Struik

Unpublished work

The introduction of a Permanent Breast Seed Implant program in Rotterdam, the Netherlands, was the basis for this thesis. This form of breast brachytherapy suits very well with our long-term vision of treating early stage breast cancer patients. The excellent oncological outcomes warrant the development of patient friendly techniques. PBSI, that reduces the 3-5 weeks radiotherapy treatment to a single hour implantation procedure, is a patient friendly technique that complies with the need for more patient friendly radiotherapy treatments. Although the concept of APBI was introduced in 1991 and several large clinical trials confirmed it's effectivity, the clinical experience with the specific technique of PBSI is limited as compared to HDR brachytherapy, intra-operative radiotherapy or 3D conformal EBRT APBI.

The technique was introduced in 2006 by Pignol as a technique similar to prostate permanent seed brachytherapy. It was evaluated in two phase I-II trials and at the end of 2015 the excellent effectivity was reported with a local recurrence rate of 1.2% at 5 years amongst 134 patients being treated in a single institute at that time. Since then, a multicenter prospective registry study has been started in several hospitals in Canada and the U.S.

Supported by this PBSI evidence we started a program in Rotterdam in 2016, being the first European hospital to do so. The program provided eligible patients with a new patient friendly radiotherapy treatment option. Research was focused on increasing treatment accuracy and reducing skin toxicity. To introduce this new technique we had to overcome several logistic and administrative hurdles. The use of Pd-103 seeds and equipment in a clinical trial, required acquisition of new radioprotection licenses, medical devices registration and ethics approval at several institutions such as: the Authority of Nuclear Safety and Radioprotection (Dutch: ANVS), the Health Inspectorate and the Medical Ethical Committee. Furthermore, the medical community in the Netherlands had to be motivated to adopt this technique as a treatment option and to refer patients to our program. Lastly, local protocols had to be developed and tested and staff had to be adequately trained.

The project was presented at local and (inter)national scientific meetings and a training program for radiotherapy staff was designed and performed. Finally, in September 2017 we were able to treat the first PBSI patient in the Netherlands. A number of 80 patients were referred from all breast cancer centers in the Rotterdam area as well as the rest of the Netherlands for eligibility screening in the first half year of the program. Of those patients 29 patients were included and successfully treated. A team of 3 breast radiation oncologists was trained by prof. Pignol to independently perform the PBSI procedure. In that period our program was the fastest recruiting PBSI program internationally. Several international breast surgeons and brachytherapists were visiting the Erasmus MC to see the technique.

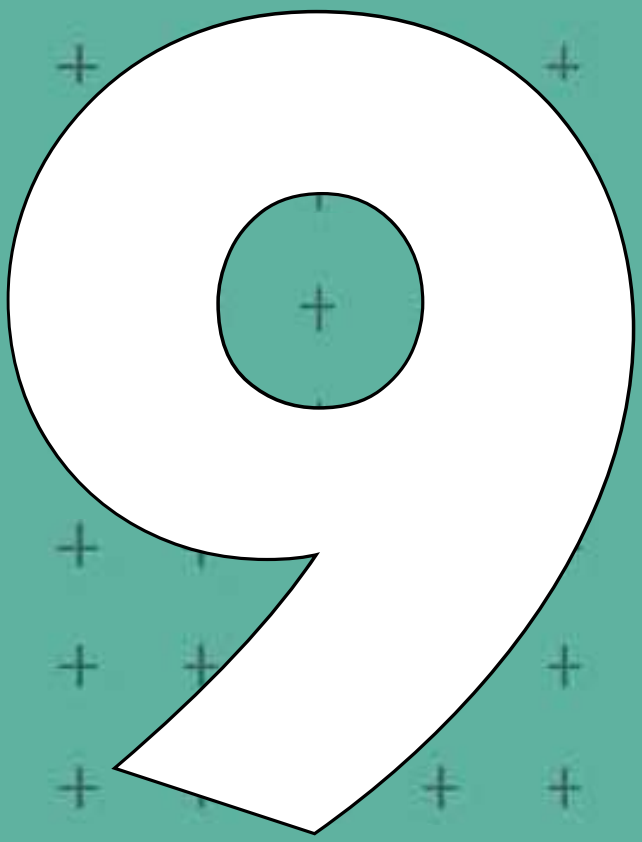
In April 2018 prof. Pignol left the Erasmus MC and the program was continued by the team of radiation oncologists that were trained previously. To adjust the PBSI procedure to the specific skills of the new team some changes to the protocol were made, including an extra post-implant CT-scan at the day of implant. By doing so, more direct feedback was provided on the quality of the implant. After two successful procedures, the inclusion rate slowed down. In June 2018 the first two PBSI

procedures in the new Erasmus MC facility were performed. Although during the procedures no complications were recognized, an unexpected adverse event was discovered on the post-implant CT-scan; the full implant was performed at the wrong depth and angle. This resulted in four of the implantation needles entering the chest wall and several seeds were located in the pleural cavity. This complication was never reported in previous PBSI series. The patient did not experience any complaints and no additional treatments were required. The department management put the PBSI procedures on-hold and a local incident analysis (PRISMA) was performed. More extensive evaluation of the PBSI procedure as performed by the current radiation oncology staff, pointed out that further investments in training and procedural accuracy were warranted before continuation of the protocol. The radiation oncology staff and management evaluated that, after prof. Pignol left, the(ir) expertise for this specific procedure was currently not sufficient. Therefore they decided as yet to stop performing PBSI at the Erasmus MC in December 2018. Currently, the clinical trial as described in chapter 6 is still ongoing as all included patients are still in follow-up, but no new patients are included at time of writing this thesis.

As described in **chapter 6**, no interim analysis was planned and therefore no results on the effect of a subcutaneous spacer during PBSI on (skin) dosimetry and PROMs are reported in this thesis. Currently, our study group is working on continuation of the clinical trial elsewhere. The introduction of PBSI in the Erasmus MC learned that it is challenging to implement this technique in a center with limited breast brachytherapy experience. Although the current implantation technique has shown to be safe and effective in previous reports, minor adjustments could make it more feasible for radiation oncologist with limited brachytherapy experience. The use of 3D ultrasound, hydrogel markers and/or pre-implanted catheters could help radiation oncologist to easier implant the fiducial needle. Another possibility would be to get surgeons and/or radiologists more involved in the implantation procedure.

Chapter 5, 6 and 7 describe the research projects that were directly related to the PBSI program in Rotterdam. It clearly shows the potential spin-off of such a research project. Although the clinical trial is currently not recruiting patients in Rotterdam, in the successful start of the program we were able to finish some valuable research. The use of skin spacers and in vivo film dosimetry is applicable to other APBI techniques too. Apart from the lesson learned as described in **chapter 8** this project has provided proof-of-concept data for skin spacing and in vivo film dosimetry, that could be the basis for new research. Efforts are made to restart the PBSI program in the Netherlands, as it suits very well in the tailormade breast cancer treatment nowadays ánd the treatment is very convenient for patients.

CHAPTER NINE



Injection of radiopaque hydrogel at time of lumpectomy improves the target definition for adjuvant radiotherapy

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Abstract

Background and purpose: During oncoplastic breast-conserving surgery (BCS), the surgical cavity is closed to reduce seroma formation. This makes the radiotherapy target definition using clips challenging, leading to poor inter-observer agreement and potentially geographical misses. We hypothesize that injecting a radiopaque hydrogel in the lumpectomy cavity before closure improves radiotherapy target definition and agreement between observers.

Methods: Women undergoing BCS in a single university hospital were prospectively accrued in the study. Three to 9 ml of iodined PolyEthylene Glycol (PEG) hydrogel and clips were inserted in the lumpectomy cavity. A CT-scan was performed at 4 to 6 weeks. CT images of BCS patients with standard clips only were used as control group, matched on age, specimen weight, and distance between clips. Six radiation oncologists delineated the tumor bed volumes and rated the cavity visualization score (CVS). The primary endpoint was the agreement between observers measured using a Conformity Index (Cx).

Results: Forty-two patients were included, 21 hydrogel procedures and 21 control, resulting in 315 observer pairs. The feasibility of the intervention was 100%. The median Cx was higher in the intervention group (Cx=0.70, IQR [0.54-0.79]) than in the control group (Cx=0.54, IQR [0.42-0.66]), $p<0.00$, as were the CVS (3.5 [2.5-4.5] versus 2.5 [2-3.5], $p<0.001$) The rate of surgical site infections was similar to literature.

Conclusion: The use of radiopaque PEG enables to identify the lumpectomy cavity, resulting in a high inter-observer agreement for radiotherapy target definition. This intervention is easy to perform and blend well into current practice.

Introduction

For localized cancers, breast-conserving therapy (BCT), including limited surgery and adjuvant whole breast radiotherapy, is equivalent to mastectomy in regard to oncological outcomes while enabling breast preservation[1]. Oncoplastic techniques have been increasingly used worldwide to improve cosmesis[2-4]. Those techniques involve, at minimum, a simple volume displacement (level I oncoplastic technique), as the breast parenchyma is approximated to close the lumpectomy cavity[5]. In so doing, the seroma is limited in size, and it often becomes invisible on a CT-scan. Eventually this technique creates challenges for tumor bed delineation at the time of adjuvant radiotherapy planning[6]. Accurate tumor bed delineation to target breast radiotherapy is particularly critical for accelerated partial breast irradiation (APBI) or when a boost dose is required. During APBI, only the part of the breast immediately surrounding the tumor bed is irradiated[7-11]. Also, young or high-risk patients are benefiting from a boost dose to the tumor bed after or during whole breast radiotherapy[12].

Inaccurate target definition carries the risk of a radiation geographical miss, which, in turn, might lead to an increased risk of local recurrence, especially for APBI. Furthermore, if the tumor bed delineation is enlarged due to uncertainties, there is an increased risk of toxicity[13-15]. Finally, if the target cannot be appropriately defined, some patients may be declined for patient-friendly APBI techniques[15-19]. Traditionally, surgical clips are placed at the time of surgery to guide the tumor bed delineation. However, a recent study by den Hartogh shows that radiotherapy target definition using clips has poor inter-observer agreement in patients following oncoplastic surgery[6]. Thus, the attempt to improve surgical outcome by performing oncoplastic techniques might impair radiotherapy treatment outcomes.

A recent development in radiation oncology is the use of temporary injectable hydrogels. Among others, polyethylene glycol (PEG) radiopaque hydrogel is successfully used as a spacer to remove critical structures from the high dose area, such as the rectum in prostate radiotherapy[20]. Also, PEG hydrogel has been proposed as a tissue marker[21].
Ciernik et al. tested a PEG hydrogel marker to visualize the cavity after lumpectomy and suggested a high level of inter-observer agreement for target delineation[22]. The marker contains PEG with less than 1% iodine, and this material has a high imaging contrast on CT, MRI and, to a lesser extent, on ultrasound up to 3 months. Reabsorption and clearance takes place approximately 7 months after implantation.

We report a prospective clinical cohort study testing the radiopaque hydrogel to improve radiotherapy target definition following oncoplastic breast conserving surgery. Our aim was to assess if the injection in the lumpectomy cavity before closure was safe, feasible, and increased inter-observer agreement for the radiotherapy target definition.

Patients and Methods

Study population

The study design was a prospective intervention cohort study with a matched control group. The study was approved by the Erasmus MC research ethic board and registered at the Netherlands Trial Register (NTR-6610).

Eligible patients included women with a diagnosis of breast cancer or DCIS planned for breast-conserving surgery, with full-thickness closure corresponding to level 1 oncoplastic breast surgery, and adjuvant radiotherapy. Patients with oncoplastic surgery of level 2 or more (volume replacement), pre-operative indication for adjuvant chemotherapy, or an allergy for PEG or iodine were excluded. Selected patients were included after written informed consent was obtained.

Treatments

Surgical procedures were performed in a single large secondary teaching hospital in Rotterdam, the Netherlands (Franciscus Gasthuis and Vlietland). After tumor resection and hemostasis were achieved, five surgical clips were placed, according to standard protocol, to define the cavity walls: including one positioned deep toward the fascia pectoralis and four in each radial direction[23]. Subsequently, any undermining of the fibroglandular tissue from the pectoralis muscle and/or skin was performed. Then, 3 to 9 ml of radiopaque PEG hydrogel (TraceIT©, Augmenix Inc, Bedford, MA) was instilled in the cavity and coated onto the tumor cavity walls with the fingertips. The cavity was closed following oncoplastic protocol with the suture of at least one deep, glandular, layer and closure of the most superficial layer and the skin. The amount of product used was recorded and ease of use scored using the System Usability Scale (SUS)[24]. This 10 question 5-point scale is a simple and reliable tool to measure usability of new technology or products, and has been used in medical research before[25]. After referral to radiation oncology, a standard CT-simulation for radiotherapy planning purpose was acquired with images of 2.5 mm thickness and a resolution of 1 x 1 mm^2 at 120 kilovoltpeak (kVp). The surgical scar and the glandular tissue were marked on the skin with a CT compatible wire.

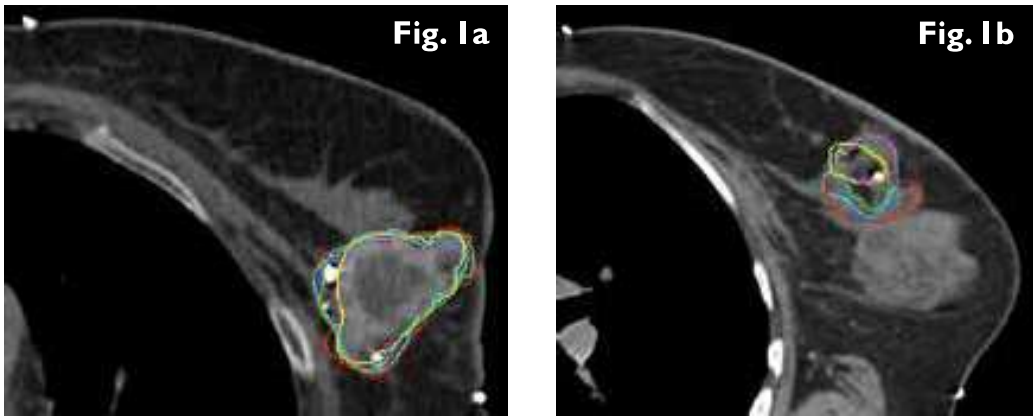
Patients treated with the hydrogel were matched 1:1 with a cohort of patients treated by the same team of surgeons also performing a level 1 oncoplastic surgery with placement of five surgical clips[23], but without instillation of the hydrogel. Matching was performed on factors known to influence interobserver variability of target definition and/or cavity visibility, ensuring similar resected specimen weight and maximum distance between clips (as predictors of target volume)[26-29], and age (below or above 70 years) as surrogate for breast composition[26].

Target volume delineation

Anonymized CT image sets of both group of patients were transferred to a MIM Symphony 6.6 imaging station (MIM Software Inc, Cleveland, OH). Six experienced and senior radiation oncologists delineated the target volumes in a random sequence and were blinded for each other's contours, by

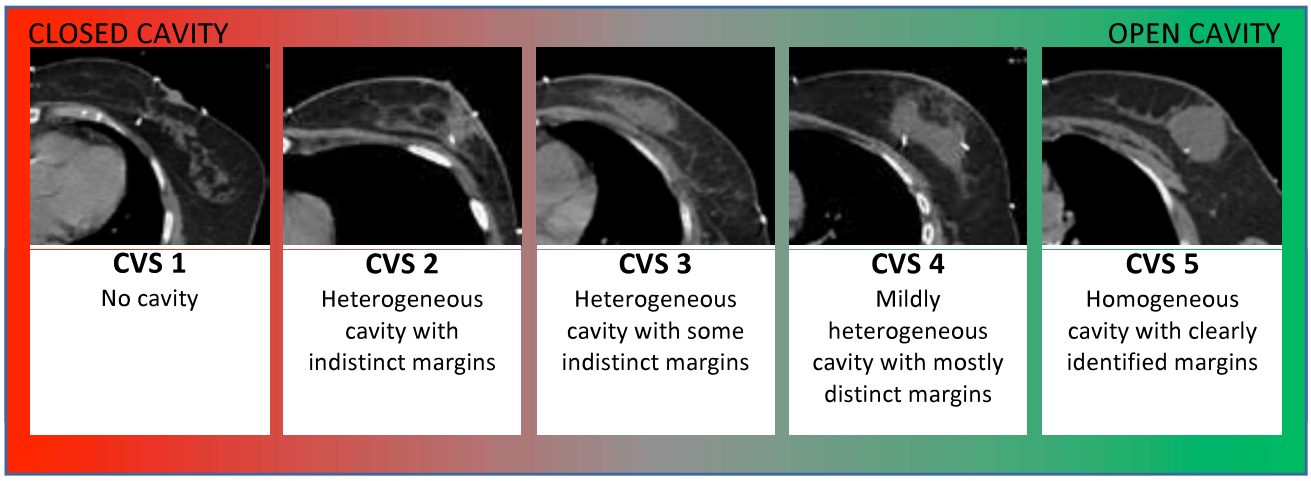
making the sets of CT-images available to each radiation oncologist separately (Fig. 1). Each patient's pre-operative information and imaging, surgical report and pathology report were available.
For the patients in the intervention group, the radiation oncologists were asked to contour the tumor bed with the following instruction: "Please contour the tumor bed volume as usual, using information of the CT density (including the hydrogel) and the clips". For the control group, the radiation oncologists were asked to delineate using the following instruction: "Please contour the tumor bed volume as usual, using information of the CT density and the clips".

Figure 1-a/b: Example of tumor bed delineation on CT with (a) and without (b) hydrogel



Additionally, all six radiation oncologists were asked to rate the cavity visualization score (CVS)[26, 27, 30] and record the time needed for contouring per patient. The CVS assesses the visibility of the lumpectomy cavity on CT on a 5-point scale ranging from "no cavity visible" (CVS 1) to "homogeneous cavity with clearly identified margins" (CVS 5) (fig. 2). It is commonly used in studies on target definition[6, 31].

Figure 2: Cavity visualization Score*



*all example CT-images are captured from patients in the control group of this study

Analysis

The primary outcome measure was the Conformity Index (Cx), defined by the ratio between the volume of agreement of the defined target volumes divided by the encompassing volume for each observer pair[6]. Secondary outcome measures included the distance between the center of mass of the target volumes (dCOM), the target volumes in cc, the CVS[27, 30], the feasibility of hydrogel injection, adverse events, and ease of use.

A sample size of 21 patients times 6 observers was calculated, leading to 315 observer pairs in both the intervention and control group. Based on an expected SD in Cx of 0.19[6, 32], alpha=0.05 and beta =0.2, this sample size would make it possible to detect an effect size of 0.044 of the primary outcome (Cx) with 95% confidence. Even for a subgroup analysis (alpha=0.025) on CVS≤3 with an expected number of n=10 patients in each group the detectable effect size would be 0.068, which was deemed acceptable.

