ACCELERATING ADJUVANT BREAST RADIOTHERAPY:

THE COST OF CONVENIENCE

CHRIS MONTEN

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ACCELERATING ADJUVANT BREAST RADIOTHERAPY: ` THE COST OF CONVENIENCE

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Prof. Dr. L. Veldeman, Md, Phd — Ghent University
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THE SECRET OF LIFE,
THOUGH, IS TO FALL
SEVEN TIMES AND
TO GET UP EIGHT TIMES

The Alchemist,
Paul Coelho

TO BE SURE WHERE YOU ARE,
YOU MUST KNOW WHERE
YOU HAVE BEEN, AND THUS
BE ABLE TO BETTER PREDICT WHAT
THE FUTURE IS LIKELY TO BE

Dr. Bernard Fisher

INHOUDSOPGAVE

ABBREVIATIONS

3D-CRT	Three-dimensional conformal radiotherapy
ABC (or TD-ABC)	Activity-based costing (or Time driven activity-based costing)
AJCC	American Joint Committee on Cancer
ALND	Axillary lymph node dissection
AMT	Anterior myocardial territory
APBI	Accelerated partial breast irradiation
ASTRO	American Society for Radiation Oncology
BCS	Breast conserving surgery
BCSM	Breast cancer specific mortality
BCSS	Breast cancer speficic survival
BCT	Breast conserving therapy (includes radiotherapy)
bid.	bis in diem (twice per day)
BMI	Body mass index (kg/m^2)
CA	Cost analysis
CALGB	Cancer and leukemia group B
CBA	Cost benefit analysis
CC	Cost comparison
CEA	Cost effectiveness analysis
CHEERS	Consolidated health economic evaluation reporting standards
CLBC	Contralateral breast cancer
CMA	Cost minimization analysis
CT	Computed tomography
CTV	Clinical Target Volume
CUA	Cost utility analysis
D50/D95/D98	Dose received by 50%/95%/98% of the volume
DCIS	Ductal carcinoma in situ
DFS	Disease free survival
DiBH	Deep inspirational breath-hold
DM	Distant metastasis
Dmax	Maximum dose
Dmean	Mean dose

DNA	Deoxyribonucleic acid
EBCTCG	Early breast cancer trialists' collaborative group
EBRT	External beam radiotherapy
EIC	Extensive intraductal component
EORTC	European organisation for Research and Treatment of Cancer
EQD2	Equivalent dose in 2Gy fractions
ER	Oestrogen receptor
ESBC	Early stage breast cancer
ESTRO	European society for radiotherapy & oncology
GEC-ESTRO	Groupe Europeen de curietherapie-European society for radiotherapy & oncology
GTV	Gross Target Volume
GUH	Ghent university hospital
Gy	Gray
HAI-5	Highly accelerated irradiation in 5 fractions
HEE	Health economic evaluation
HER2 or ErbB2	Herceptin receptor
HR	Hazard ratio, also ratio of hazards rates
IBTR	In-breast true recurrence
ICER	Incremental cost-effectiveness ratio
IDC	Invasive ductal cancer
IGRT	Image-guided radiotherapy
IMNI	Internal mammary node irradiation
IMRT	Intensity modulated radiotherapy
IOERT	Intraoperative electron radiotherapy
IORT	Intraoperative radiotherapy
ISPOR	International society for pharmaco-economic and outcomes research
kV	Kilovolt
LABC	Locally advanced stage breast cancer
LAD	Anterior interventricular branch of left coronary artery
LNI	Lymph node irradiation
LQ	Linear quadratic model
LR	Local recurrence
LRR	Loco-regional recurrence
LVSI	Lympho-vascular space invasion
LYG	Life years gained
ME	Mastectomy
MHD/MLD	Mean Heart Dose/Mean Lung Dose