For the primary outcome measure, we reported median values and accompanying interquartile ranges (IQRs) and, as Shapiro–Wilk normality tests showed this variable was not normally distributed, assessed significance using a Mann-Whitney U-test.

Descriptive statistics were used for the analysis of secondary endpoints, assuming independency of groups. Differences between groups were also assessed using a Mann-Whitney U-test. Multiple linear regression analysis testing the factors influencing the Cx included the following independent variables: group (intervention versus control), mean target volume, CVS per observer pair, and the matching factors as described above. Effect modification was modelled as an interaction effect of group (intervention versus control) times target volume. The feasibility of the hydrogel marker injection and adverse events were described as percentages. IBMM SPSS Statistics version 24 was used with two-sided p-values below 0.05 considered statistically significant.

Results

Twenty-four patients were included in the interventional group. Three patients were excluded because they had positive margins on the pathology report and they had a second surgery for re-excision. In these three cases , during re-excision the hydrogel was clearly identifiable, being solid in the surgical cavity and easy to remove. In the control group we randomly matched 21 patients out of 100 possible controls. Patient characteristics are detailed in Table 1. The groups were well balanced in regard to tumor diameter, histology, resected specimen weight, and maximum distance between clips. In the intervention group, patients were 5 years younger, leading to potentially more dense breasts.

Table 1: Patient characteristics between groups. Data are presented as median values, and inter-quartile ranges within brackets.

	Intervention group (hydrogel+clips) n=21	**Control group (clips only) n=21**
Age, years	57 [50-64]	62 [50-65]
Microscopic tumor diameter in mm	14.5 [12-18]	15 [9.5-21]
Resected specimen weight in grams	42 [28-66]	45 [35-61]
Histology	19 ductal carcinoma 1 DCIS 1 mucinous carcinoma	15 ductal carcinoma 4 DCIS 1 lobular carcinoma 1 apocrine carcinoma
Laterality	5 Left 16 Right	9 Left 12 Right
Interval between surgery and CT-simulation in days	39 [31-46]	36 [24-55]
Maximum distance between surgical clips on CT in mm	46 [39-52]	45 [31-55]

The use of hydrogel was technically feasible in all patients. The product was easy to use, with a median SUS score of 100 (IQR [96-100]). Two patients (9.5%) in the intervention group developed a superficial surgical site infection, and two patients (9.5%%) had clinically apparent seroma formation, all being grade 1-2 out of 5 according to the Clavien Dindo classification[33].

Patients in the intervention group had their CT-simulation performed at a median of 39 days post-surgery (IQR [31-46]). For most patients, the hydrogel was easily identified in the surgical cavity on the radiotherapy planning CT. The occurrence of seroma in some cases caused dilution of the hydrogel or, in other cases, formation of a level of hydrogel, not completely filling up the cavity (Fig. 3).

The median conformity index was higher in the intervention group, with a Cx of 0.70 (IQR [0.54-0.79]), compared to the control group, with a Cx of 0.54 (IQR [0.42-0.66]), suggesting that the target delineation was less variable in the presence of hydrogel ($p<0.001$). On the other-hand, contouring in the presence of hydrogel took slightly more time - 5 minutes instead of 4 ($p<0.001$) – and also led to target volumes two and a half times larger being contoured - 26.2 cc instead of 10.2cc ($p<0.001$).

Table 2: Results for various radiotherapy target delineation metrics. Data are presented as median values with inter-quartile ranges within brackets.

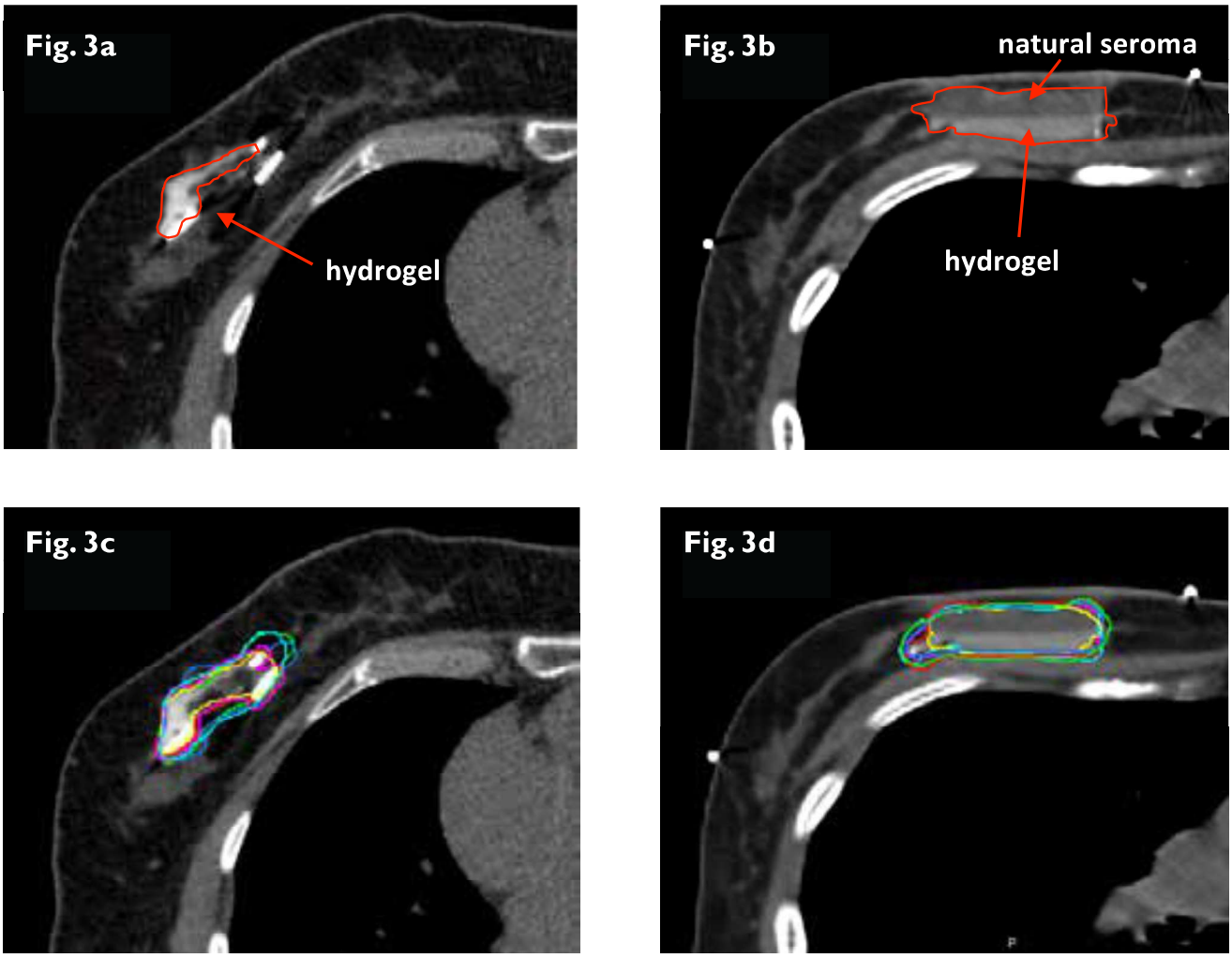
	Intervention group (hydrogel+clips) n=315**	**Control group (clips only) n=315****	**P-value***
Cx	0.70 [0.54-0.79]	0.54 [0.42-0.66]	<0.001
CVS	3.5 [2.5-4.5]	2.5 [2-3.5]	<0.001
dCOM in mm	2.0 [1.1-4.3]	3.1 [1.6-5.3]	<0.001
Target volume in cc	26.2 [15.1-43.8])	10.2 [5.8-22.9]	<0.001
Time needed for delineation in minutes	5 [4-7]	4 [3-5]	<0.001.

* Mann-Whitney-U-test, ** n= number of observer pairs

Multiple linear regression analysis showed that the adjusted Beta coefficient was 0.09 (95% CI [0.05 - 0.17]) for group and 0.002 (95% CI [0.001 - 0.004]) for mean target volume, meaning that both the presence of hydrogel and of a large target volume were significantly associated with a better Cx. Adding the interaction term of intervention times target volume to the model showed that the increase in Cx per unit volume is larger in the presence of gel (adjusted Beta coefficient was 0.005 (95% CI [0.004 - 0.006]). meaning that with every 2 cc larger volume, the presence of gel, leads to an extra 0.01 increase of Cx. Mean CVS per observer pair was eventually excluded from the model as variable group is positively correlated with a CVS (Spearman's correlation coefficient 0.326, $p<0.001$). This is logical since the intervention is intended to increase the seroma visibility.

The effect of the intervention was strongest in the matched group of patients with a CVS ≤ 3 in the control group (median Cx 0.67 with hydrogel and clips versus 0.49 with clips alone, $p<0.001$), meaning in the group of patients where the seroma was difficult to identify, compared to the group of patients with a CVS > 3 in the control group (median Cx 0.74 versus 0.68, $p<0.001$).

Figure 3: Example of case without natural seroma (a) and a case with natural seroma (b), showing some dilution and formation of a level of hydrogel, not completely filling up the cavity (shown in red) and the resulting six contours for both cases (c and d).



Discussion

This study demonstrates that using a hydrogel loaded with iodine during lumpectomy cavity closure, reduces the variability of target contouring in a population of well trained and highly specialized radiation oncologists.

We report on a simple surgical intervention adding to other solutions to improve radiotherapy target definition for breast cancer patients, including the use of clips, 3D ultrasound or MR image fusion or simulation. Since inter-observer variability is indicative of the difficulty to accurately define the treatment target volumes among practitioners, those studies examining these options have used the conformity index (Cx) as a measure of accuracy in defining the target volume[29]. Our results compare well with other studies using standardized contouring protocols and surgical clips, which is the current gold standard in radiotherapy[15]. Previous studies evaluating the interobserver

agreement for delineation with clips found comparable Cx to the one we reported here for the control group, between 0.56 to 0.61[28, 29, 34]. Another study reports a higher agreement using gold fiducial markers, with a Cx of 0.70[35]. However, none of these studies were performed in a context of a level 1 oncoplastic intervention. A study by Den Hartogh showed that radiotherapy target definition using clips alone for patients with full thickness closure (FTC) has a much poorer inter-observer agreement, with a median Cx of 0.44[6].

The significantly higher Cx in our intervention group than in our control group can probably be explained by the also significantly higher CVS (3.5 versus 2.5 respectively). The median CVS score of 2.5 (heterogeneous cavity with no to minimal distinct margins) in our control group seems intuitively higher than expected. However, a median CVS score of 3 was found in the study by den Hartogh et al.[6]after FTC. This means that a FTC not always translate into a loss of cavity. In several cases in our study the full-thickness closure was limited to a single suture, which could be the explanation of the existence of a visible seroma. The high conformity index found in our intervention group, where all patients had oncoplastic intervention, should be considered as a good result for improving the quality of the radiation treatment. The larger median target volume found in the intervention group (26.2 versus 10.2 cc) did not alone explain the difference in Cx, since the regression analysis adjusting for target volume showed that the use of hydrogel was an independent factor of improved Cx. The hydrogel itself accounted for a 9% increase in Cx on average, which is clinically relevant. Interestingly, although the hydrogel itself adds some volume (3 to 9 cc in this study) which may preserve part of the seroma, the median target volume in our intervention group, 26.2 cc, is comparable to the 23 cc found in the study by den Hartogh[6]. In those cases with a relatively large seroma, the visualization was however facilitated by the presence of radio-opaque gel on the border of the seroma. Finally, the effect of hydrogel on mean target volumes and consequent planned target volumes (PTVs) could be more formally concluded in a randomized controlled trial or a comparison within the same patient.

The hydrogel injection intervention was found feasible, safe and easy to perform. The rate of infection (9.5%) and the formation of a clinically apparent seroma (9.5%) after injection of hydrogel was comparable to the literature for breast-conserving surgery[36-39].

A higher Cx results in a lower risk of geographical miss of the administered radiotherapy, which, in turn, may result in a better outcome in term of local control. Additionally, with less inter-observer variability, smaller margins accounting for delineation variation could be used. This could reduce radiotherapy related toxicity, such as skin effects and breast fibrosis, and compensate for the possibly larger volume delineated when using a hydrogel injection. Also, as shown in figure 1, some observers have smaller volume contoured compared to other. This would mean a lower volume treated using APBI and potentially an improvement of the treatment tolerance. Furthermore, by

helping target definition in patients with low CVS, more patients may be eligible for more patient friendly APBI techniques as patients with a poorly defined cavity are generally excluded[15-17, 40, 41]. A gel with good MRI visibility could also be very useful in an era when new machines, including the MR-linac, are used for improved image guided radiotherapy (IGRT)[42].

An important caveat in breast radiotherapy target definition is the fact that the tumor bed needs treatment and does not necessarily match the lumpectomy cavity. The discussion about the volume to be treated lead the GEC-ESTRO to develop complex contouring guidelines and recommends using the exact microscopic surgical margins in all directions to realize the volume expansion from seroma to clinical target volume (CTV). The hydrogel helps to better define the lumpectomy cavity, but still the contouring guidelines should be followed.

A limitation of the intra-operative injection of the hydrogel is that in 9 out of 21 cases the seroma as defined by the gel showed some leveling with fluid or dilution resulting in imprecise contours. Since the CT scan was performed on average 5.5 weeks after the surgery, we assume that post-operative healing, inflammation and fluid production may have deteriorated the visibility of the gel. In such cases the observers have unanimously incorporated the diluted cavity into the target volume."

In our study, patients with a CVS ≤ 3 had the most benefit from the hydrogel. To better select patients with a low CVS, that could benefit from a hydrogel injection, a future direction would be to change the timing of the intervention to the moment of radiotherapy planning when the healing process is largely completed. This would also partly resolve some of the limitations caused by dilution of the gel as described above.

In conclusion, this study shows that the use of a radiopaque hydrogel during BCS enables breast surgeons to clearly demarcate the lumpectomy cavity, resulting in a high inter-observer agreement of radiotherapy target definition. This intervention is easy to perform and can easily blend into standard practice.

References

1. Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707-16.
2. Asgeirsson KS, Rasheed T, McCulley SJ, Macmillan RD. Oncological and cosmetic outcomes of oncoplastic breast conserving surgery. Eur J Surg Oncol. 2005;31(8):817-23.
3. Driul L, Bernardi S, Bertozzi S, Schiavon M, Londero AP, Petri R. New surgical trends in breast cancer treatment: conservative interventions and oncoplastic breast surgery. Minerva Ginecol. 2013;65(3):289-96.

4. Kim MK, Kim T, Moon HG, Jin US, Kim K, Kim J, et al. Effect of cosmetic outcome on quality of life after breast cancer surgery. Eur J Surg Oncol. 2015;41(3):426-32.
5. Chatterjee A, Dayicioglu D, Khakpour N, Czerniecki BJ. Oncoplastic Surgery: Keeping It Simple With 5 Essential Volume Displacement Techniques for Breast Conservation in a Patient With Moderate- to Large-Sized Breasts. Cancer Control. 2017;24(4):1073274817729043.
6. den Hartogh MD, van den Bongard HJ, Davidson MT, Kotte AN, Verkooijen HM, Philippens ME, et al. Full-thickness closure in breast-conserving surgery: the impact on radiotherapy target definition for boost and partial breast irradiation. A multimodality image evaluation. Ann Surg Oncol. 2014;21(12):3774-9.
7. Correa C, Harris EE, Leonardi MC, Smith BD, Taghian AG, Thompson AM, et al. Accelerated Partial Breast Irradiation: Executive summary for the update of an ASTRO Evidence-Based Consensus Statement. Pract Radiat Oncol. 2017;7(2):73-9.
8. Polgar C, Van Limbergen E, Potter R, Kovacs G, Polo A, Lyczek J, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Europeen de Curietherapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). Radiother Oncol. 2010;94(3):264-73.
9. Shah C, Vicini F, Wazer DE, Arthur D, Patel RR. The American Brachytherapy Society consensus statement for accelerated partial breast irradiation. Brachytherapy. 2013;12(4):267-77.
10. Shaitelman SF, Lin HY, Smith BD, Shen Y, Bedrosian I, Marsh GD, et al. Practical Implications of the Publication of Consensus Guidelines by the American Society for Radiation Oncology: Accelerated Partial Breast Irradiation and the National Cancer Data Base. Int J Radiat Oncol Biol Phys. 2016;94(2):338-48.
11. Consensus Statement for Accelerated Partial Breast Irradiation: the American Society of Breast Surgeons; 2011 [updated August 15, 2011; cited 2017 2017/1/10]. Available from: https://www.breastsurgeons.org/new_layout/about/statements/PDF_Statements/APBI.pdf.
12. Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. Lancet Oncol. 2015;16(1):47-56.
13. Borger JH, Kemperman H, Smitt HS, Hart A, van Dongen J, Lebesque J, et al. Dose and volume effects on fibrosis after breast conservation therapy. Int J Radiat Oncol Biol Phys. 1994;30(5):1073-81.
14. den Hartogh MD, van Asselen B, Monninkhof EM, van den Bosch MA, van Vulpen M, van Diest PJ, et al. Excised and irradiated volumes in relation to the tumor size in breast-conserving therapy. Breast Cancer Res Treat. 2011;129(3):857-65.
15. Strnad V, Hannoun-Levi JM, Guinot JL, Lossl K, Kauer-Dorner D, Resch A, et al. Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost Partial Breast Irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery. Radiother Oncol. 2015;115(3):342-8.
16. NRG Oncology (2018). NSABP Clinical Trials OverviewProtocol B-39/RTOG 0413 [Available from: http://www.nsabp.pitt.edu/B-39.asp.
17. Major T, Gutierrez C, Guix B, van Limbergen E, Strnad V, Polgar C. Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. Radiother Oncol. 2016;118(1):199-204.

18. Ott OJ, Strnad V, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. GEC-ESTRO multicenter phase 3-trial: Accelerated partial breast irradiation with interstitial multicatheter brachytherapy versus external beam whole breast irradiation: Early toxicity and patient compliance. Radiother Oncol. 2016;120(1):119-23.
19. Vicini F, Shah C, Tendulkar R, Wobb J, Arthur D, Khan A, et al. Accelerated partial breast irradiation: An update on published Level I evidence. Brachytherapy. 2016;15(5):607-15.
20. Hamstra DA, Mariados N, Sylvester J, Shah D, Karsh L, Hudes R, et al. Continued Benefit to Rectal Separation for Prostate Radiation Therapy: Final Results of a Phase III Trial. International Journal of Radiation Oncology • Biology • Physics. 2017;97(5):976-85.
21. Bair RJ, Bair E, Viswanathan AN. A radiopaque polymer hydrogel used as a fiducial marker in gynecologic-cancer patients receiving brachytherapy. Brachytherapy. 2015;14(6):876-80.
22. Ciernik IF, Voss H, Wosle M. Standardization of the target volume for boost or partial breast radiation therapy after lumpectomy of breast cancer. Int J Radiat Oncol Biol Phys. 2014;89(3):690-1.
23. Kirby AN, Jena R, Harris EJ, Evans PM, Crowley C, Gregory DL, et al. Tumour bed delineation for partial breast/breast boost radiotherapy: what is the optimal number of implanted markers? Radiother Oncol. 2013;106(2):231-5.
24. Brooke J. SUS - A quick and dirty usability scale. In: P. W. Jordan BT, B. A. Weerdmeester, A. L. McClelland, editor. Usability evaluation in industry. London: Taylor and Francis; 1996. p. 189-94.
25. Pei YC, Chen JL, Wong AMK, Tseng KC. An Evaluation of the Design and Usability of a Novel Robotic Bilateral Arm Rehabilitation Device for Patients with Stroke. Front Neurorobot. 2017;11:36.
26. Kader HA, Truong PT, Pai R, Panades M, Jones S, Ansbacher W, et al. When is CT-based postoperative seroma most useful to plan partial breast radiotherapy? Evaluation of clinical factors affecting seroma volume and clarity. Int J Radiat Oncol Biol Phys. 2008;72(4):1064-9.
27. Landis DM, Luo W, Song J, Bellon JR, Punglia RS, Wong JS, et al. Variability among breast radiation oncologists in delineation of the postsurgical lumpectomy cavity. Int J Radiat Oncol Biol Phys. 2007;67(5):1299-308.
28. Petersen RP, Truong PT, Kader HA, Berthelet E, Lee JC, Hilts ML, et al. Target Volume Delineation for Partial Breast Radiotherapy Planning: Clinical Characteristics Associated with Low Interobserver Concordance. International Journal of Radiation Oncology*Biology*Physics. 2007;69(1):41-8.
29. Yang TJ, Tao R, Elkhuizen PHM, van Vliet-Vroegindeweij C, Li G, Powell SN. Tumor bed delineation for external beam accelerated partial breast irradiation: A systematic review. Radiotherapy and Oncology. 2013;108(2):181-9.
30. Smitt MC, Birdwell RL, Goffinet DR. Breast electron boost planning: comparison of CT and US. Radiology. 2001;219(1):203-6.
31. Shaikh T, Narra V, Goyal S, Ahlawat S, Kirstein L, Kearney T, et al. Lumpectomy closure technique does not affect dosimetry in patients undergoing external-beam-based accelerated partial breast irradiation. Ann Surg Oncol. 2013;20(4):1323-8.
32. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14:135.
33. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
34. Atrchian S, Sadeghi P, Cwajna W, Helyer L, Rheaume D, Nolan M, et al. Improvement of consistency in delineating breast lumpectomy cavity using surgical clips. J Surg Res. 2018;221:30-4.

35. Shaikh T, Chen T, Khan A, Yue NJ, Kearney T, Cohler A, et al. Improvement in Interobserver Accuracy in Delineation of the Lumpectomy Cavity Using Fiducial Markers. International Journal of Radiation Oncology • Biology • Physics. 2010;78(4):1127-34.
36. Degnim AC, Throckmorton AD, Boostrom SY, Boughey JC, Holifield A, Baddour LM, et al. Surgical site infection after breast surgery: impact of 2010 CDC reporting guidelines. Ann Surg Oncol. 2012;19(13):4099-103.
37. Panhofer P, Ferenc V, Schutz M, Gleiss A, Dubsky P, Jakesz R, et al. Standardization of morbidity assessment in breast cancer surgery using the Clavien Dindo Classification. Int J Surg. 2014;12(4):334-9.
38. Struik GM, Vrijland WW, Birnie E, Klem TM. A randomized controlled trial on the effect of a silver carboxymethylcellulose dressing on surgical site infections after breast cancer surgery. PLoS One. 2018;13(5):e0195715.
39. Williams N, Sweetland H, Goyal S, Ivins N, Leaper DJ. Randomized trial of antimicrobial-coated sutures to prevent surgical site infection after breast cancer surgery. Surg Infect (Larchmt). 2011;12(6):469-74.
40. Edmundson GK, Vicini FA, Chen PY, Mitchell C, Martinez AA. Dosimetric characteristics of the MammoSite RTS, a new breast brachytherapy applicator. International Journal of Radiation Oncology • Biology • Physics. 2002;52(4):1132-9.
41. Pignol JP, Keller B, Rakovitch E, Sankreacha R, Easton H, Que W. First report of a permanent breast 103Pd seed implant as adjuvant radiation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2006;64(1):176-81.
42. Henke LE, Contreras JA, Green OL, Cai B, Kim H, Roach MC, et al. Magnetic Resonance Image-Guided Radiotherapy (MRIgRT): A 4.5-Year Clinical Experience. Clinical Oncology. 2018;30(11):720-7.

CHAPTER TEN

10

Development and psychometric evaluation of a Dutch-translated shorter Breast Cancer Treatment Outcome Scale (Dutch BCTOS-13)

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Abstract

Purpose: To create a Dutch translated short version of the Breast Cancer Treatment Outcome Scale (BCTOS) and validate it in patients who have completed both breast conserving surgery and adjuvant radiotherapy.

Methods: The BCTOS consists of items comparing the treated with the untreated breast. After forward and backward translation, we tested the BCTOS-12 plus 5 additional items. Two-hundred breast cancer patients treated with breast conserving therapy (BCT) between January 2016 and December 2017, were asked to complete the BCTOS items twice with a 2 week interval. The EORTC QLQ-BR23 breast and arm symptoms subscales were completed once in parallel. Feasibility was assessed by missing or non-unique answer rates and content validity with floor and ceiling effect analysis. Construct validity was evaluated with 1) principal component analysis (PCA) 2) convergent validity and 3) known groups comparison (clinical validity differentiating between patients with and without locoregional side effects). From all potential items with good feasibility, content and construct validity, items were selected for the Dutch BCTOS based on clinical validity. The relation to the EORTC QLQ-BR23 subscales and reliability was tested for the new Dutch BCTOS.

Results: Hundred and one of 200 (50.5%) approached patients participated in this study, with follow-up after surgery ranging from 5 to 29 months. Feasibility was high (1.5% missing answers). Content validity testing showed a floor effect >20% in all 17 items. PCA showed that all items loaded well (>0.4) into the assigned subscale and revealed two distinct subscales: cosmesis and function. Based on clinical validity, item "breast shape" was replaced by "breast elevation/position" and "overall skin appearance". Very good clinical validity (Cohen's d=1.38) was found for the new Dutch BCTOS-13. Correlation to the EORTC QLQ-BR23 subscales was high (ICC=0.65-0.85) for both subscales. Test-retest reliability (Cohen's d = 0.105) and internal consistency (Cronbach's α =0.90) were excellent.

Conclusion: Psychometric evaluation of a newly developed Dutch BCTOS-13 questionnaire in BCT patients showed excellent results, that were slightly better than the original BCTOS-22 and the shortened BCTOS-12. The good clinical validity makes the BCTOS-13 a useful tool to identify patients with unfavorable cosmetic and functional outcomes, requiring specific attention.

Introduction

Breast conserving therapy (BCT), consisting of a wide local excision and adjuvant radiotherapy, is equally effective as breast amputation in early stage breast cancer patients[1]. Furthermore, it has cosmetic and functional benefits, which are directly related to patients' quality of life[2, 3]. Oncoplastic techniques are increasingly used to further improve the cosmetic outcome of the surgical treatment[4]. The effect of high conformal or partial irradiation techniques on cosmetic outcome of adjuvant radiotherapy has been investigated in several clinical trials[5-12] showing benefit in most of these studies. With the excellent oncological outcomes in this patient group, patient reported outcome measures (PROMs) are increasingly important to indicate healthcare quality and compare different surgical and radiotherapeutic techniques[13-15]. Brouwers et al. found that PROMs can be used to identify breast cancer patients who experience a heavy burden of late side-effects (≥3 months after completion of the radiation treatment), requiring specific attention. The use of PROMs instead of a standard outpatient clinical visit potentially spares visits in those patients with good cosmetic and functional outcomes[16].

Among others, the validated 22-item English Breast Cancer Treatment Outcome Scale (BCTOS)[17] is a questionnaire that is widely used[14, 18-23]. Its outcome is based on the comparison of the treated and untreated breast by the patient. It is clearly structured, comprehensive and assesses the most important aspects of morbidity after BCT. The questionnaire includes a cosmetic, functional and breast sensitivity subscale. The original BCTOS-22 was validated in patients after completing all treatment, so also including radiotherapy in the majority of patients. Therefore, it is widely used as a PROM in radiotherapy clinical trials[24-26].

However, for the best adoption of a questionnaire, besides being valid and comprehensive it should also be concise. Therefore, a shortened 12-item English version (BCTOS-12) has been developed and tested recently. The study by Hennigs et al.[22] showed good validity, without loss of information. In this shortened version the 12 items are assigned to two, instead of three, subscales: aesthetic and functional status. In contrast to the original version, the shortened BCTOS-12 was only validated in patients within a week after surgery.

The aim of the present study is to create a Dutch translated short version of the Breast Cancer Treatment Outcome Scale (BCTOS) and validate it in patients who have completed both breast conserving surgery and adjuvant radiotherapy. A translated version of the English BCTOS-12 was used in this study. As the aim of this study is to create a version of the BCTOS that is specifically valid for use in patients after adjuvant radiotherapy, we included 5 additional exploratory items in the cosmetic subscale, to anticipate for any differences in outcome in our population compared to the study by Hennigs[22]. The additional items were selected on the expectation that cosmesis, and more specifically skin outcome, could be influenced by the adjuvant radiotherapy. Selection of

items to be included in the final questionnaire will be based on psychometric properties, specifically focusing on the clinical validity to identify patients with locoregional side effects related to the BCT.

Methods

The protocol of this cross-sectional validation study was reviewed by the TWOR regional medical research ethics committee (MREC), Rotterdam, the Netherlands. Ethical clearance for this study was granted (2018-16).

Study population

Our study population consisted of breast cancer patients treated with BCT, including adjuvant radiotherapy in the vast majority. All patients had their surgical treatment in the period January 2016 to December 2017 in the Franciscus Gasthuis and Vlietland, a large secondary teaching hospital in Rotterdam, the Netherlands. We chose this population as we are aiming to create a PROM that is valid to assess both surgical ánd radiotherapy outcomes. All participants were at least 18 years of age and able to understand the Dutch language. Patients that underwent major reconstructive surgery were excluded, since specific questionnaires have been developed for this group[27]. Bilateral breast cancer and mastectomy patients were excluded, as a comparison between the treated and untreated breast is not possible in these patients. Finally, patients with (planned) locoregional breast cancer treatment during data collection were excluded. All patients gave their written informed consent for study participation.

Study instruments: BCTOS-12, additional exploratory items, the European organization for research and treatment of cancer (EORTC) QLQ-BR23 questionnaire

We used the Hennigs' BCTOS-12 questionnaire[22] as basis for the items to be tested in our study. The patients in their study were asked to complete the BCTOS questionnaire within a week after surgery. In our study patients will have completed both surgery as well as radiotherapy at a minimum of 2-3 months after surgery. A previous study by Heil et al.[20] found that functional outcome as scored with the BCTOS is stable over time, while cosmetic outcome is not. Therefore, we anticipated on differences in cosmetic outcomes of our study population compared to that of Hennigs' study[22], by adding five exploratory items to the cosmetic subscale. The three cosmetic subscale items that showed high factor loadings in the original BCTOS (but were removed when the shortened BCTOS-12 was developed) were included for exploration ("breast size", "breast elevation/position" and "fit of clothing"). Two protocol specific items, that were expected to specifically capture radiotherapy related skin toxicity and fibrosis, were also included for exploration ("overall skin appearance" and "overall breast appearance"). These five exploratory items are also in use in ongoing breast radiotherapy clinical trials[28-30] to investigate cosmetic outcome.

The final questionnaire consists of 17 items, which are assigned to two subscales; 12 in a cosmetic subscale, 5 in a functional subscale. For details see additional file 1. Patients were asked to rate each item of the questionnaire on a four-point scale evaluating the differences between the treated and the untreated breast (1 = no difference, 2 = slight difference, 3 = moderate difference, 4 = large difference). The score for each subscale is the unweighted mean of the ratings over all items belonging to that subscale. A higher score reflects less symmetry between the treated and the untreated breast and is therefore considered a measure of poor status.

An additional questionnaire containing 7-items of the EORTC QLQ-BR23 (additional file 2) was completed once for external convergent validity testing. We chose this questionnaire as it is widely used and available and validated in the Dutch language[31]. We only used the two relevant subscales of the EORTC QLQ-BR23 assessing the same determinants as the BCTOS; breast symptoms subscale to compare with the BCTOS cosmetic subscale and arm symptoms subscale to compare with the BCTOS functional subscale.

Development of the Dutch BCTOS

The Dutch BCTOS was developed according to the adaptation process as described by Bullinger et al[32]. A forward translation of the 17 items from English into Dutch was performed by three Dutch native speakers with extensive knowledge of the English language. The aim was to obtain conceptual equivalence using simple language, rather than achieving a literal translation. Any difficulties in the translation were discussed with the principal investigator until consensus was reached on an optimal Dutch phrasing. A backward translation to English was performed by two native English speakers who are fluent in Dutch. These backward translations were compared with the original items, and any differences were analyzed. Finally, necessary changes in the formulation of the Dutch version were made in order to arrive at the exact original English formulation after backtranslation.
The pilot version (additional file 3) was tested in five patients treated with BCT in our center. They were asked to comment on readability and comprehension of the questionnaire. No relevant comments were made, so no additional changes were made hereafter.

Study design

Included patients were invited to complete the 17 items BCTOS pilot questionnaire twice with a two week interval for psychometric data collection. EORTC QLQ-BR23 breast and arm symptoms subscales were added in parallel with the first BCTOS for external convergent validation purposes.

Psychometric evaluation

Psychometric evaluation consisted of the following analyses. These analyses were based on pairwise complete data of items in the first BCTOS and the EORTC QLQ BR-23. Data from the second BCTOS was only used for test-retest analysis.

Feasibility

Missing (no option chosen) or non-unique responses (>1 option chosen) were considered invalid and reported as n and percentages. Feasibility of the questionnaire was evaluated by response rates and missing answer percentages. Questionnaires with more than one invalid response were excluded from further analyses. There is no recommendation on handling missing data by the authors of the original BCTOS or BCTOS-12. With only 4 out of 105 patients excluded in our study, it is unlikely that this has impacted the outcome of this study.

Content validity

Floor and ceiling effects were measured by calculating the percentage of patients scoring the minimum (floor) and maximum (ceiling) score for each item[27].

Construct validity

1. PCA

Since the original BCTOS-22 consists of 3 subscales (cosmetic status, functional status and breast specific pain) and Hennigs' shortened BCTOS-12 uses 2 subscales (aesthetic and functional status) we considered both a 2 and 3 factor solution. Two criteria were used to assess the validity of both options: Kaiser criterion (Eigen values>1) and a scree plot analysis.

To identify items that did not load distinctly on a single factor, a principal component analysis with orthogonal Varimax rotation was performed on the original factor loadings. We used the same criteria as the original BCTOS development study[17] to select items eligible for exclusion from the questionnaire: items with a low (<0.4) factor loading on their main factor and a high loading on the other factor (>0.3).

2. Convergent validity

Convergent validity was assessed on the item and subscale level. Convergent validity of an item was confirmed when item-total correlation with the assigned subscale was high (ICC>0.4) and discriminant validity was confirmed when an item had an ICC with the assigned subscale that was >2 standard errors higher than its ICC with the other subscale .

3a. Known group comparison

It was hypothesized that the new Dutch BCTOS would be clinically valid by identifying patients with radiotherapy or surgery related toxicity. Toxicity scoring as performed by the treating physicians (i.e. surgeons/radiation oncologists) during clinical follow-up visits and recorded in the electronic patient file, according to RTOG/EORTC[33], LENTSOMA[34], and CTCAE[35] toxicity scales, was used in our analysis. The clinical validity per item was assessed with the effect size[36] and an unpaired Student's t test for both all grades and ≥ grade 2 toxicity.

3b. Selection of the items to form the new Dutch BCTOS

As the aim of this study is to create a Dutch version of the BCTOS that is clinically valid for use in patients treated with both breast conserving surgery and adjuvant radiotherapy, final decision on the selection of items was made based on the known group comparison analysis. The shortened BCTOS-12 set of items was the starting point. If any of the 5 additional exploratory items showed good content and convergent validity ánd showed better clinical validity than any of the retained original items, this could result in a replacement of that item. This decision was made after a meeting of the research group, before continuing further analysis for the new set of BCTOS items.

4. Relationship to the EORTC QLQ-BR23

Convergent validity of the conceptual related subscales of the new BCTOS (cosmesis and function) and the acknowledged EORTC QLQ-BR23 (breast symptoms and arm symptoms) was assessed using interclass correlation coefficient (ICC model[37]: two-way mixed-a fixed number of instruments and all instruments are used in all patients (thereby, instruments and patients are two sources of data variation); single measures-as based on the individual patient data in the study instead of group averages; consistency- scores are measured on different scales).

Reliability

Two aspects of reliability were evaluated. To assess whether items evaluate the same concept (cosmesis, function), internal consistency of subscale items was measured using Cronbach's α, which should exceed 0.70[38].

Test–retest reliability was assessed with the intraclass correlations (ICC model[37], two-way mixed - a fixed number of instruments and all instruments are used in all patients (thereby, instruments and patients are two sources of data variation); single measures - as based on the individual patient data in the study instead of group averages; absolute agreement - scores are measured on the same scale) and effect size (Cohen's d calculated as d= mean difference (retest-test)/SD_{test}[39] and interpreted as 0.01≤ d <0.2 =very small, 0.2≤ d <0.5 = small, 0.5≤ d <0.8 = medium, 0.8≤ d <1.2 = large, 1.2 ≤ d <2.0 = very large, and d ≥2.0 = huge)[40].

Descriptive statistics were used to describe the study sample. All statistical tests were performed with IBM SPSS Statistics version 24.0, with two-sided p-values below 0.05 considered statistically significant. In case of one missing answer, that item was not included in the subscale average score.

Results

Study sample

101 of the 200 (50.5%) approached patients participated in this study by completing at least the first BCTOS questionnaire and the EORTC QLQ-BR23 questionnaire. Patient characteristics are shown in table 1.

Table 1: Patient characteristics

Total patients	101
Median age, years (range)	61 (39-86)
Type of surgery	
Lumpectomy only	5 (5.0%)
Lumpectomy + SNB	81 (80.2%)
Lumpectomy + ALND	6 (5.9%)
Lumpectomy + SNB + volume replacement (level 2)	5 (5.0%)
Lumpectomy + ALND + volume replacement (level 2)	2 (2.0%)
Wedge resection for Paget's disease	2 (2.0%)
Follow-up since surgery, months, median (range)	14.9 (5-29)
History of breast radiotherapy	97 (96.0%)
Axillary radiotherapy	6 (5.9%)
Locoregional side-effects[a]	
Any surgery or radiotherapy related	56 (61%)
Radiotherapy related	29 (32%)
Surgery related	13 (14%)
Radiotherapy and surgery related	14 (15%)
Grade 1	26 (28%)
Grade 2	24 (26%)
Grade 3	6 (7%)

SNB: Sentinel node biopsy; ALND: Axillary lymph node dissection;
[a]side effects not reported in 9 patients

Feasibility

Missing answer rate for the BCTOS was 1.5%, ranging from 0 % (item 2, 5-7, 13-17) to 4.0% (item 3, 8, 10). Four patients were excluded for further analysis because of >1 missing answers in any of the questionnaires.