MV	Megavolt
NS	Not significant
NSABP	National Surgical Adjuvant breast and Bowel Project
NST	Non-special type
NTCP	Normal tissue complication probability
OAR	Organ at risk
OECD	Organisation for Economic Co-operation and Development
OS	Overall survival
PBI	Partial breast irradiation
PMRT	Post-mastectomy radiotherapy
PR	Progesterone receptor
PRV	Planning volume for organs at risk
PTV	Planning Target Volume
QALY	Quality adjusted life years (gained)
QHES	Quality in health economic studies
R0	Resection margins not involved with tumour
R1/2	Resection margins involved with tumour, microscopically/macroscopically
RAPID-trial	Randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiotherapy
RIBP	Radiation induced brachial plexopathy
RR	Relative risk
RT	Radiotherapy
RTOG	Radiation therapy oncology group
SBRT	Stereotactic body radiotherapy
SEER	Surveillance, Epidemiology, and End Results Program
SIB	Simultaneously integrated boost
SIR	Standard incidence ratio
SLND	Sentinel lymph node dissection
SN	Sentinel node
START	UK Standardisation of Breast Radiotherapy
TN	Triple negative (hormone and Herceptin receptor negative)
UICC	Union for International Cancer Control
UK	United Kingdom
US	United States
VMAT	Volumetric modulated arc radiotherapy
WBI	Whole breast irradiation
WTP	Willingness-to-pay

INTRODUCTION

Breast cancer ranks second in cancer incidence worldwide (baso-cellular skin cancer excluded) and is the most frequent cancer type in women: with an incidence of 1,671,000 cases diagnosed per year it represents 25% of all cancers diagnosed in women[1].

In Belgium, it is even the most common cancer: in 2014, the Belgian Cancer Registry recorded 10,466 new diagnoses of invasive breast cancer, of which 6021 new cases in Flanders, with a medium age of 62.5 years[2]. The majority of diagnoses comes at an early stage - 43% were stage I and 33.9% stage II in 2014 – with a small minority of patients (5.9% of cases) presenting with metastasized disease at diagnosis. These figures suggest that each year over 9000 Belgian women present with an indication for curative intent breast cancer treatment, including a local treatment – surgery most frequently combined with radiotherapy - and systemic therapy, i.e. chemotherapy, targeted therapy, hormonal therapy, alone or combined.

The incidence rates of new cancer diagnoses typically increase with age. This also holds true for breast cancer. In Belgium, in 2014, 417 and 419 new invasive breast cancer diagnoses were recorded per 100,000 women between 60 and 69 years and older than 70 years, respectively, compared to respectively 23.5, 202 and 306 per 100,000 for the age groups below 40 years, 40-49 years and 50-59 years. Contrarily to yearly declining incidences in the other age groups, in women over 70, incidence has been rising since 2005. Possible explanations for this continuing increase may be an improved awareness for breast cancer in older women or the increasing life expectancy in women (average life expectancy of 83.9 years in 2014, compared to 76.7 years in 1980[3]).

Adjuvant radiotherapy is an evidence-based part of breast cancer treatment, improving local control and overall survival [4, 5]. Excellent results however come at the cost of radiation toxicity and burdensome treatment courses, which may hamper optimal radiotherapy utilization, especially in the older patient population. Following evidence-based recommendations, radiotherapy is indicated in 86% of all newly diagnosed Belgian breast

cancer patients[6]. However, despite the known negative impact on loco-regional control and disease-specific survival of omitting radiotherapy, even in elderly patients, this specific population often foregoes irradiation in Belgium[7, 8]. A recent conjoint study of the Belgian College for Physicians in Radiotherapy and Oncology and the Belgian Cancer Registry, linking reimbursement data to individual cancer patients, demonstrated that the overall high utilization of radiotherapy in breast cancer did not as such apply for elderly patients. A difference in uptake was observed between patients younger versus older than 65 years (86% vs. 63%), with an even more pronounced difference when the cut off was placed at 80 years (83% vs. 36%)[6].

In answer to these obstacles, accelerated and partial breast radiotherapy approaches have been introduced for early stage breast cancer (ESBC), with acceleration aiming to address the problem of protracted schedules and reduced target volumes to avoid the potential toxicity of high fraction doses. Acceleration using treatment schedules of 5 fractions only may lower the threshold for adequate radiotherapy utilization. Two large randomized trials have been performed in the UK to evaluate the safety and efficacy of this fractionation schedule, mainly focusing on whole breast irradiation (WBI) in the context of breast conserving treatment[9, 10]. The question of accelerated partial breast irradiation, on the other hand, has been addressed in a multitude of studies, evaluating the safety, clinical outcome and toxicity of various technical approaches[11-16].