Content validity

The proportion minimum score of "1" (floor effect) was 0.46 (SD=0.18), ranging from 0.24 (item 11) to 0.83 (item 17). A floor effect >20% occurred in 17/17 items.
The proportion of maximum score of "4" (ceiling effect) was 0.08 (SD=0.04), ranging from 0.01 (item 17) to 0.14 (item 3). A ceiling effect >20% occurred in 0/17 items.
This means there is a floor effect and no ceiling effect in all the BCTOS items tested.

Construct validity:

1.PCA

Based on the Kaiser criterion and scree plot analysis, a two or three factor solution would be possible: Eigenvalue of 2.5 for 2 subscales with a cumulative explained variance of 58.6%, or Eigenvalue of 1.1 for 3 subscales with a cumulative explained variance of 65.3%. The difference between the two and three factor solution was that the items "breast texture", "nipple appearance", "scar tissue", "breast sensitivity" and "breast tenderness" were forming a separate subscale in the three factor solution. However, with the Eigen value being only slightly >1 and the difficulty to create three clinically relevant subscales based on the pattern of factor loadings, we opted for the two factor solution for further analysis.

The principal component analysis with two factor solution (Table 2) including all 17 items shows that all of the tested items loaded well (>0.4) into the subscale we assigned them to. The item "breast swelling" (Dutch: Zwelling van de borst) loaded well (>0.4) in both subscales. None of the items was eligible for exclusion.

All five additional cosmetic items had high factor loadings (range 0.65-0.85) for cosmesis and low factor loadings for function (range 0.01-0.32). Cronbach's α if item deleted, was very similar for all cosmetic items (range 0.91-0.92). Also, all the additional exploratory items were highly correlated (ICC>0.6) with at least one of the shortened BCTOS-12 cosmetic items.

Table 2: Principal component analysis. Items and factor loadings of all items explored for the Dutch BCTOS.

Item	Subscale	
	Cosmesis	**Function**
1 Breast size*	0.77	0.01
2 Breast texture (hardening)	0.67	0.37
3 Nipple appearance	0.63	0.17
4 Breast shape	0.69	0.19
5 Breast elevation / position*	0.65	0.32

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Item	Subscale	
	Cosmesis	**Function**
6 Scar tissue	0.63	0.04
7 Breast swelling	0.50	0.45
8 Fit of bra	0.80	0.20
9 Breast sensitivity	0.73	0.18
10 Fit of clothing*	0.69	0.03
11 Overall breast appearance*	0.85	0.10
12 Overall skin appearance*	0.72	0.27
13 Breast tenderness	0.48	0.40
14 Arm heaviness	0.19	0.90
15 Shoulder discomfort	0.11	0.81
16 Arm discomfort	0.19	0.89
17 Arm swelling	0.06	0.85

*Displayed are factor loadings after varimax rotation. Underlining of the factor loading indicates to which subscale it was assigned. *additional items that were not included in the study by Hennigs22.*

2. Convergent validity

Convergent validity was confirmed for all 17 items. Discriminant ability was also confirmed for all items.

3a. Known group comparison

Of the retained original items, "breast shape" showed poorest clinical validity to differentiate between patients with and without locoregional radiotherapy or surgery related side effects, with very small effect sizes (Cohen's d=0.34 for any grade and 0.11 for ≥ grade 2).

Of the five additional items tested, "overall skin appearance" showed a large effect size for side effects of any grade (Cohen's d=1.18) and medium effect size for ≥ grade 2 (Cohen's d=0.71). "Breast elevation/position" showed large effect size for side effects of any grade (Cohen's d=1.00) and medium effect size for ≥ grade 2 (Cohen's d=0.62). The other items showed only small effect sizes, meaning little clinical validity.

3b. Selection of the items to form the new Dutch BCTOS-13

With the content and convergent validity being acceptable to good for all items, our item selection was fully based on clinical validity of the single items. Therefore, we decided to remove the original item "breast shape" and to add the exploratory items "breast elevation/position" and "overall skin appearance" to form the new Dutch BCTOS-13. The new Dutch BCTOS-13 showed very good clinical validity (mean score of 2.08 (SD=0.60) in patients with vs. 1.42 (SD=0.39), Cohen's d=1.38

in patients without any locoregional side effects, and 2.22 (SD=0.58) vs. 1.60 (SD=0.51), Cohen's d=1.17 for ≥grade 2 side effects. The BCTOS-13 was used for further analysis (table 3, 4, 5). In comparison, the EORTC QLQ-BR23 questionnaire showed a smaller effect size in this regard (Cohen's d=1.03 and 0.32).

Table 3: Principal component analysis. Items and factor loadings of the all items in the new Dutch BCTOS-13.

	Subscale	
Item	**Cosmesis**	**Function**
1 Breast texture (hardening)	0.78	0.27
2 Nipple appearance	0.63	0.10
3 Breast elevation / position	0.63	0.31
4 Scar tissue	0.70	-0.05
5 Breast swelling	0.58	0.41
6 Fit of bra	0.78	0.18
7 Breast sensitivity	0.77	0.11
8 Overall skin appearance	0.79	0.20
9 Breast tenderness	0.61	0.30
10 Arm heaviness	0.22	0.90
11 Shoulder discomfort	0.14	0.81
12 Arm discomfort	0.24	0.88
13 Arm swelling	0.12	0.85

Displayed are factor loadings after varimax rotation. Underlining of the factor loading indicates to which subscale it was assigned.

4. Relationship to EORTC QLQ-BR23

Convergent validity testing showed that correlation to the EORTC QLQ BR23 subscales was high for both the functional (ICC=0.85 (95%CI [0.78-0.90]) and the new cosmetic subscale (ICC=0.65 (95%CI [0.52-0.75]) (table 4).

Table 4: Correlations (ICCs[95%CI]) of the new Dutch BCTOS-13 with arm and breast symptoms EORTC QLQ-BR23 subscales

EORTC QLQ-BR23 subscale	**BCTOS-13 cosmesis**	**BCTOS-13 function**	**BCTOS-13 total**
Breast symptoms	0.65 [0.52-0.75]	0.59 [0.44-0.70]	0.74 [0.63-0.82]
Arm symptoms	0.37 [0.18-0.53]	0.85 [0.78-0.90]	0.62 [0.47-0.73]
Total	0.58 [0.43-0.70]	0.75 [0.65-0.83]	0.75 [0.64-0.82]

all correlations are significant at the 0.001 level

Reliability (table 5)

Mean BCTOS-13 scores were 1.81 (SD=0.62) in the test versus 1.74 (SD=0.56) in the re-test and test-retest effect size was very small, Cohen's d = 0.105. There was a high correlation between the test and re-test BCTOS-13 scores, ICC was 0.91 (95%CI[0.87-0.94]). A high correlation was also found on a subscale and single-item level (table 5).

Internal consistency was high; Cronbach's α was 0.90 for all Dutch BCTOS-13 items, 0.89 for the cosmetic subscale and 0.90 for the functional subscale.

Table 5: Reliability analysis showing the test-retest effect sizes and intra-class correlation coefficient (ICC) and internal consistency.

	Test re-test reliability (n=93)					**Correlation**		**Internal consistency**[a]
BCTOS item	Test		Re-test		Effect size	ICC [95%CI]		Cronbach's α
	Mean	SD	Mean	SD	Cohen's *d*	Test re-test, n=93	Item-subscale total[ab] n=101	n=101
Cosmetic subscalea	1.95	0.69	1.88	0.61	0.112	0.89 [0.84-0.93]		0.89
1 Breast texture (hardening)	2.06	0.92	2.03	0.83	0.034	0.82 [0.74-0.87]	0.79 [0.69-0.85]	
2 Nipple appearance	1.93	1.08	1.86	1.05	0.074	0.85 [0.78-0.90]	0.60 [0.45-0.72]	
3 Breast elevation/ position	1.86	1.00	1.81	0.92	0.053	0.76 [0.66-0.84]	0.65 [0.52-0.75]	
4 Scar tissue	2.12	0.94	2.09	0.86	0.034	0.82 [0.74-0.88]	0.60 [0.45-0.71]	
5 Breast swelling	1.62	0.91	1.50	0.79	0.132	0.83 [0.75-0.89]	0.62 [0.39-0.76]	
6 Fit of bra	1.84	0.93	1.71	0.90	0.130	0.76 [0.66-0.84]	0.75 [0.65-0.83]	
7 Breast sensitivity	2.15	0.99	2.05	0.94	0.099	0.72 [0.60-0.80]	0.70 [0.56-0.79]	

	Test re-test reliability (n=93)					Correlation		Internal consistency[a]
BCTOS item	Test		Re-test		Effect size	ICC [95%CI]		Cronbach's α
8 Overall skin appearance	1.85	0.88	1.70	0.78	0.172	0.79 [0.69-0.86]	0.77 [0.67-0.84]	
9 Breast tenderness	2.11	0.97	2.07	0.93	0.043	0.79 [0.71-0.86]	0.63 [0.49-0.74]	
Functional subscalea	1.46	0.73	1.43	0.67	0.032	0.90 [0.86-0.93]		0.90
10 Arm heaviness	1.49	0.87	1.51	0.85	0.024	0.84 [0.78-0.89]	0.92 [0.88-0.95]	
11 Shoulder discomfort	1.49	0.93	1.48	0.87	0.011	0.83 [0.75-0.88]	0.84 [0.77-0.89]	
12 Arm discomfort	1.60	0.89	1.55	0.87	0.058	0.86 [0.80-0.90]	0.91 [0.86-0.94]	
13 Arm swelling	1.24	0.58	1.19	0.47	0.090	0.87 [0.81-0.91]	0.78 [0.69-0.85]	
All itemsa	1.81	0.62	1.74	0.56	0.105	0.91 [0.87-0.94]		0.90

[a]*analysis performed for the new BCTOS-13* [b]*analysis performed on test*

Discussion

The aim of this study was to validate a Dutch translation of the BCTOS with a specific focus on the clinical validity in patients treated with breast conserving surgery ánd adjuvant radiotherapy.

The original BCTOS was developed to create a measure of perceived aesthetic and functional status after breast-conserving surgical treatment (BCT) and radiotherapy. It was validated in patients after completion of all locoregional treatment. The BCTOS is clearly structured, with the patient comparing the treated with the untreated breast. Although the BCTOS-22 is widely used, a shorter version, with any redundant items removed might be more practical and further improve clinical adoption. We used the recently validated shortened version, the BCTOS-12, as a base for our translated version. As our goal was to create a PROM valid to differentiate between favorable and unfavorable BCT outcomes, we tested five additional items in the cosmetic subscale. By doing this, we anticipated for specifically better capturing unfavorable radiotherapy outcomes in our study population. The reason to do this was that we included patient after completing all locoregional treatment with a broad range of 5 to 29 months follow-up after surgery, instead of 1 week post-surgery in the study by Hennigs[22]. The additional exploratory items were selected on the expectation that cosmesis, and more specifically skin outcome, could be influenced by

the adjuvant radiotherapy. We did not expect any differences in functional outcomes, as very few patients received axillary radiotherapy or axillary lymph node dissection. Also, a previous study by Heil et al.[20] found that functional outcome as scored with the BCTOS is stable over time, while cosmetic outcome is not.

Psychometric evaluation of the proposed new Dutch BCTOS items showed comparable to slightly better results than both the original version and the shortened BCTOS-12. Feasibility was high, with an overall missing answer rate of only 1.5% (compared to 5.5% for the English BCTOS-12)[22] and construct and convergent validity was good. Clinical validity testing resulted in the removal of one item from the BCTOS-12 ("breast shape"). Two of the additional exploratory items tested ("breast elevation / position" and "overall skin appearance") showed specific value in differentiation between favorable and unfavorable BCT outcome and were added to form the new Dutch BCTOS-13. Consistent with the study by Hennigs[22], this questionnaire comprises two subscales: cosmesis and function.

Reliability was high with only a very small test-retest effect size (Cohen's d=0.105). Internal consistency was high with a Cronbach's α of 0.89 for the cosmetic subscale and 0.90 for the functional subscale. This is comparable to the original BCTOS-22 questionnaire that showed an Cronbach's α of 0.89 for cosmesis and a 0.91 for function. Notably, internal consistency of our Dutch BCTOS-13 is higher than the English BCTOS-12, which showed an α of 0.86 and 0.81 respectively.

Correlation to the EORTC BR23 subscales was stronger for our BCTOS-13 (strong for functional subscale to arm symptoms and moderate for cosmetic subscale to breast symptoms) compared to both the English original BCTOS-22 and the shortened BCTOS-12 (weak to moderate for both subscales). The higher internal consistency and correlation to the EORTC BR23 that was found in our study than in the BCTOS-13 study, might be explained by the timing of filling out the questionnaire. We hypothesize that patients are more consistent after getting used to certain symptoms or treatment outcomes (reduction of post-surgery complaints, perhaps adaptation and/or coping). This higher consistency will also increase correlation between the two conceptual comparable questionnaires (i.e. BCTOS and EORTC BR23).

Content validity analysis showed that in this study there was a floor effect>20% in all items. This effect was most prominent in the functional subscale, with a mean proportion of minimum scores of 71%, compared to 34% in the cosmetic subscale. In the studies by Stanton et al. and Hennig et al. no floor/ceiling effect analysis was reported. However, the distribution of scores was comparable in the original BCTOS and the shortened BCTOS-12, which would probably result in a similar floor effect in those studies, although not reported.

The floor effect that was found, could be considered as a limitation of the BCTOS. However, with the good cosmetic and functional outcomes in BCT patients this finding was expected to occur in

our study, consistent with other studies testing the BCTOS in BCT patients[17, 22]. In our study only 8 patients underwent axillary lymph node dissection and in 6 patients the axilla was irradiated. Results might be different in a high risk patient population undergoing breast conserving surgery. We would not recommend changing a scale that is already widely used, as this will impede comparison between studies. A better option would be to use the categories to interpret scores as suggested by Hennigs[22]: good (1.00 - 1.75); intermediate (1.76 - 2.50), fair (2.51 - 3.25), and poor (3.26 - 4.00) outcome. More important here is the good clinical validity of the Dutch BCTOS-13 that was demonstrated, which supports clinical use of the BCTOS to differentiate between favorable and unfavorable BCT outcomes.

Another limitation of our study was that we only used the two relevant EORTC subscales (breast symptoms and arm symptoms), instead of the complete EORTC QLQ-BR23 questionnaire. We chose to specifically focus on locoregional outcome, thereby limiting patient burden for participation. Doing this is common, related studies also analyzed correlation on a subscale level. However, therefore we were not able to draw any conclusions on the correlation between cosmetic and functional outcomes with overall quality of life. The previously found strong correlation between functional outcome and overall quality of life should be confirmed in subsequent research. Furthermore, our study population was quite homogenous regarding the received treatment. The vast majority underwent lumpectomy with sentinel node biopsy and adjuvant whole breast irradiation. Results might be different in other patient groups undergoing axillary lymph node dissection and/or irradiation, level 2 oncoplastic surgery or partial breast irradiation more frequently. Further validation should be performed in these specific patient groups. On the other hand, our study population was very heterogeneous regarding time after surgery, ranging from 5 to 29 months. This means that all of our patients completed locoregional treatment. Therefore, in contrast to the study by Hennigs[22], our questionnaire has now been validated for use in both breast cancer surgery and adjuvant radiotherapy.

Implications of our study findings are the recommendation to use the Dutch BCTOS-13 questionnaire as a PROM in all breast cancer research assessing cosmetic and functional outcome after adjuvant radiotherapy in the Netherlands. Clinical validity is superior to the commonly used EORTC QLQ-BR23 for this specific patient group. The BCTOS-13 could be used to identify patients with unfavorable BCT cosmetic and functional outcomes that require specific attention. Furthermore, in patients with favorable outcome, using the BCTOS-13 potentially reduces the need for clinical visits to assess BCT outcome.

In conclusion, we developed a shorter Dutch version of the BCTOS (Dutch BCTOS-13). Despite the reduced number of items, psychometric evaluation showed excellent results that were slightly better than the original BCTOS-22 and the shortened BCTOS-12. The design makes it suitable for assessment of cosmetic and functional outcomes in patients treated with breast conserving surgery ánd adjuvant radiotherapy.

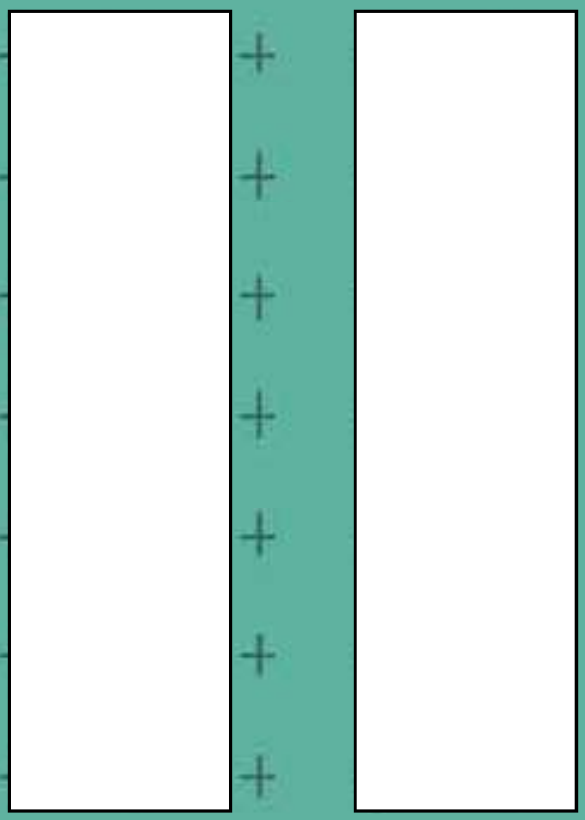
References

1. Early Breast Cancer Trialists' Collaborative G, Darby S, McGale P, Correa C, Taylor C, Arriagada R, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet. 2011;378(9804):1707-16.
2. Kim MK, Kim T, Moon HG, Jin US, Kim K, Kim J, et al. Effect of cosmetic outcome on quality of life after breast cancer surgery. Eur J Surg Oncol. 2015;41(3):426-32.
3. Sun Y, Kim SW, Heo CY, Kim D, Hwang Y, Yom CK, et al. Comparison of quality of life based on surgical technique in patients with breast cancer. Jpn J Clin Oncol. 2014;44(1):22-7.
4. Clough KB, Kaufman GJ, Nos C, Buccimazza I, Sarfati IM. Improving breast cancer surgery: a classification and quadrant per quadrant atlas for oncoplastic surgery. Ann Surg Oncol. 2010;17(5):1375-91.
5. Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, et al. Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. Eur J Cancer. 2015;51(4):451-63.
6. Olivotto IA, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, et al. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol. 2013;31(32):4038-45.
7. Polgar C, Fodor J, Major T, Sulyok Z, Kasler M. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. Radiother Oncol. 2013;108(2):197-202.
8. Rabinovitch R, Winter K, Kuske R, Bolton J, Arthur D, Scroggins T, et al. RTOG 95-17, a Phase II trial to evaluate brachytherapy as the sole method of radiation therapy for Stage I and II breast carcinoma--year-5 toxicity and cosmesis. Brachytherapy. 2014;13(1):17-22.
9. Rodriguez N, Sanz X, Dengra J, Foro P, Membrive I, Reig A, et al. Five-year outcomes, cosmesis, and toxicity with 3-dimensional conformal external beam radiation therapy to deliver accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys. 2013;87(5):1051-7.
10. Shah C, Khwaja S, Badiyan S, Wilkinson JB, Vicini FA, Beitsch P, et al. Brachytherapy-based partial breast irradiation is associated with low rates of complications and excellent cosmesis. Brachytherapy. 2013;12(4):278-84.
11. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016;387(10015):229-38.
12. Vicini FA, Chen P, Wallace M, Mitchell C, Hasan Y, Grills I, et al. Interim cosmetic results and toxicity using 3D conformal external beam radiotherapy to deliver accelerated partial breast irradiation in patients with early-stage breast cancer treated with breast-conserving therapy. Int J Radiat Oncol Biol Phys. 2007;69(4):1124-30.
13. Hu ES, Pusic AL, Waljee JF, Kuhn L, Hawley ST, Wilkins E, et al. Patient-reported aesthetic satisfaction with breast reconstruction during the long-term survivorship Period. Plast Reconstr Surg. 2009;124(1):1-8.
14. Kanatas A, Velikova G, Roe B, Horgan K, Ghazali N, Shaw RJ, et al. Patient-reported outcomes in breast oncology: a review of validated outcome instruments. Tumori. 2012;98(6):678-88.
15. Ou KW, Yu JC, Ho MH, Chiu WK, Ou KL, Chen TM, et al. Oncological safety and outcomes of nipple-sparing mastectomy with breast reconstruction: a single-centered experience in Taiwan. Ann Plast Surg. 2015;74 Suppl 2:S127-31.

16. Brouwers PJAM, van Loon J, Houben RMA, Paulissen J, Engelen SME, Heuts M, et al. Are PROMs sufficient to record late outcome of breast cancer patients treated with radiotherapy? A comparison between patient and clinician reported outcome through an outpatient clinic after 10years of follow up. Radiotherapy and Oncology. 2018;126(1):163-9.
17. Stanton AL, Krishnan L, Collins CA. Form or function? Part 1. Subjective cosmetic and functional correlates of quality of life in women treated with breast-conserving surgical procedures and radiotherapy. Cancer. 2001;91(12):2273-81.
18. Chen CM, Klassen AF, Cano SJ, Pusic AL. BCTOS in Measuring HR-QoL After Breast-Conserving Therapy. The Breast Journal. 2011;17(4):443-.
19. Costa Vieira R, Brandini Silva F, da Silva J, Ferreira L, Santos Paulista J, Alves de Lima M, et al. Aesthetic and functional results of quality of life after breast conserving surgery evaluated by Portuguese/Brazil version of breast cancer treatment outcome scale (BCTOS). The Breast. 2017;32:S131.
20. Heil J, Czink E, Golatta M, Schott S, Hof H, Jenetzky E, et al. Change of aesthetic and functional outcome over time and their relationship to quality of life after breast conserving therapy. Eur J Surg Oncol. 2011;37(2):116-21.
21. Heil J, Holl S, Golatta M, Rauch G, Rom J, Marme F, et al. Aesthetic and functional results after breast conserving surgery as correlates of quality of life measured by a German version of the Breast Cancer Treatment Outcome Scale (BCTOS). Breast. 2010;19(6):470-4.
22. Hennigs A, Heil J, Wagner A, Rath M, Moosbrugger H, Kelava A, et al. Development and psychometric validation of a shorter version of the Breast Cancer Treatment Outcome Scale (BCTOS-12). Breast. 2018;38:58-65.
23. Mashouf S, Fleury E, Lai P, Merino T, Lechtman E, Kiss A, et al. Clinical Significance of Accounting for Tissue Heterogeneity in Permanent Breast Seed Implant Brachytherapy Planning. Int J Radiat Oncol Biol Phys. 2016;94(4):816-23.
24. Pignol JP, Truong P, Rakovitch E, Sattler MG, Whelan TJ, Olivotto IA. Ten years results of the Canadian breast intensity modulated radiation therapy (IMRT) randomized controlled trial. Radiother Oncol. 2016;121(3):414-9.
25. Jethwa KR, Kahila MM, Mara KC, Harmsen WS, Routman DM, Pumper GM, et al. Patient-reported outcomes of catheter-based accelerated partial breast brachytherapy and whole breast irradiation, a single institution experience. Breast Cancer Res Treat. 2018;169(1):189-96.
26. Swanick CW, Lei X, Shaitelman SF, Schlembach PJ, Bloom ES, Fingeret MC, et al. Longitudinal analysis of patient-reported outcomes and cosmesis in a randomized trial of conventionally fractionated versus hypofractionated whole-breast irradiation. Cancer. 2016;122(18):2886-94.
27. Winters ZE, Afzal M, Rutherford C, Holzner B, Rumpold G, da Costa Vieira RA, et al. International validation of the European Organisation for Research and Treatment of Cancer QLQ-BRECON23 quality-of-life questionnaire for women undergoing breast reconstruction. Br J Surg. 2018;105(3):209-22.
28. Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, et al. Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. Lancet. 2017;390(10099):1048-60.
29. Crook J, Pignol JP. A Multicenter Registry Study of Breast Microseed Treatment for Early Stage Breast Cancer 2016 [Available from: https://clinicaltrials.gov/ct2/show/NCT02701244.
30. Struik GM, Godart J, Verduijn GM, Kolkman-Deurloo IK, de Vries KC, de Boer R, et al. A randomized controlled trial testing a hyaluronic acid spacer injection for skin toxicity reduction of brachytherapy accelerated partial breast irradiation (APBI): a study protocol. Trials. 2018.

31. Sprangers MA, Groenvold M, Arraras JI, Franklin J, Velde At, Muller M, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. Journal of Clinical Oncology. 1996;14(10):2756-68.
32. Bullinger M, Alonso J, Apolone G, Leplege A, Sullivan M, Wood-Dauphinee S, et al. Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. International Quality of Life Assessment. J Clin Epidemiol. 1998;51(11):913-23.
33. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995;31(5):1341-6.
34. Force RTOGRaLENTT. LENT SOMA scales for all anatomic sites. Int J Radiat Oncol Biol Phys. 1995;31(5):1049-91.
35. CTCAE 4.03 quick reference [Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.
36. Borenstein M. Effect sizes for continuous data. In: H. Cooper LVH, & J. C. Valentine, editor. The handbook of research synthesis and meta analysis. New York: Russell Sage Foundation.; 2009. p. 221-37.
37. Streiner DL, Norman GR, Cairney J. Health measurement scales. A practical guide to their development and use. 5th edition ed. Oxford: Oxford University Press; 2014.
38. Bland JM, Altman DG. Cronbach's alpha. BMJ. 1997;314(7080):572.
39. Becker BJ. Synthesizing standardized mean-change measures. British Journal of Mathematical and Statistical Psychology. 1988;41(2):257-78.
40. Sawilowsky SS. New Effect Size Rules of Thumb. Journal of Modern Applied Statistical Methods 2009;8(2):597-9.

CHAPTER ELEVEN



General discussion and future prospects

General discussion

Breast cancer is the most common malignancy among women in western countries; one out of eight women will develop one during their lifetime[1]. Overall, breast cancer is still the leading cause of cancer-related deaths and disability-adjusted life years (DALYs) among women globally[1]. 5-year relative survival for patients with a cancer with loco-regional (stage 2-3) or distant spread (stage 4) is 85.5% and 27.4% respectively in most recent SEER data[2].

Thanks to mammography screening and improved imaging techniques, tumors are increasingly detected at an early stage. In more than 60% of the patients, the cancer is localized to the breast tissue at time of diagnosis and no loco-regional or distant metastasis have occurred[2, 3]. For these early stage breast cancer patients, outcomes are excellent with a 5-year relative survival rate of 98,8%[2]. Breast conserving therapy, consisting of a wide local excision and adjuvant radiotherapy, is equally effective as mastectomy for these patients, in terms of local control and disease specific and overall survival[4, 5]. In addition, the use of adjuvant systemic treatment, including antihormonal- and chemotherapy, has increased over the years. This also resulted in improved survival and reduced locoregional recurrences[6, 7].

Given the excellent outcomes in this specific low-risk patient group, there is a paradigm shift towards treatment modalities with reduced morbidity and treatment burden leading to improved cosmesis and quality of life. The treatment of early stage breast cancer patients is increasingly tailored to the specificity of each patient. Optimal patient selection is essential.

Breast conservation is possible in an increasing number of patients. Currently, up to 65% of patients is treated with breast conserving surgery in the Netherlands, and this proportion is still increasing[8]. The increase in breast conservation can be explained by several developments over the last decades: improved imaging, the use of neo-adjuvant chemotherapy, pre-operative tumor localization and oncoplastic surgical techniques allowing for breast conservation in larger tumors. Recent publications[9, 10] reporting an overall survival benefit of BCT (including radiotherapy) over mastectomy in early stage breast cancer patients were the start of an ongoing debate[10-12]. The reported survival benefit in the study by van Maaren[10] could be caused by confounding by severity causing selection bias and the lack of important biological prognostic factors (ER, PR and HER-2 expression and Ki 67 levels) in the multivariate analysis. Therefore further research is warranted and promoting BCT to patients purely for oncological safety reasons would be premature.

After a lumpectomy with focally positive margins, in a large Dutch retrospective cohort study Vos et al. [13] found that omitting a re-excision does not increase local recurrence rates compared to performing a re-excision. Several authors[13, 14] suggest to omit re-excision in these patients, under the condition of adjuvant radiotherapy to the whole breast including a boost. Although omitting re-excision would reduce surgical morbidity for patients, the need for a tumor bed boost might outweigh that patient benefit due to radiation induced morbidity. Therefore, an RCT comparing re-excision to omitting re-excision without increasing the radiotherapy dose would be valuable.

The use of percutaneous tumor ablation techniques has been explored in several pilot studies or small RCTs in patients with small, low-risk tumors[15-19], showing promising results. Currently ongoing RCTs comparing tumor ablation to lumpectomy will provide more high level evidence. The potential role of the stimulation of an immune response in thermal ablation effectivity is an interesting research topic.

New insights in adjuvant radiotherapy have resulted in hypofractionation regimens and the development of several partial breast irradiation techniques. Omitting radiotherapy in specific low-risk patient groups is subject of research in several ongoing clinical trials.

This thesis describes several techniques all aiming to improve accuracy and safety of the surgery, reducing post-operative complications, improving the accuracy of radiotherapy and hence increasing the proportion of patients for more friendly technique with less long-term potentially lethal complications like secondary cancers, and developing strategies to evaluate those benefits.

Breast conserving surgery

The first part of this thesis is focused on the surgical treatment of early stage breast cancer patients. Preserving the breast has cosmetic and functional benefits, which are directly related to patients' quality of life[20-23]. However, in unfavorable cases BCT can result in poor outcomes. Most important morbidity after breast conserving surgery is caused by surgical site infections, re-operations and poor cosmesis.

One surgical strategy to reduce re-operation rate and improve cosmetic outcome would be to omit re-excision in patients with focal positive resection margins. The disadvantage of this strategy however, is that most of these patients get a tumor bed boost instead, potentially increasing morbidity[13, 24].

Another strategy to reduce re-operation rate and improve cosmetic outcome is pre-operative tumor localization. Tumor localization techniques are aiming at increased treatment accuracy and consequently reduced positive margin rates while resecting similar or smaller volume, which is associated with improved cosmesis.

Optimal tumor localization

While wire guided localization of small or non-palpable breast lesions has been the gold standard since its introduction in the 1970s[25], point source techniques have been developed over the last two decades. Radioactive seed localization (RSL) was found to be an equal alternative to WGL in terms of positive margin rates in a Cochrane review in 2012[26]. Potential improved patient satisfaction and its advantage in treatment planning, compared to WGL resulted in the recommendation to use RSL by two authors of the most recent RCTs comparing both techniques[27, 28]. However, strict regulations on radiation safety have impaired adoption of RSL worldwide until now. A novel magnetic marker localization (MaMaLoc) technique was developed recently[29]. It is proposed to have the same advantages as RSL, being a point source, without the issues related to radioactivity. **Chapter 2**

describes the first use of MaMaLoc as sole tumor localization technique in a randomized controlled comparison to WGL in 68 early stage breast cancer patients. This study demonstrated a 100% success rate for both techniques, but the primary outcome parameter of surgical usability was scored significantly higher for MaMaLoc (SUS score of 70/100) than for WGL (SUS score of 58/100). MaMaLoc usability was more often scored as above-average than WGL usability. Also, in retrospect, the surgeon would have preferred MaMaLoc guided surgery in 56% of the cases, while WGL was the preferred method in only 7% of cases. These findings confirmed the results of the feasibility study using the magnetic marker localization (MaMaLoc) technique[29]. In line with recent studies comparing RSL to WGL, we also found a higher patient satisfaction using MaMaLoc than with WGL. These results might be biased by the more frequent use of local anesthesia in the MaMaLoc group in our study. Interesting results were found in our exploratory data. Fewer positive or close margins were found in the MaMaLoc group than in the WGL group, while resected specimen weights were not different. This is in contrast with comparable studies on RSL that found higher resected specimen weights with RSL as opposed to WGL. It could be hypothesized that surgeons are able to resect tumors with similar diameters more accurately (i.e. fewer positive or close margins) using MaMaLoc without removing more tissue, compared to WGL. These findings are relevant as the presence of close margins, although not recommended in international guidelines, in daily practice often results in re-operation or extra tumorbed boost radiotherapy, with consequent increase in patient burden and cosmetic deterioration[30-32]. This study supports the hypothesis that MaMaLoc combines the surgical advantages of a point source without the need to use radioactivity.

Prevention of surgical site infections

SSI are a relatively common complication of breast cancer surgery; incidence ranges between 3 and 19%[33-36], resulting in morbidity and reduced cosmesis. A Cochrane review in 2014 concluded that high-quality research on the role of wound dressings in the prevention of SSIs was needed[37]. In **chapter 3** we describe the results of an RCT testing the effect of a silver containing wound dressing (Aquacel) on the occurrence of SSIs in 230 patients after breast cancer surgery. We found an SSI risk of 6.6% for the Aquacel group and 12.9% for the control group. Patient satisfaction was higher and the mean costs were lower with Aquacel, both significantly.

The SSI rate in the our control group is comparable to previous studies in recent literature using CDC criteria for definition of SSI[33, 35, 36]. Our study showed a relative SSI risk reduction of approximately 50% using of AQUACEL AG Surgical dressing approximately compared with standard dressing. Unfortunately the study was underpowered and a significant reduction of this size could not be demonstrated. Interestingly, in the subgroup of breast conserving surgery a risk reduction of 83% was found. It could be hypothesized that in ablative surgery other factors than type of wound dressing contribute more to the development of SSI, like e.g. seroma/hematoma formation and compromised skin flap vascularization. Early dressing change (within 48 hours) was found to be an independent risk factor for SSI in our study. As the use of Aquacel lowered the need for changing

the dressing, this could be an explanation of the SSI reduction found in the Aquacel group. Also, we would therefore propose to extent the CDC recommendation to not changing the dressing in the first 48 hours.

Interpretation of SSI reduction rates should be balanced against the nature of the intervention, the setting and the related morbidity, quality of life and costs. This easy to use dressing has no disadvantage/harm for patients and there is proven benefit in terms of patient satisfaction and costs. Therefore, the rather large effect size of SSI reduction in this study could be relevant for daily practice.

Optimal radiotherapy

By allowing for breast preservation, the role of adjuvant radiotherapy is primarily to provide a cosmetic and quality of life benefit[21]. However, the standard regimen of 3-5 weeks of daily radiation fractions add a significant burden to the treatment journey. APBI, treating only the tissue surrounding the original tumor bed, is an efficient strategy for well-selected low-risk patients. As opposed to standard EBRT, it reduces treatment burden without increasing side-effects[38-47].

Accelerated Partial Breast Irradiation (APBI)

Secondary cancer risk reduction

The second part of this thesis focuses on APBI and our work on skin toxicity reduction. Firstly, **Chapter 4** shows the advantage of APBI with regards to secondary cancer risk; another incentive for APBI. We performed a phantom study measuring scattered dose to various organs with WBI and several APBI techniques. Secondary cancers Lifetime Attributable Risks (LAR) were calculated from that doses using a modified BEIR-VII formalism. In our calculations, the lifetime risks of secondary cancer are high, up to 4.3% (lung cancers accounting for 3.8%) for a woman treated with WBI at 50 years old, eventually resulting in a 2.4% excess mortality due to secondary lung cancer. Our study shows that all APBI techniques produce less scatter dose compared to whole breast radiotherapy, which translates into a 2-4 times lower secondary cancer risk. The magnitude of secondary cancer mortality in our analysis is about 4 times higher than the reported cardiac mortality. This strongly supports the generalization of partial breast irradiation as standard for early stage breast cancers or DCIS instead of whole breast radiotherapy.

On top of the evidence on APBI effectivity and reduced treatment burden the new evidence presented in **chapter 4** on secondary cancer risk reduction will further stimulate APBI adoption in the near future. Keeping in mind that radiotherapy essentially has a cosmetic and quality of life benefit, it is of high importance to perform research on reducing treatment related side effects. In breast radiotherapy, the critical structure is the skin. Skin toxicity can be permanent and result in poor cosmesis and reduced quality of life. A high skin dose is the main risk factor for skin toxicity. In **chapter 5, 6 and 7** we present our work on skin toxicity reduction and improvement of treatment accuracy in LDR seed breast brachytherapy.

Skin toxicity reduction

To prevent skin toxicity in breast APBI, most authors recommend to keep a distance of at least 5 mm between the planning target volume (PTV)[48, 49] and the skin and limiting the skin dose to 70%[42]. However, such constraints are not always achievable. This resulted in the rationale of the PBSI trial which is described in **chapter 6**: A simple solution to reduce the skin dose would be the use of a skin spacer to move the skin out of the high dose region[50].