These new techniques and fractionation schedules are bound to have an economic impact: in acceleration, costs may be lower due to reduced resource needs; the introduction of more complex techniques, on the other hand, may translate into higher costs. Because of the large patient population to which these new treatment approaches apply, the impact on the health care budget may be substantial. Yet, a simple answer to the question of the economic consequences is not readily available, due the multitude in fractionation schemes, technical approaches and health care contexts, and calls for an in-depth analysis of how the different parameters impact on the cost and cost-effectiveness. This is the domain of health economics, a science that explores the changes in costs of new strategies in relation to its incremental clinical effectiveness and thus provides an answer to the question if new interventions are worthwhile from a societal perspective.

Staging and prognosis of breast cancer

Breast cancer treatment options, including surgery, radiotherapy and systemic treatment, depend on staging and prognostic features. In the non-metastasized disease, where curation is the goal, a more aggressive approach will be chosen for more advanced tumour stages, whereas early stages justify a more gentile approach. The most commonly used staging systems are the UICC and the AJCC, which take into account tumour size, lymph node status and distant metastasis. Based on these anatomic features, breast cancer can roughly be divided into an early stage (ESBC), a locally advanced stage (LABC) and metastasized breast cancer. Although no real consensus exists on these categories, stage I and II breast cancer are commonly referred to as ESBC (T1-2 N0-1 and T3N0 disease), stage III as LABC (including T0-2 N2-3, T3 N1-3, T4 any N disease), and any M1 disease as metastasized breast cancer.

Prognostic factors in breast cancer predict the likelihood of tumour recurrence after surgery if no adjuvant therapy is given. Some of these prognostic factors have also a predictive value, identifying which systemic therapy the tumour may best respond to[17]. A recent update advises to complement the prognostic information from actual anatomic staging with other prognostic characteristics, including hormonal status, Her2 status, index of mitotic activity (Ki67)[18], molecular profiling… Additional prognostic factors in breast cancer are age[19, 20], grade[21] and lymphovascular invasion[22, 23]. Hormonal status [24, 25] and Her2/neu combine a prognostic with a predictive value.

'Favourable' breast cancer is usually reserved for the combination of ESBC with hormone sensitive breast cancer. In search for radiotherapy schedules and techniques that are gentler and less cumbersome for the patient (see section 6), guidelines from two scientific bodies, the Groupe Européen de Curiethérapie-European society for radiotherapy & oncology (GEC-ESTRO) and the American Society of Radiation Oncologists (ASTRO) are available. Both define risk groups for APBI, giving guidance as to which prognostic groups are suitable for APBI, or on the contrary, need caution or are even contra-indicated[26-28]. Groups are based on prognostic factors including age, tumour stage and microscopic characteristics. Molecular profiling is not yet retained.

Role of radiotherapy in breast cancer

Long-term follow-up of large randomized trials comparing breast conserving therapy (BCT) with mastectomy has embedded the role of radiotherapy after breast conserving surgery (BCS) in achieving similar overall survival[29-31]. In the NSABP-06 trial, BCS for stage I-II disease with tumours ≤ 4cm was compared to BCS with adjuvant radiotherapy or total mastectomy. The combined treatment was found a safe alternative to total mastectomy, with no significant difference in survival between the three arms. However, adding radiotherapy after tumourectomy led to a significant reduction in ipsilateral recurrences. In the group with tumour-free resection margins, radiotherapy after tumourectomy reduced the incidence of breast-cancer-specific mortality (BCSM). The result was partially offset by death from other causes, but this may be due to older radiotherapy techniques[29]. The most recent update of the EORTC 10801 trial in 2012 showed a 20-year overall survival of 44.5% after ME and 39.1% after BCT (not significantly different) with young age (< 50 years) or pathologically positive lymph nodes as risk factors[31]. Differentiation between breast-cancer specific mortality or mortality due to other malignant disease was not possible. However, death from malignant disease was similar in the first five years and showed a non-significant difference at 20 years (37.4% for ME and 43.3% for BCT, p = 0.13).