Chapter 5 describes the results of the Spacer Study. This preclinical study was the first to investigate the possible use of a subcutaneous spacer injection to reduce the risk of skin toxicity with breast brachytherapy. We found a high success rate of the intervention, and in all 22 cases a stable spacer volume was created under ultrasound guidance in real human breast specimens using either hyaluronic acid or PEG. This suggests that the spacer technique would also be technically feasible in breast cancer patients. In the present study, a spacer thickness of more than 5 mm always significantly reduced the skin dose; a 1 cm^2 area of the skin would never receive more than 90% of the prescribed dose, a metric that is significantly correlated with a higher risk of long term skin toxicity[51]. However, performing a specific LDR seed brachytherapy dosimetry study on specimens had a limitation: the spacer partly pushed the skin away, but it also expanded the breast volume laterally and inferiorly, possibly explained by the absence of a thoracic wall. Therefore, the full effect of a spacer injection may not have been completely evaluated.

Although this is a proof-of-concept, the impact on dose distribution including skin dose and clinical outcomes should still be confirmed in a randomized clinical trial. An example of a clinical trial that could not demonstrate that a dosimetry benefit translates into better patient outcomes, is the breast intensity modulated radiation therapy (IMRT) trial[52]. To test if the dosimetry benefit of the spacer, that was found in our pre-clinical study[5353], translates in a real patient benefit, a randomized clinical trial was designed. The protocol of this ongoing trial testing the use of a skin spacer to reduce late skin toxicity of Permanent Breast Seed Implants, a form of brachytherapy, is summarized in **Chapter 6.** As the seeds are already in place during the spacer injection in this trial, we expect that any change in PTV geometry caused by the spacer will not compromise the PTV coverage. However, the exact effect of the spacer on skin dose and PTV geometry and coverage will be investigated in this study. Primary outcome of this intervention trial is the occurrence of telangiectasia at two years after radiotherapy. The rationale for this is that telangiectasia are a form of late skin toxicity and a specific marker of radiation [50, 54] Although rates are lower than with whole breast irradiation, in breast brachytherapy still 10-27% of the patients develop some grade of telangiectasia. Rates of telangiectasia normally peak at 2 years till it stabilizes. Most of the lesions are permanent resulting in decreased quality of life. Other skin toxicity scales (pigmentation, induration, fibrosis) are less specific for capturing radiation induced side effects. Skin dose outcomes will potentially lead to updated skin dose constraints in treatment planning. PROMs assess the effect of the skin spacer on cosmesis, function and quality of life. Furthermore, by using internationally recognized PROMs a better comparison

with other radiotherapy techniques is possible. As our study specifically evaluates the use of skin spacer in LDR seed brachytherapy as an APBI technique, outcomes cannot be generalized to single balloon or strut based breast brachytherapy techniques since the dose fall-off is much less abrupt in those techniques[55, 56]. On the other hand, similar results are anticipated for external beam radiotherapy including stereotactic body radiotherapy (SBRT)[57] or 3D-CRT[58] and multicatheter brachytherapy[59] since steep dose gradients are also achieved around the target volume with these techniques.

In **Chapter 7** we evaluate early in vivo skin dosimetry using Gafchromic films in 18 patients undergoing LDR seed breast brachytherapy. Patients had the film patched for 24 hours on the high skin dose area immediately after the palladium-103 radiation sources were implanted in the breast. The main finding of this study is the strong correlation of the early measured in vivo maximum skin dose with the skin toxicities and with the post-planning maximum skin dose. This suggests that in vivo skin dosimetry using Gafchromic films is a useful tool for early prediction of skin toxicity. An excess in the early skin dose measurement could justify an intervention to reduce the skin dose, for example the spacer injection as described in **chapter 5 and 6**.

Interesting finding of this study was that pre-planning skin dosimetry was a poor predictor of acute clinical skin toxicity. This might be explained by the inaccuracy of the seed positioning during the procedure and/or the changes in the breast anatomy after the seeds implantation including the occurrence of edema. There is a very high sensitivity of the skin dose to those factors because of the rapid dose fall-off around radioactive seeds. Post-implant dosimetry better predicted skin toxicity in this study than pre-planning did. However, post-implant calculated maximum skin doses were on average 30% higher than the those measured in vivo. The skin dose calculations in regions of electronic disequilibrium are challenging, such that the calculated dose would be overestimated. In addition, wearing it for 24 hours, Gafchromic film may better capture the changes in skin dose over time caused when patients are changing position and could hence be a more realistic evaluation of the true skin dose.

Lastly, in vivo dosimetry with Gafchromic films provide a rapid and accurate estimation, within 24 hours, of the potential skin overdosage, without causing any patient discomfort. At that time only 4% of the total dose has been delivered, giving plenty of time to schedule an intervention. This intervention is a good example of improving treatment accuracy and thereby creating possibilities to reduce side effects.

Chapter 5, 6 and 7 describe the research projects that were directly related to the PBSI program in Rotterdam. It clearly shows the potential spin-off of such a research project. Although the clinical trial is currently not recruiting patients in Rotterdam, during the start of the program we were able successfully treat 29 patients and finish some valuable research. The use of skin spacers and in vivo film dosimetry is applicable to other APBI techniques too.

Interaction between surgeon and radiation oncologist in BCT

The third part of this thesis describes the challenges in target definition for partial breast (and boost) radiotherapy and a novel intervention to improve treatment accuracy. With oncoplastic techniques becoming standard practice in BCT and the increasing number of patients being treated with APBI this is very relevant in current breast cancer treatment. In **chapter 9** we describe the Target-1 study: a radiopaque hydrogel was used during lumpectomy to improve tumor bed delineation for breast radiotherapy. This study in which post-operative CT-scans of 42 patients were contoured by a team of 6 well trained and highly specialized radiation oncologists demonstrates that using a hydrogel loaded with iodine during lumpectomy cavity closure, reduces the variability of target contouring. This simple surgical intervention adds to other solutions to improve radiotherapy target definition for breast cancer patients, including the use of clips, 3D ultrasound or MR image fusion or simulation. The results compare well with other studies using standardized contouring protocols and surgical clips that found comparable Cx to the one we reported here for the control group, between 0.56 and 0.61. However, none of these studies were performed in a context of a level I oncoplastic intervention. A study by Den Hartogh showed that radiotherapy target definition using clips alone for patients with full thickness closure (FTC) has a much poorer inter-observer agreement, with a median Cx of 0.44. The high conformity index of 0.70 found in our intervention group, where all patients had oncoplastic intervention, should be considered as a good result for improving the quality of the radiation treatment. A higher Cx results in a lower risk of geographical miss of the administered radiotherapy, which, in turn, may result in a better outcome in term of local control. Additionally, with less inter-observer variability, smaller margins accounting for delineation variation could be used. This could reduce radiotherapy related toxicity, such as skin effects and breast fibrosis, and compensate for the possibly larger volume delineated when using a hydrogel injection. Furthermore, by helping target definition in patients with low CVS, more patients may be eligible for more patient friendly APBI techniques as patients with a poorly defined cavity are generally excluded[60-64]. A limitation of this approach however is that with the intra-operative injection of the hydrogel in almost half of the cases the seroma as defined by the gel showed some leveling with fluid or dilution resulting in imprecise contours. An important caveat in breast radiotherapy is the fact that tumor bed does not necessarily match the lumpectomy cavity. Better defining the lumpectomy cavity will eventually improve treatment accuracy, but still contouring guidelines should be followed. In conclusion, this study showed that the use of a radiopaque hydrogel during BCS enables breast surgeons to clearly demarcate the lumpectomy cavity, resulting in a high inter-observer agreement of radiotherapy target definition. This intervention is easy to perform, safe and can easily blend into standard practice.

Patients' perspective of treatment quality

In **chapter 10** the psychometric evaluation of a Dutch translated shorter version of the BCTOS questionnaire is presented. This tool gives the patient the opportunity to rate differences between the treated and untreated breast, making it very useful in the evaluation of breast conserving therapy outcomes. Recently the English version was shortened by Hennigs et al[65], making it more concise but keeping the validity good. As our goal was to create a PROM valid to differentiate between favorable and unfavorable BCT outcomes, we tested five additional items in the cosmetic subscale. By doing this, we anticipated for specifically better capturing unfavorable radiotherapy outcomes in our study population. The reason to do this was that we included patients after completing all locoregional treatment with a broad range of 5 to 29 months follow-up after surgery, instead of 1 week post-surgery in the study by Hennigs. Psychometric evaluation of the newly developed Dutch BCTOS-13 questionnaire in 101 BCT patients showed excellent results, that were slightly better than the original BCTOS-22 and the shortened BCTOS-12. The good clinical validity makes the BCTOS-13 a useful tool to identify patients with unfavorable cosmetic and functional outcomes of both the surgical ánd radiotherapeutic treatment, requiring specific attention. Because we did not include all EORTC QLQ-BR23 subscales we were not able to draw any conclusions on the correlations between the BCTOS-13 and overall quality of life. Compared to Hennigs we validated our questionnaire in patient after completing all locoregional treatment. However, additional validation in other patient groups like patients undergoing axillary lymph node dissection, level 2 oncoplastic surgery, axillary irradiation or partial breast irradiation could be considered.

Future prospects

In the treatment of early stage breast cancer patients, improvement in cosmesis and quality of life is of high importance. Over the last decade, value based health care (VBHC) has gained attention in breast cancer care. In the Netherlands the ministry of Health recently stated the ambition, to have health outcome data available for 50% of the total disease burden in 2022. The International Consortium for Health Outcomes Measurement (ICHOM) created a standard breast cancer outcome set in 2016[66]. Patient-reported outcome measures (PROMs) accounting for approximately 75% of outcomes in this set while the other 25% are related to clinical outcomes. Lagendijk et al. performed a large study to evaluate the complete set of PROs proposed in the ICHOM breast cancer set per type of surgery with adjustment for potential confounders[67].

It is expected that VBHC will be increasingly important in the near future. In this thesis we present several techniques all aiming to improve accuracy and safety of the surgery, reducing post-operative complication, improving the accuracy of radiotherapy and hence increasing the proportion of patients for more friendly techniques with less long-term potentially lethal complication like secondary cancers, and developing strategies to evaluate those benefits. Besides improvement of clinical outcomes we also aim at improving PROMs for these patients, which is in line with the development towards VHBC. The newly designed Dutch BCTOS that is presented in this thesis is a

PROM that helps to better detect patients with impaired cosmetic or functional outcome following BCT. This gives the opportunity to give special attention to patients with unfavorable outcomes, while clinical visits could be reduced in patients with favorable outcomes. We therefore recommend standard use of the Dutch BCTOS-13 questionnaire in the evaluation breast conserving therapy quality of patients in the Netherlands.

Magnetic marker localization (MaMaLoc) was shown effective in our RCT and a high surgical usability was demonstrated. MaMaLoc could be offered as an alternative to WGL or RSL. To further improve surgical usability and potentially clinical outcomes including cosmesis, further research should focus on technical improvements of the technique. A specifically powered trial comparing MaMaLoc to RSL or WGL could detect any potential benefit on positive margin rates and resected specimen weights. This is important, as reduction of positive margin rates in early RSL studies could not be confirmed in subsequent studies. Furthermore, for adoption of this technique, a health care analysis of impact on costs and logistics would be valuable.

The use of silver-containing dressings, as described in **Chapter 3,** resulted in high patient satisfaction and reduced wound-related cost. A rather large SSI reduction was found using this dressing, especially in breast conserving surgery, but not significantly. Given the cost benefit and high patient satisfaction it could be proposed as standard of care in breast conserving surgery. However, replication of our findings would be valuable, preferably in an adequately powered RCT. Of course, other infection prevention strategies should be explored additionally. Based on our microbiology findings, S. aureus eradication would be an interesting approach, also supported by the recent publication of Lelieveld et al.[68]

The future of APBI

Over the last decade, strong evidence has been generated on the effectivity of the APBI concept for selected low-risk breast cancer patients. Given the reduced treatment time and patient burden for these techniques compared to standard WBI regimens, APBI could become standard practice in this patient group. This is of major importance since APBI techniques could greatly reduce the risk of secondary lung cancer mortality. In 2016 Manyam et al. showed that 90% of the early stage breast cancer patients are eligible for APBI using the GEC-ESTRO guidelines[69], whereas this would have been only 41% using the older and more conservative ASTRO guidelines. To increase the proportion of early stage breast cancer patients treated with APBI, some steps have to be made over the next years. Firstly, older international guidelines, like f.e. the ASTRO guideline should be updated, recommending APBI for low-risk breast cancer patients. Secondly, selecting low-risk patients is crucial in APBI and patient selection criteria should be constantly updated based on ongoing research. Tumor biology will play an important role in this. Strikingly, even if a patient is found to be 'suitable' or APBI based on patient criteria, still only 15% APBI was used in a a large national database study by Shaitelman et al[70]. This is probably explained by technical limitations of

specific APBI techniques and uncertainties in target definition. Therefore, it would be recommended for radiotherapy centers to have a set of APBI techniques available, such that technical limitations of a certain technique in individual cases does not directly result in APBI ineligibility for that patient. Each APBI technique has specific technical considerations. In the coming years, technical improvements should make all of these techniques easier implementable for the general radiation oncology community. Futhermore, multidisciplinary collaboration between surgeons, radiation oncologists, radiologists and medical physicists will be crucial, especially in technically challenging techniques like f.e. PBSI. Thirdly, better target definition for APBI using either improving imaging techniques or innovative tools like f.e. the iodine hydrogel marker as described in **chapter 9** of this thesis, will result into more patients being eligible for APBI techniques. To better select patients that would benefit from a iodine hydrogel marker injection to improve radiotherapy target definition, we are currently performing the Target-2 study. In this study patients with a low cavity visualization score on original planning CT-scan will undergo an ultrasound guided injection of hydrogel in the lumpectomy cavity to improve visibility on CT. The effect of hydrogel on mean target volumes and consequent planned target volumes (PTVs) will be analyzed in this ideal comparison within the same patient. By doing so, we aim to further improve target definition in these patients. This would eventually result in less geographical misses and less side-effects. This tool is a good example of interdisciplinary collaboration to improve treatment accuracy.

Apart from the lessons learned on introducing a new breast brachytherapy APBI technique in a center with limited breast brachytherapy experience - as described in **chapter 8 -** this thesis has provided proof-of-concept data for skin spacing and *in vivo* film dosimetry that could be the basis for new research. The clinical use of skin spacers is still under investigation. If a reduction of skin toxicity is demonstrated, the intervention could also be applied to other APBI techniques with a rapid dose fall-off. In a clinical setting, the procedure would be realized as follows: first perform the seed implant and afterwards the spacer injection. This allows for the most accurate seed placement. We recommend to select patients at risk of skin toxicity using the simple tool of 24h Gafchromic film dosimetry as well as for quality assurance purposes. If excessive dose is detected preventative measures could be decided. This would allow to only inject a spacer in patients with a high skin dose, that benefit from a spacer being injected at 24 hours after the implant when only a fraction of the dose has been delivered. For HDR brachytherapy using multicatheter, balloon brachytherapy or even breast stereotactic body radiotherapy, the spacer could be injected between successive fractions.

Efforts are made to restart the PBSI program in the Netherlands, as it suits very well in the tailormade breast cancer treatment nowadays ánd the treatment is very convenient for patients.

In summary, in the future the treatment of breast cancer will be increasingly tailored to the specificity of each patient. The goal of innovation will be maintaining oncological effectivity while increasing cosmetic outcomes and reducing patient burden. In this thesis we described some strategies to obtain this increasing treatment accuracy and reducing side-effects of breast conserving therapy.

References

1. Global Burden of Disease Cancer C, Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-years for 32 Cancer Groups, 1990 to 2015: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2017;3(4):524-48.
2. SEER database. Cancer Stat Facts: Female Breast Cancer 2017 [Available from: https://seer.cancer.gov/statfacts/html/breast.html.
3. Peto R, Boreham J, Clarke M, Davies C, Beral V. UK and USA breast cancer deaths down 25% in year 2000 at ages 20-69 years. Lancet. 2000;355(9217):1822.
4. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233-41.
5. Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347(16):1227-32.
6. Early Breast Cancer Trialists' Collaborative G, Peto R, Davies C, Godwin J, Gray R, Pan HC, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet. 2012;379(9814):432-44.
7. Sukel MP, van de Poll-Franse LV, Nieuwenhuijzen GA, Vreugdenhil G, Herings RM, Coebergh JW, et al. Substantial increase in the use of adjuvant systemic treatment for early stage breast cancer reflects changes in guidelines in the period 1990-2006 in the southeastern Netherlands. Eur J Cancer. 2008;44(13):1846-54.
8. (NBCA) NBCA. Jaarrapportage NBCA 2016. 2016.
9. Lagendijk M, van Maaren MC, Saadatmand S, Strobbe LJA, Poortmans PMP, Koppert LB, et al. Breast conserving therapy and mastectomy revisited: Breast cancer-specific survival and the influence of prognostic factors in 129,692 patients. Int J Cancer. 2018;142(1):165-75.
10. van Maaren MC, de Munck L, de Bock GH, Jobsen JJ, van Dalen T, Linn SC, et al. 10 year survival after breast-conserving surgery plus radiotherapy compared with mastectomy in early breast cancer in the Netherlands: a population-based study. Lancet Oncol. 2016;17(8):1158-70.
11. Franceschini G, Orlandi A, Sanchez AM, Calegari MA, Masetti R. Mastectomy in precision oncology era: myth or reality? Translational Cancer Research. 2016:S544-S5.
12. Mao J-H, Diest PJv, Perez-Losada J, Snijders AM. Revisiting the impact of age and molecular subtype on overall survival after radiotherapy in breast cancer patients. Sci Rep. 2017;7(1):12587-.
13. Vos EL, Siesling S, Baaijens MHA, Verhoef C, Jager A, Voogd AC, et al. Omitting re-excision for focally positive margins after breast-conserving surgery does not impair disease-free and overall survival. Breast Cancer Res Treat. 2017;164(1):157-67.
14. Bosma SC, van der Leij F, van Werkhoven E, Bartelink H, Wesseling J, Linn S, et al. Very low local recurrence rates after breast-conserving therapy: analysis of 8485 patients treated over a 28-year period. Breast Cancer Res Treat. 2016;156(2):391-400.
15. Mauri G, Sconfienza LM, Pescatori LC, Fedeli MP, Ali M, Di Leo G, et al. Technical success, technique efficacy and complications of minimally-invasive imaging-guided percutaneous ablation procedures of breast cancer: A systematic review and meta-analysis. Eur Radiol. 2017;27(8):3199-210.

16. Peek MCL, Ahmed M, Napoli A, Usiskin S, Baker R, Douek M. Minimally invasive ablative techniques in the treatment of breast cancer: a systematic review and meta-analysis. International Journal of Hyperthermia. 2017;33(2):191-202.
17. Zhou W, Zha X, Liu X, Ding Q, Chen L, Ni Y, et al. US-guided percutaneous microwave coagulation of small breast cancers: a clinical study. Radiology. 2012;263(2):364-73.
18. Garcia-Tejedor A, Guma A, Soler T, Valdivieso A, Petit A, Contreras N, et al. Radiofrequency Ablation Followed by Surgical Excision versus Lumpectomy for Early Stage Breast Cancer: A Randomized Phase II Clinical Trial. Radiology. 2018;289(2):317-24.
19. Kinoshita T. RFA experiences, indications and clinical outcomes. International journal of clinical oncology. 2019;24(6):603-7.
20. Cipora E, Konieczny M, Karwat ID, Roczniak W, Babuska-Roczniak M. Surgical method of treatment and level of satisfaction with life among women diagnosed with breast cancer, according to time elapsed since performance of surgery. Ann Agric Environ Med. 2018;25(3):453-9.
21. Kim MK, Kim T, Moon HG, Jin US, Kim K, Kim J, et al. Effect of cosmetic outcome on quality of life after breast cancer surgery. Eur J Surg Oncol. 2015;41(3):426-32.
22. Klassen AF, Pusic AL, Scott A, Klok J, Cano SJ. Satisfaction and quality of life in women who undergo breast surgery: a qualitative study. BMC Womens Health. 2009;9:11.
23. Sun Y, Kim SW, Heo CY, Kim D, Hwang Y, Yom CK, et al. Comparison of quality of life based on surgical technique in patients with breast cancer. Jpn J Clin Oncol. 2014;44(1):22-7.
24. Brouwers PJAM, van Werkhoven E, Bartelink H, Fourquet A, Lemanski C, van Loon J, et al. Predictors for poor cosmetic outcome in patients with early stage breast cancer treated with breast conserving therapy: Results of the Young boost trial. Radiotherapy and Oncology. 2018;128(3):434-41.
25. Hall FM, Frank HA. Preoperative localization of nonpalpable breast lesions. AJR Am J Roentgenol. 1979;132(1):101-5.
26. Chan BK, Wiseberg-Firtell JA, Jois RH, Jensen K, Audisio RA. Localization techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database Syst Rev. 2015(12):CD009206.
27. Bloomquist EV, Ajkay N, Patil S, Collett AE, Frazier TG, Barrio AV. A Randomized Prospective Comparison of Patient-Assessed Satisfaction and Clinical Outcomes with Radioactive Seed Localization versus Wire Localization. Breast J. 2016;22(2):151-7.
28. Langhans L, Tvedskov TF, Klausen TL, Jensen MB, Talman ML, Vejborg I, et al. Radioactive Seed Localization or Wire-guided Localization of Nonpalpable Invasive and In Situ Breast Cancer: A Randomized, Multicenter, Open-label Trial. Ann Surg. 2017;266(1):29-35.
29. Schermers B, van der Hage JA, Loo CE, Vrancken Peeters M, Winter-Warnars HAO, van Duijnhoven F, et al. Feasibility of magnetic marker localisation for non-palpable breast cancer. Breast. 2017;33:50-6.
30. Association of Breast Surgery at B. Surgical guidelines for the management of breast cancer. Eur J Surg Oncol. 2009;35 Suppl 1:1-22.
31. Kreienberg R, Albert US, Follmann M, Kopp IB, Kühn T, Wöckel A. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms. Senologie - Zeitschrift für Mammadiagnostik und -therapie. 2013;10(03):164-92.
32. Landercasper J, Whitacre E, Degnim AC, Al-Hamadani M. Reasons for re-excision after lumpectomy for breast cancer: insight from the American Society of Breast Surgeons Mastery(SM) database. Ann Surg Oncol. 2014;21(10):3185-91.

33. Degnim AC, Throckmorton AD, Boostrom SY, Boughey JC, Holifield A, Baddour LM, et al. Surgical site infection after breast surgery: impact of 2010 CDC reporting guidelines. Ann Surg Oncol. 2012;19(13):4099-103.
34. El-Tamer MB WB, Schifftner T, Neumayer L, Khuri S, Henderson W. Morbidity and mortality following breast cancer surgery in women: national benchmarks for standards of care. Annals of Surgery. 2007:665-71.
35. Gulluoglu BM, Guler SA, Ugurlu MU, Culha G. Efficacy of prophylactic antibiotic administration for breast cancer surgery in overweight or obese patients: a randomized controlled trial. Ann Surg. 2013;257(1):37-43.
36. Williams N, Sweetland H, Goyal S, Ivins N, Leaper DJ. Randomized trial of antimicrobial-coated sutures to prevent surgical site infection after breast cancer surgery. Surg Infect (Larchmt). 2011;12(6):469-74.
37. Dumville JC GT, Walter CJ, Sharp CA, Page T. Dressings for the prevention of surgical site infection. Cochrane Database of Systematic Reviews. 2014.
38. Bethune WA. Partial breast irradiation for early breast cancer. J Natl Med Assoc. 1991;83(9):768, 800, 8.
39. Fisher ER, Sass R, Fisher B, Gregorio R, Brown R, Wickerham L. Pathologic findings from the National Surgical Adjuvant Breast Project (protocol 6). II. Relation of local breast recurrence to multicentricity. Cancer. 1986;57(9):1717-24.
40. NSABP. Protocol B-39/RTOG 0413, A Randomized Phase III Study of Conventional Whole Breast Irradiation (WBI) Versus Partial Breast Irradiation (PBI) for Women with Stage 0, I, or II Breast Cancer [Available from: http://www.nsabp.pitt.edu/B-39.asp.
41. Pignol JP, Caudrelier JM, Crook J, McCann C, Truong P, Verkooijen HA. Report on the Clinical Outcomes of Permanent Breast Seed Implant for Early-Stage Breast Cancers. Int J Radiat Oncol Biol Phys. 2015;93(3):614-21.
42. Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, et al. 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. Lancet. 2016;387(10015):229-38.
43. Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Saunders C, et al. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). Health Technol Assess. 2016;20(73):1-188.
44. Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. 2013;14(13):1269-77.
45. Vicini F, Winter K, Straube W, Wong J, Pass H, Rabinovitch R, et al. A phase I/II trial to evaluate three-dimensional conformal radiation therapy confined to the region of the lumpectomy cavity for Stage I/II breast carcinoma: initial report of feasibility and reproducibility of Radiation Therapy Oncology Group (RTOG) Study 0319. Int J Radiat Oncol Biol Phys. 2005;63(5):1531-7.
46. Vicini FA, Chen PY, Fraile M, Gustafson GS, Edmundson GK, Jaffray DA, et al. Low-dose-rate brachytherapy as the sole radiation modality in the management of patients with early-stage breast cancer treated with breast-conserving therapy: preliminary results of a pilot trial. Int J Radiat Oncol Biol Phys. 1997;38(2):301-10.
47. White J, Winter K, Kuske RR, Bolton JS, Arthur DW, Scroggins T, et al. Long-Term Cancer Outcomes From Study NRG Oncology/RTOG 9517: A Phase 2 Study of Accelerated Partial Breast Irradiation With Multicatheter Brachytherapy After Lumpectomy for Early-Stage Breast Cancer. Int J Radiat Oncol Biol Phys. 2016;95(5):1460-5.

48. Strnad V, Ott O, Potter R, Hildebrandt G, Hammer J, Resch A, et al. Interstitial brachytherapy alone after breast conserving surgery: interim results of a German-Austrian multicenter phase II trial. Brachytherapy. 2004;3(3):115-9.
49. Wazer DE, Kaufman S, Cuttino L, DiPetrillo T, Arthur DW. Accelerated partial breast irradiation: an analysis of variables associated with late toxicity and long-term cosmetic outcome after high-dose-rate interstitial brachytherapy. Int J Radiat Oncol Biol Phys. 2006;64(2):489-95.
50. Mashouf S, Fleury E, Lai P, Merino T, Lechtman E, Kiss A, et al. Clinical Significance of Accounting for Tissue Heterogeneity in Permanent Breast Seed Implant Brachytherapy Planning. Int J Radiat Oncol Biol Phys. 2016;94(4):816-23.
51. Keller BM, Ravi A, Sankreacha R, Pignol JP. Permanent breast seed implant dosimetry quality assurance. Int J Radiat Oncol Biol Phys. 2012;83(1):84-92.
52. Pignol JP, Truong P, Rakovitch E, Sattler MG, Whelan TJ, Olivotto IA. Ten years results of the Canadian breast intensity modulated radiation therapy (IMRT) randomized controlled trial. Radiother Oncol. 2016;121(3):414-9.
53. Struik GM, Pignol JP, Kolkman-Deurloo IK, Godart J, Verduijn GM, Koppert LB, et al. Subcutaneous spacer injection to reduce skin toxicity in breast brachytherapy: A pilot study on mastectomy specimens. Brachytherapy. 2019;18(2):204-10.
54. Cuttino LW, Heffernan J, Vera R, Rosu M, Ramakrishnan VR, Arthur DW. Association between maximal skin dose and breast brachytherapy outcome: a proposal for more rigorous dosimetric constraints. Int J Radiat Oncol Biol Phys. 2011;81(3):e173-7.
55. Gitt A, Bose-Ribeiro H, Nieder C, Kup PG, Hermani H, Buhler H, et al. Treatment Results of MammoSite Catheter in Combination with Whole-breast Irradiation. Anticancer Res. 2016;36(1):355-60.
56. Yashar C, Attai D, Butler E, Einck J, Finkelstein S, Han B, et al. Strut-based accelerated partial breast irradiation: Report of treatment results for 250 consecutive patients at 5 years from a multicenter retrospective study. Brachytherapy. 2016;15(6):780-7.
57. Obayomi-Davies O, Kole TP, Oppong B, Rudra S, Makariou EV, Campbell LD, et al. Stereotactic Accelerated Partial Breast Irradiation for Early-Stage Breast Cancer: Rationale, Feasibility, and Early Experience Using the CyberKnife Radiosurgery Delivery Platform. Front Oncol. 2016;6:129.
58. Weed DW, Edmundson GK, Vicini FA, Chen PY, Martinez AA. Accelerated partial breast irradiation: A dosimetric comparison of three different techniques. Brachytherapy. 2005;4(2):121-9.
59. Major T, Stelczer G, Pesznyak C, Meszaros N, Polgar C. Multicatheter interstitial brachytherapy versus intensity modulated external beam therapy for accelerated partial breast irradiation: A comparative treatment planning study with respect to dosimetry of organs at risk. Radiother Oncol. 2017;122(1):17-23.
60. NRG Oncology (2018). NSABP Clinical Trials OverviewProtocol B-39/RTOG 0413 [Available from: http://www.nsabp.pitt.edu/B-39.asp.
61. Edmundson GK, Vicini FA, Chen PY, Mitchell C, Martinez AA. Dosimetric characteristics of the MammoSite RTS, a new breast brachytherapy applicator. International Journal of Radiation Oncology • Biology • Physics. 2002;52(4):1132-9.
62. Major T, Gutierrez C, Guix B, van Limbergen E, Strnad V, Polgar C. Recommendations from GEC ESTRO Breast Cancer Working Group (II): Target definition and target delineation for accelerated or boost partial breast irradiation using multicatheter interstitial brachytherapy after breast conserving open cavity surgery. Radiother Oncol. 2016;118(1):199-204.

63. Pignol JP, Keller B, Rakovitch E, Sankreacha R, Easton H, Que W. First report of a permanent breast^{103} Pd seed implant as adjuvant radiation treatment for early-stage breast cancer. Int J Radiat Oncol Biol Phys. 2006;64(1):176-81.
64. Strnad V, Hannoun-Levi JM, Guinot JL, Lossl K, Kauer-Dorner D, Resch A, et al. Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost Partial Breast Irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery. Radiother Oncol. 2015;115(3):342-8.
65. Hennigs A, Heil J, Wagner A, Rath M, Moosbrugger H, Kelava A, et al. Development and psychometric validation of a shorter version of the Breast Cancer Treatment Outcome Scale (BCTOS-12). Breast. 2018;38:58-65.
66. Ong WL, Schouwenburg MG, van Bommel ACM, Stowell C, Allison KH, Benn KE, et al. A Standard Set of Value-Based Patient-Centered Outcomes for Breast Cancer: The International Consortium for Health Outcomes Measurement (ICHOM) Initiative. JAMA Oncol. 2017;3(5):677-85.
67. Lagendijk M, van Egdom LSE, van Veen FEE, Vos EL, Mureau MAM, van Leeuwen N, et al. Patient-Reported Outcome Measures May Add Value in Breast Cancer Surgery. Annals of Surgical Oncology. 2018;25(12):3563-71.
68. Anneke, Peter, Lelieveld G. The incidence of decolonizing patients of Staphylococcus Aureus nasal carriage undergoing breast cancer surgery in the Netherlands. 2018.
69. Mangram AJ HT, Pearson ML, Silver LC, Jarvis WR. Guideline for Prevention of Surgical Site Infection, 1999. Centers for Disease Control and Prevention (CDC) Hospital Infection Control Practices Advisory Committee. American Journal of Infection Control. 1999:97-132.
70. Shaitelman SF, Lin HY, Smith BD, Shen Y, Bedrosian I, Marsh GD, et al. Practical Implications of the Publication of Consensus Guidelines by the American Society for Radiation Oncology: Accelerated Partial Breast Irradiation and the National Cancer Data Base. Int J Radiat Oncol Biol Phys. 2016;94(2):338-48.

CHAPTER TWELVE

12

Summary

Breast cancer is the most common malignancy among women in western countries. Thanks to mammography screening and improved imaging techniques, tumors are increasingly detected at an early stage; in more than 60% of the patients the cancer is localized to the breast tissue at time of diagnosis and no loco-regional or distant metastasis have occurred. For these early stage breast cancer patients, outcomes are excellent with a 5-year relative survival rate of 98,8%. Breast conserving therapy, consisting of a wide local excision and adjuvant radiotherapy, is equally effective as mastectomy for these patients, in terms of local control and disease specific and overall survival. Currently, up to 65% of patients is treated with breast conserving surgery in the Netherlands, and this proportion is still increasing. Recent publications reported an overall survival benefit of BCT (including radiotherapy) over mastectomy in early stage breast cancer patients. However, because of potential bias further research on that subject is warranted and promoting BCT to patients purely for oncological safety reasons would be premature. Additionally, patients are often treated with adjuvant systemic treatment, including antihormonal- and chemotherapy. Given the excellent outcomes in this specific low-risk patient group, there is a paradigm shift towards treatment modalities with reduced morbidity and treatment burden leading to improved cosmesis and quality of life. The treatment of early stage breast cancer patients is increasingly tailored to the specificity of each patient. Optimal patient selection is essential.

Chapter 1 provides an introduction to the current treatment of early stage breast cancer patients including strategies to improve patient outcomes (cosmesis and quality of life). Also, it outlines different aspects described in this thesis.

Preserving the breast has cosmetic and functional benefits, which are directly related to patients' quality of life. However, in unfavorable cases BCT can result in poor outcomes. Most important morbidity after breast conserving surgery is caused by surgical site infections, re-operations and poor cosmesis. To reduce this morbidity omitting re-excision in patients focally positive lumpectomy margins is considered. Several author suggest to omit re-excision in these patients, under the condition of adjuvant radiotherapy to the whole breast including a boost. Although omitting re-excision would reduce surgical morbidity for patients, the need for a tumor bed boost might outweigh that patient benefit due to radiation induced morbidity. The use of percutaneous tumor ablation techniques potentially reduces morbidity of the primary BCT dramatically. However strong evidence is scarce and adoption of the techniques is yet limited. The first part of this thesis describes two new surgical strategies aiming to improve accuracy and safety of the surgery, and reducing post-operative complications.

Tumor localization techniques are aiming at increased treatment accuracy and consequently reduced positive margin rates while resecting similar or smaller volume, which is associated with improved cosmesis. **Chapter 2** describes the first use of MaMaLoc as sole tumor localization technique in a randomized controlled comparison to the gold standard of WGL in 68 early stage breast cancer patients. This study demonstrated a higher surgical usability for MaMaLoc (SUS score

of 70/100) than for WGL (SUS score of 58/100). In line with recent studies comparing RSL to WGL, a higher patient satisfaction was found using MaMaLoc than with WGL. This study supports the hypothesis that MaMaLoc combines the surgical advantages of a point source without the need to use radioactivity. **In chapter 3** we describe the results of an RCT testing the effect of a silver containing wound dressing (Aquacel) on the occurrence of SSIs in 230 patients after breast cancer surgery. We found an SSI risk of 6.6% for the Aquacel group and 12.9% for the control group. Patient satisfaction was higher and the mean costs were lower with Aquacel, both significantly. This easy to use dressing has no disadvantage/harm for patients and there is proven benefit in terms of patient satisfaction and costs. Therefore, given the rather large effect size of SSI reduction in this study, this could be an easy tool to reduce surgical morbidity of BCT.

By allowing for breast preservation, the role of adjuvant radiotherapy is primarily to provide a cosmetic and quality of life benefit. However, the standard regimen of 3-5 weeks of daily radiation fractions add a significant burden to the treatment journey. APBI, treating only the tissue surrounding the original tumor bed, is an efficient strategy for well-selected low-risk patients. As opposed to standard EBRT, it reduces treatment burden without increasing side-effects. New insights in adjuvant radiotherapy have resulted in hypofractionation regimens and the development of several partial breast irradiation techniques. Omitting radiotherapy in specific low-risk patient groups is subject of research in several ongoing clinical trials. The second part of this thesis focuses on improving the accuracy of APBI radiotherapy and hence increasing the proportion of patients for more friendly technique with less long-term potentially lethal complication like secondary cancers, but also reduced skin toxicity, and developing strategies to evaluate those benefits.

Firstly, **chapter 4** shows the advantage of APBI with regards to secondary cancer risk in a phantom study; another incentive for APBI. Our study shows that all APBI techniques produce less scatter dose compared to whole breast radiotherapy, which translates into a 2-4 times lower secondary cancer risk. This strongly supports the generalization of partial breast irradiation as standard for early stage breast cancers or DCIS instead of whole breast radiotherapy. On top of the evidence on APBI effectivity and reduced treatment burden the new evidence presented in chapter 4 on secondary cancer risk reduction will further stimulate APBI adoption in the near future. Keeping in mind that radiotherapy essentially has a cosmetic and quality of life benefit, it is of high importance to perform research on reducing treatment related side effects. In breast radiotherapy, the critical structure is the skin. Skin toxicity can be permanent and result in poor cosmesis and reduced quality of life. A high skin dose is the main risk factor for skin toxicity. **In chapter 5, 6 and 7** we presented our work on skin toxicity reduction and improvement of treatment accuracy in LDR seed breast brachytherapy.