The primary effect of radiotherapy after BCS relies in avoiding loco-regional relapses. Robust data come from a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), summarizing the results of 17 randomized studies that compare BCS only with BCS and radiotherapy for ESBC. Adding radiotherapy reduces the 10-year loco-regional recurrence from 35.0% to 19.3%, a 15.7% absolute risk reduction. This loco-regional control translates into a 15-year risk absolute reduction for BCSM of 3.3%. The benefit observed is greatest in lymph node positive breast cancer, with an 8.5% absolute BCSM risk reduction. Loco-regional relapses influence overall survival, with one breast cancer death avoided by year 15 for every 4 recurrences by year 10[4].

Radiotherapy does however come with adverse effects. In search of an acceptable balance between toxicity and benefit of adjuvant radiotherapy for ESBC, it was questioned if radiotherapy could safely be omitted in very early stages. A trial by Wickberg et al. on

381 women with stage pT1N0 R0 breast cancer compared overall survival and cumulative incidence of first breast cancer-related events after 20 years after BCS with or without radiotherapy[32]. They confirmed the added value of radiotherapy in this selected group (30.9% if radiotherapy was added versus 45.1% if not, HR 0.58; OS 49.6% versus 46%) and even in an anticipated low-risk group (>55 years, non-lobular or comedo-type breast cancer), adding radiotherapy improved outcome (any recurrence of 24.8% with and 36.1% without radiotherapy). The difference was obtained within the first five years after treatment and maintained in the following years. This last finding may indicate that radiotherapy is mainly responsible for eradicating undetected cancer foci present at surgery. Beyond 5 years, both groups presented with similar rates of local recurrence, most likely to be new primary tumours. Fyles et al. confirmed the additive effect of radiotherapy on local control in favourable ESBC in a trial with 769 patients, randomized between tamoxifen only (LR 7.7%) or tamoxifen with radiotherapy (LR 0.6%). Overall survival and distant metastases rates were similar in both arms[33]. The results of two more recent trials on this subject in elderly patients with favourable ESBC (CALGB 9343 and PRIME trial) will be discussed latier (chapter 6.1). These two trials reported respectively increased 10-year loco-regional and 5-year local relapse rates, however without impacting breast cancer specific or overall survival.

Although breast conserving surgery is usually aimed for, mastectomy is advised when a breast tumour is multifocal, exceeds 4cm, if no negative surgical margins can be obtained without severely compromising the aesthetic outcome of the breast or if a patient wishes to avoid radiotherapy[34]. An EBCTCG meta-analysis pooled studies between '64 and '86 on the effect of post-mastectomy radiotherapy (PMRT). In case of negative lymph nodes, PMRT does not result in a significant benefit for LRR (1.6 vs. 3.0%), overall recurrence risk (21.1 vs. 22.4%) or BCSM (26.6 vs. 28.8%). However, in regionally advanced breast cancer, with invaded lymph nodes, radiotherapy improves LRR as well as BCSM, with a larger benefit in more advanced lymph node stages (absolute reduction of LRR 16.5% in pN1 vs. 22.1% in pN2, or BCRM 7.9% in pN1 vs. 10.1% in pN2)[5].

LNI in lymph node positive breast cancer results in a benefit in BCSM[35], even though mean heart and lungs doses increase, especially in case of internal mammary chain irradiation (IMNI)[36]. Such higher doses come however with toxicity[37]. The French trial

could not demonstrate a benefit in overall survival for IMNI after ME[38]. In contrast, the Danish trial did find a small but significant improvement in OS (HR 0,82), at least for right-sided lymph-node positive breast cancer[39]. This finding cannot be extrapolated to left-sided breast cancer, as heart doses are most influenced by IMNI in the left-sided situation. Whereas the AMAROS trial has demonstrated that lymphadenectomy can safely be replaced by LNI in ESBC[40], the publication of the Z0011 trial has put into question the need for lymphadenectomy and LNI in clinically node-negative breast cancer with pathologic tumour invasion of maximally two sentinel nodes [41, 42]. As a result, guidelines diverge from omission of lymphadenectomy and LNI in cN0 but sentinel positive breast cancer, to LNI including axillary level I if a positive sentinel is not followed by axillary lymphadenectomy or even to LNI including IMNI in node negative breast cancers, when the tumour is located medially or centrally in the breast.