To prevent skin toxicity in breast APBI, most authors recommend limiting the skin dose to 70%. However, such constraints are not always achievable. This resulted in the rationale of the PBSI trial which is described in **chapter 6**: A simple solution to reduce the skin dose would be the use of a skin spacer to move the skin out of the high dose region which was tested in a preclinical study

as described in **chapter 5.** In all 22 cases a stable spacer volume was created under ultrasound guidance in real human breast specimens using either hyaluronic acid or PEG.
Although this is a proof-of-concept for the use of skin spacers, the impact on dose distribution including skin dose and clinical outcomes should still be confirmed in the randomized clinical trial. Primary outcome of this intervention trial is the occurrence of telangiectasia at two years after radiotherapy as that is a specific marker of late radiation induced skin toxicity. Rates of telangiectasia normally peak at 2 years and they are mostly permanent; resulting in decreased quality of life. **Chapter 7** evaluated early *in vivo* skin dosimetry in 18 patients undergoing LDR seed breast brachytherapy, by wearing Gafchromic films pathed on the skin for 24h. The main finding of this study is the strong correlation of the early measured in vivo maximum skin dose with the skin toxicities and with the post-planning maximum skin dose. In vivo dosimetry with Gafchromic films provide a rapid and accurate estimation, within 24 hours, of the potential skin overdosage, without causing any patient discomfort. At that time only 4% of the total dose has been delivered, giving plenty of time to schedule an intervention. This method is a good example of improving treatment accuracy and thereby creating possibilities to reduce side effects, f.e. by performing a spacer injection as described in **chapter 5 and 6**. **Chapter 5, 6 and 7** describe the research projects that were directly related to the PBSI program in Rotterdam. It clearly shows the potential spin-off of such a research project. Although the clinical trial is currently not recruiting patients in Rotterdam, during the start of the program we were able to successfully treat 29 patients and already finish valuable research. The use of skin spacers and in vivo film dosimetry is applicable to other APBI techniques too. The introduction of PBSI in the Netherlands provided valuable information for other centers considering to implement this patient friendly new APBI technique.
The third part of this thesis describes the challenges in target definition of the lumpectomy cavity for partial breast (and boost) radiotherapy and a novel intervention to improve treatment accuracy. With oncoplastic techniques becoming standard practice in BCT and the increasing number of patients being treated with APBI this is very relevant in current breast cancer treatment. **Chapter 9** describes de results of Target Study. Post-lumpectomy CT-scans of 42 patients were contoured by a team of 6 well trained and highly specialized radiation oncologists demonstrating that using a hydrogel loaded with iodine during lumpectomy cavity closure, reduces the variability of target contouring. This simple surgical intervention adds to other solutions to improve radiotherapy target definition for breast cancer patients, including the use of clips, 3D ultrasound or MR image fusion or simulation. A better target definition results eventually in better local control and reduced radiotherapy related toxicity. Furthermore, more patients may be eligible for more patient friendly APBI techniques as patients with a poorly defined cavity are generally excluded. This intervention is easy to perform, safe and can easily blend into standard practice.
In **chapter 10** the psychometric evaluation of a Dutch translated shorter version of the BCTOS questionnaire is presented. The good clinical validity makes the BCTOS-13 a useful tool to identify

patients with unfavorable cosmetic and functional outcomes of both the surgical ánd radiotherapeutic treatment, requiring specific attention.

In **Chapter 11** the main findings of this thesis are discussed. The increasing number of breast cancer patients that are diagnosed at an early stage are treated with BCT and these specific patients have excellent oncological outcomes. This thesis focuses on improving cosmetic outcome and patient satisfaction by improving treatment accuracy and reducing side effects of BCT. Improved tumor localization and the use of silver-containing dressings are described to reduce surgical morbidity (re-operations, poor cosmesis and SSIs). APBI is extensively discussed as a strategy to 1. reduce treatment burden for patients; 2. reduce secondary cancer risk; 3. reduce skin toxicity. Skin spacing and *in vivo* film dosimetry add to the tools to improve treatment accuracy and reduce side effects of the radiation treatment of early stage breast cancer. A better interaction between surgeons and radiation oncologist, f.e. by using hydrogel marker for target definition, will improve treatment accuracy in the future. Further technical improvements and better patient selection will make patient friendly treatments increasingly available for breast cancer patients in the future. Value based health care and the use of PROMs will help to further improve patient outcomes and tailor the breast cancer treatment to the specificity of the individual patient in the future.

Nederlandse samenvatting

Borstkanker is de meest voorkomende vorm van kanker onder vrouwen in westerse landen. Dankzij mammografie screening en verbeterde beeldvormende technieken, worden tumoren steeds vaker ontdekt in een vroeg stadium; in meer dan 60% van de patiënten is de kanker beperkt tot het borstweefsel ten tijde van de diagnose en zijn er geen loco-regionale of afstandsmetastasen opgetreden. Voor deze vroeg-stadium borstkankerpatiënten zijn de uitkomsten uitstekend, met een relatieve 5-jaars overleving van 98,8%. Borstsparende therapie (BST), bestaande uit een ruime lokale excisie (of: lumpectomie) en aanvullende radiotherapie, is even effectief als een borstamputatie (of: mastectomie) voor deze patiënten, wat betreft lokale controle en ziekte specifieke overleving. Momenteel wordt 65% van de patiënten in Nederland behandeld met borstsparende chirurgie, en dit percentage neemt nog steeds toe. Recente publicaties rapporteerden een verbeterde overleving van patiënten na BST (inclusief radiotherapie) ten opzichte van een borstamputatie bij vroeg stadium borstkankerpatiënten. Echter, vanwege mogelijke bias is verder onderzoek op dat gebied gerechtvaardigd en zou het promoten van BST bij patiënten, puur om oncologische redenen, voorbarig zijn. Aanvullend worden patiënten vaak behandeld met adjuvante systemische behandeling, waaronder anti-hormonale en chemotherapie. Gezien de uitstekende resultaten in deze specifieke laag-risico patiëntengroep, vind er een verschuiving plaats naar behandelmodaliteiten met een verminderde morbiditeit en patiëntbelasting, die leidt tot verbeterde cosmetiek en kwaliteit van leven. De behandeling van vroeg stadium borstkanker is in toenemende mate afgestemd op de individuele patiënt. Optimale patiëntselectie is hierin essentieel.

Hoofdstuk 1 introduceert de huidige behandeling van vroeg stadium borstkankerpatiënten, inclusief strategieën om patiëntuitkomsten (cosmetiek en kwaliteit van leven) te verbeteren. Ook schetst het de verschillende aspecten hiervan die in dit proefschrift worden beschreven.

Het behoud van de borst heeft cosmetische en functionele voordelen, die rechtstreeks gerelateerd zijn aan de kwaliteit van leven van de patiënt. Echter, in ongunstige gevallen kan BST leiden tot slechte uitkomsten. De belangrijkste morbiditeit na borstsparende chirurgie wordt veroorzaakt door wondinfecties, re-operaties en slechte cosmetische uitkomsten. Om deze morbiditeit te verminderen wordt overwogen om een re-excisie achterwege te laten bij patiënten met een focaal irradicale resectie. Verschillende auteurs suggereren om bij deze patiënten geen re-excisie te verrichten, onder de voorwaarde dat adjuvante radiotherapie van de gehele borst, inclusief een boost, wordt toegepast. Hoewel het achterwege laten van een re-excisie de chirurgische morbiditeit voor patiënten zou verminderen, kan de noodzaak van een boostbestraling van het tumorbed dit voordeel opheffen door de straling-geïnduceerde morbiditeit. In potentie vermindert het gebruik van percutane tumorablatietechnieken de morbiditeit van de primaire BST aanzienlijk. Sterk wetenschappelijk bewijs is echter schaars en de toepassing van de technieken is tot op heden nog relatief beperkt. Het eerste deel van dit proefschrift beschrijft twee nieuwe chirurgische strategieën die als doel hebben de nauwkeurigheid en veiligheid van de operatie te verbeteren en postoperatieve complicaties te verminderen.

Tumorlokalisatie technieken zijn gericht op het verhogen van de behandelnauwkeurigheid en zodoende het verminderen van positieve resectie marges, terwijl een vergelijkbaar of kleiner volume wordt gereseceerd, wat is geassocieerd met verbeterde cosmetiek. **Hoofdstuk 2** beschrijft het eerste gebruik van MaMaLoc als enige tumorlokalisatie techniek in een gerandomiseerd vergelijkend onderzoek (randomized controlled trial (RCT)) met de gouden standaard van draadgeleide lokalisatie (DGL) bij 68 patiënten met vroeg stadium borstkanker. Deze studie toonde een hoger chirurgisch gebruiksgemak voor MaMaLoc (SUS-score van 70/100) dan voor DGL (SUS-score van 58/100). In overeenstemming met recente studies waarin lokalisatie met radioactieve zaadjes (RSL) werd vergeleken met DGL, werd een hogere patiënttevredenheid gevonden met MaMaLoc dan met WGL. Deze studie ondersteunt de hypothese dat MaMaLoc de chirurgische voordelen van een puntbron combineert zonder het gebruik van radioactiviteit. In **hoofdstuk 3** beschrijven we de resultaten van een RCT die het effect van een zilverhoudend wondverband (Aquacel) op het optreden van postoperatieve wondinfecties test bij 230 patiënten na borstkankeroperaties. We vonden een infectierisico van 6.6% in de Aquacel-groep en 12.9% in de controlegroep. De patiënttevredenheid was hoger en de gemiddelde kosten waren lager bij Aquacel, beiden significant. Dit gebruiksvriendelijke verband heeft geen nadeel/schade voor patiënten en er is een bewezen voordeel qua patiënttevredenheid en kosten. Daarom kan, gezien de behoorlijke reductie van wondinfecties in dit onderzoek, zilverhoudend wondverband een eenvoudig hulpmiddel zijn om chirurgische morbiditeit van BST te verminderen.

Door het behoud van de borst mogelijk te maken, is de rol van adjuvante radiotherapie in de eerste plaats het bieden van een cosmetisch voordeel en betere kwaliteit van leven. Het standaard schema van 3-5 weken dagelijkse bestralingen voegt echter een aanzienlijke belasting toe aan het behandeltraject. Partiële bestraling van de borst (Accelerated Partial Breast Irradiation (APBI)), dat alleen het weefsel rond het oorspronkelijke tumorbed behandelt, is een efficiënte strategie voor geselecteerde laag-risico patiënten. In vergelijking met standaard uitwendige bestraling (External Beam Radiotherapy (EBRT)) vermindert het de patiëntbelasting zonder een toename van bijwerkingen. Nieuwe inzichten in adjuvante radiotherapie hebben geresulteerd in hypofractionering schema's en de ontwikkeling van verschillende partiële bestralingstechnieken van de borst. Het achterwege laten van radiotherapie in specifieke laag-risico patiëntengroepen wordt onderzocht in verschillende lopende klinische studies. Het tweede deel van dit proefschrift richt zich op het verbeteren van de nauwkeurigheid van APBI-radiotherapie en daarmee op het verhogen van het aandeel van patiënten voor patiëntvriendelijkere technieken met minder potentieel dodelijke complicaties zoals secundaire tumoren, maar ook verminderde huidtoxiciteit en het ontwikkelen van strategieën om die voordelen te evalueren.

Allereerst toont **hoofdstuk 4** het voordeel van partiële bestraling met betrekking tot het risico op secundaire tumoren in een fantoomonderzoek; nog een stimulans voor partiële bestraling. Onze studie toont aan dat alle partiële bestralingstechnieken minder strooistraling produceren in vergelijking met bestraling van de gehele borst, wat zich vertaalt in een 2-4 maal lager risico op

secundaire tumoren. Dit ondersteunt sterk de generalisatie van partiële bestraling als standaard voor vroeg stadium borstkanker of DCIS in plaats van volledige bestraling van de borst. Bovenop het bewijs over effectiviteit van partiële bestraling en de verminderde patiëntbelasting, zal het nieuwe wetenschappelijk bewijs in hoofdstuk 4 over risicoreductie van secundaire tumoren de acceptatie van partiële bestraling in de nabije toekomst verder stimuleren. Rekening houdend met het feit dat radiotherapie in wezen een cosmetisch en kwaliteit van leven voordeel heeft, is het van groot belang om onderzoek uit te voeren naar het verminderen van bestralingsgerelateerde bijwerkingen. Bij bestraling van de borst is de meest kwetsbare structuur de huid. Huidtoxiciteit kan permanent zijn en leiden tot slechte cosmetiek en verminderde kwaliteit van leven. Een hoge huiddosis is de belangrijkste risicofactor voor huidtoxiciteit. In **hoofdstuk 5, 6 en 7** hebben we ons onderzoek gepresenteerd over vermindering van huidtoxiciteit en verbetering van de behandelnauwkeurigheid bij inwendige bestraling van de borst met lage dosis radioactieve zaadjes.

Om huidtoxiciteit van partiële bestraling van de borst te voorkomen, adviseren de meeste auteurs de huiddosis te beperken tot 70%. Dergelijke beperkingen zijn echter niet altijd haalbaar. Dit resulteerde in de rationale van de PBSI trial die wordt beschreven in **hoofdstuk 6**: een eenvoudige oplossing om de huiddosis te verlagen zou het gebruik van een huidspacer zijn, om zo de huid uit het gebied met een hoge dosis te houden. Dit werd in een preklinische studie getest, zoals beschreven in **hoofdstuk 5**. In alle 22 gevallen werd onder echogeleide een stabiel spacer volume gecreëerd in humane borst preparaten met ofwel hyaluronzuur of PEG.

Hoewel dit een proof-of-concept is voor het gebruik van huidspacers, moet de impact op de dosisverdeling, inclusief de dosis van de huid en klinische uitkomsten, nog steeds worden bevestigd in de gerandomiseerde klinische studie. De primaire uitkomst van deze interventiestudie is het optreden van teleangiëctasieën twee jaar na radiotherapie, omdat dat een specifieke marker is voor late straling geïnduceerde huidtoxiciteit. Het optreden van teleangiëctasieën piekt normaal gesproken na 2 jaar en meestal zijn ze permanent; resulterend in verminderde kwaliteit van leven. **Hoofdstuk 7** evalueerde vroege *in vivo* huiddosimetrie bij 18 patiënten die inwendige bestraling van de borst met radioactieve zaadjes ondergingen, door het 24 uur lang dragen van Gafchromic films die op de huid waren aangebracht. De belangrijkste bevinding van dit onderzoek is de sterke correlatie van de vroeg gemeten *in vivo* maximale huiddosis, met de huidtoxiciteit en met de maximale huiddosis op de post-planning. *In vivo* dosimetrie met Gafchromic-films biedt een snelle en nauwkeurige schatting, binnen 24 uur, van de mogelijke overdosering van de huid, zonder enig ongemak voor de patiënt te veroorzaken. Op dat moment is slechts 4% van de totale dosis afgegeven, waardoor er voldoende tijd is om een interventie te plannen. Deze methode is een goed voorbeeld van het verbeteren van de behandelnauwkeurigheid en daarmee het creëren van mogelijkheden om bijwerkingen te verminderen, bijvoorbeeld door een spacer injectie uit te voeren zoals beschreven in **hoofdstuk 5 en 6**. **Hoofdstuk 5, 6 en 7** beschrijven de onderzoeksprojecten die rechtstreeks verband hielden met het PBSI-programma in Rotterdam. Het laat duidelijk de potentiële spin-off zien van een dergelijk onderzoeksproject. Hoewel de klinische studie momenteel in Rotterdam geen patiënten

includeert, werden bij de start van het programma 29 patiënten succesvol behandeld en werd er reeds waardevol onderzoek afgerond. Het gebruik van huidspacers en *in vivo* film dosimetrie is ook toepasbaar bij andere partiële bestralingstechnieken van de borst. De introductie van PBSI in Nederland leverde waardevolle informatie op voor andere centra die deze patiëntvriendelijke nieuwe partiële bestralingstechniek willen implementeren.

Het derde deel van dit proefschrift beschrijft de uitdagingen in de doeldefinitie van de operatieholte voor partiële en boost bestraling van de borst en een nieuwe interventie om de nauwkeurigheid van de radiotherapie te verbeteren. Nu oncoplastische chirurgische technieken standaard worden in BST en een toenemend aantal patiënten met partiële bestraling wordt behandeld, is dit zeer relevant in de huidige behandeling van borstkanker. **Hoofdstuk 9** beschrijft de resultaten van de Target Study. Post-lumpectomie CT-scans van 42 patiënten werden ingetekend door een team van 6 ervaren en zeer gespecialiseerde radiotherapeuten. Er werd aangetoond dat het gebruik van een jodium bevattende hydrogel tijdens het sluiten van de lumpectomie holte de variabiliteit van intekenen van het doelgebied vermindert. Deze eenvoudige chirurgische interventie is aanvullend aan andere oplossingen om de doeldefinitie van radiotherapie voor borstkankerpatiënten te verbeteren, waaronder het gebruik van clips, 3D-echografie of MRI-beeldfusie of simulatie. Een betere doeldefinitie resulteert uiteindelijk in betere lokale controle en verminderde radiotherapie gerelateerde toxiciteit. Bovendien kunnen meer patiënten in aanmerking komen voor meer patiëntvriendelijke partiële bestralingstechnieken, omdat patiënten met een slecht afgrensbare operatieholte normaal zouden worden uitgesloten van partiële bestralingstechnieken. Deze interventie is eenvoudig uit te voeren, veilig en kan gemakkelijk opgaan in de standaardpraktijk.

In **hoofdstuk 10** wordt de psychometrische evaluatie van een Nederlandse vertaling van een kortere versie van de BCTOS-vragenlijst gepresenteerd. De goede klinische validiteit maakt de BCTOS-13 een nuttig hulpmiddel om patiënten te identificeren met ongunstige cosmetische en functionele uitkomsten van zowel de chirurgische als de bestralingsbehandeling, die specifieke aandacht nodig hebben.

In **hoofdstuk 11** worden de belangrijkste bevindingen van dit proefschrift besproken. Het toenemende aantal borstkankerpatiënten dat in een vroeg stadium wordt gediagnosticeerd, wordt behandeld met borstsparende therapie en deze specifieke patiënten hebben uitstekende oncologische uitkomsten. Dit proefschrift richt zich op het verbeteren van de cosmetische uitkomsten en patiënttevredenheid door de nauwkeurigheid van de BST te verbeteren en de bijwerkingen te verminderen. Verbeterde tumorlokalisatie en het gebruik van zilverhoudende wondverbanden worden beschreven om chirurgische morbiditeit (re-operaties, slechte cosmetiek en wondinfecties) te verminderen. Partiële bestraling van de borst wordt uitgebreid besproken als een strategie om 1. de patiëntbelasting te verminderen; 2. het risico op secundaire tumoren te verminderen; 3. Huidtoxiciteit te verminderen. Het gebruik van huidspacers en *in vivo* filmdosimetrie zijn een aanvulling op de bestaande middelen om de nauwkeurigheid te verbeteren en bijwerkingen te verminderen van de bestralingsbehandeling bij patiënten met vroeg stadium borstkanker.

Een betere interactie tussen chirurgen en radiotherapeuten, bijvoorbeeld door een hydrogelmarker te gebruiken voor doeldefinitie, zal de nauwkeurigheid van de bestraling van de borst verbeteren. Verdere technische verbeteringen en een betere selectie van patiënten zullen in de toekomst steeds meer patiëntvriendelijke behandelingen mogelijk maken voor borstkankerpatiënten. Waardegedreven zorg en het gebruik van patiënt gerapporteerde uitkomstmaten (PROM's) zullen de uitkomsten van patiënten verder verbeteren en de behandeling van borstkanker in de toekomst nog meer afstemmen op de individuele patiënt.

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