The highest risk of tumour recurrence after BCS, is situated in the region around the primary tumour[43-45]. A logical consequence is the adding of a boost to reach a higher total and biological effective dose in this region. Bartelink et al. evaluated the effect of a boost in stage I and II breast cancer patients, treated with BCS and whole breast irradiation (WBI) to a dose of 50Gy in 25 fractions[46]. In case of negative resection margins, an electron-boost of 16Gy in 8 fractions was delivered (2661 women), whereas 1657 women were given no boost. Intermediate reporting of 5 and 10-year follow-up showed a benefit in LC of respectively 3% and 4%. Highest benefit was always observed in younger women (< 40 years) with an absolute difference in LR of 9.3% after 5 years and 10.4% after 10 years. The recent 20-year follow-up data of this trial confirm the improvement in local control with a boost (LR of 9% versus 13% if no boost)[47]. However, this does not translate in a statistically significant difference in overall survival (respectively 61.1% and 59.7%). Improved local control comes at the cost of a higher incidence of fibrosis (respectively 5.2% versus 1.8%). The largest benefit of a boost is observed in young patients, combining better local control with less occurrence of fibrosis, whereas the opposite is observed in older age groups.

In 1985 Solin suggested to introduce clips in the tumourectomy cavity, to help define the depth of the tumourectomy cavity in the breast for subsequent electron boost[48]. This technique is still used, and strongly recommended, especially if partial breast irradiation is intended[49].

Toxicity of radiotherapy

An overview of RCTs and meta-analysis reporting on radiotherapy-related toxicity in breast cancer is listed in table 1. The concept toxicity covers morbidity and mortality due to dose to surrounding organs at risk, but also aesthetic and functional impairment of the irradiated breast.

Cardiac morbidity has been found to be linearly related to heart dose (7.4%/Gy), without a threshold and coming apparent within the first years after radiotherapy[50]. Although dose increased cardiac mortality for cohorts before 1980, thus compromising the benefit of radiotherapy, this relation cannot any longer be withheld with more advanced radiotherapy techniques[51-57]. However, increased rates of cardiac morbidity, including myocardial infarction, ischemic disease and valvular disease after adjuvant breast radiotherapy, justify further efforts to reduce cardiac dose. Pre-existing cardiac disease and smoking habits increase the deleterious effect of radiotherapy on the heart[50, 55, 58]. Mean heart doses are highest in left-sided breast cancer (5.4Gy vs 3.3Gy for right-sided breast cancer) and in case the lymph node region is irradiated, most notably when the mammary chain is included (8.8Gy)[36].

The risk of radiation-induced lung cancer increases with lung-dose (8.5%/Gy), with an even higher impact in patient with smoking habits (17.3%/Gy). The effect is almost negligible in never smokers (0.6%/Gy) [59]. The relative risk of secondary lung cancer after breast radiotherapy increases with younger age and time after radiotherapy [60].

Cardiac and lung-cancer related toxicity may compromise the absolute gain in breast cancer specific survival (BCSS), which is especially relevant in case of a limited gain, as in ESBC. The impact of radiation toxicity to heart and lungs may be deducted from an analysis by Taylor et al.[61] They estimated the impact of mean lungs and heart dose on excess cumulative lung cancer death and cardiac mortality for different risk factors (eg. smoking habits). With the following formula, these excess risks per Gy are related to the absolute BCSS gain of radiotherapy :

$$1-(\textit{improvement in BCSS if RT})=1-(1-P_L)(1-P_C)$$

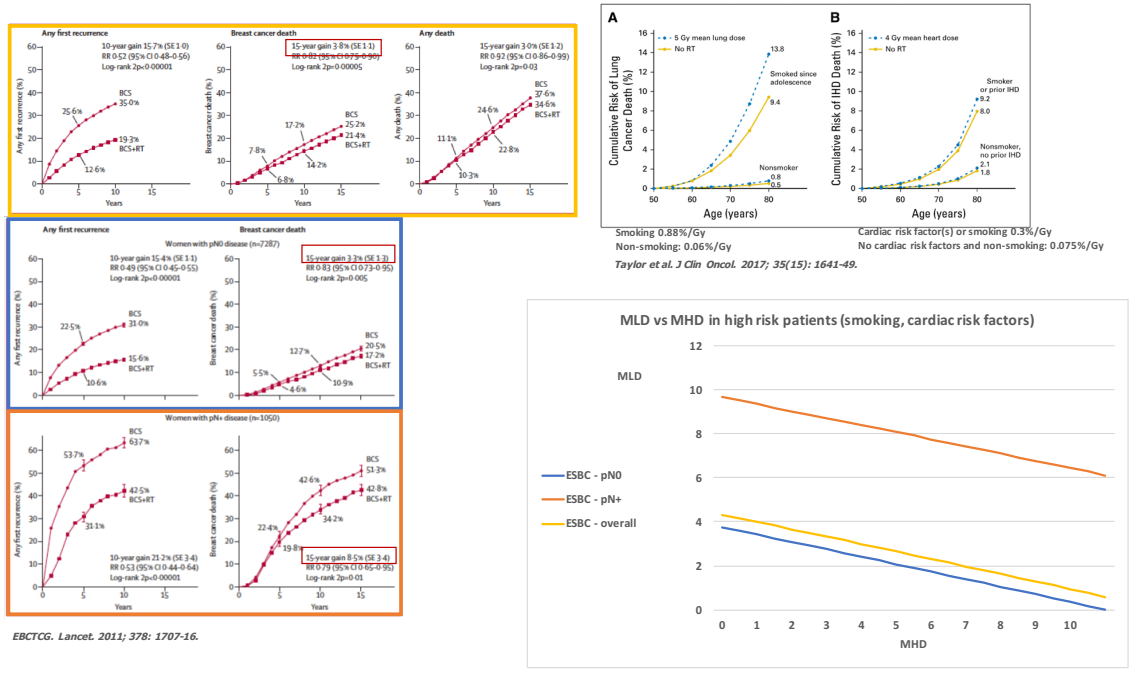
with P_L = excess risk of lung cancer mortality per Gy * mean lungs dose (MLD)

and P_C = excess risk of cardiac mortality per Gy * mean heart dose (MHD)

The formula can be transformed to the relation between MLD and MHD for a specific gain in BCSS:

$$MLD = \left(1 - \frac{BCSS}{(1\text{-}risk_{\text{cardiac mortality per Gy}})^{*MHD}}\right) / risk_{\text{lung cancer mortality per Gy}}$$

Based on BCSS as documented by the EBCTCG meta-analysis (left side of figure 1) and the excess cardiac and lung cancer mortality if risk factors are present (Taylor, right above graph), the relation between MLD and MHD for different breast cancer stages can be plotted in a graph[4]. If mean heart and lung dose remain below the lines, the benefit of adjuvant radiotherapy on BCSS exceeds loss due to its toxicity. If mean heart and lungs doses are located above the respective lines, benefit is compromised by cardiac and lung cancer mortality risk. Or also, the lower the potential BCSS benefit, the less tolerant we may be for mean heart and lungs dose.



Smoking 0.88%/Gy
Non-smoking: 0.06%/Gy

Cardiac risk factor(s) or smoking 0.3%/Gy
No cardiac risk factors and non-smoking: 0.075%/Gy

Taylor et al. J Clin Oncol. 2017; 35(15): 1641-49.

Fig 1 – The relation between MLD and MHD for different gains in BCSS of adjuvant radiotherapy after BCS is illustrated in the graph right below. Data come from the EBCTCG meta-analysis on the 15-year gain in BCSS after BCS (left side) and from Taylor et al., who estimated the risks of breast cancer radiotherapy from recent randomized trials (right above)[4, 61]. The yellow line is based on a gain in BCSS of 3.8% (all ESBC included), blue on 3.3% (pN0 only) and orange on: 8.5% (pN+ only) (with courteousy to Prof. W. De Neve, the architect of this formula).

The development of contralateral breast cancer is strongly age related, with turn point at age 40-45 [62, 63]. In patients with a strong family history of breast cancer, the joint effect was found higher than the sum of both risks (HR 3.52)[62]. Angiosarcoma is the most prevalent secondary sarcoma after breast RT, occurring mostly in or adjacent to the radiated fields. However, the absolute risk remains very small (0.09% increase in cumulative incidence at 15 years)[64].

Ipsilateral toxicity of breast radiotherapy is mainly related to aesthetic problems with colour changes, fibrosis, breast retraction, as well as pain and oedema (figure 2).

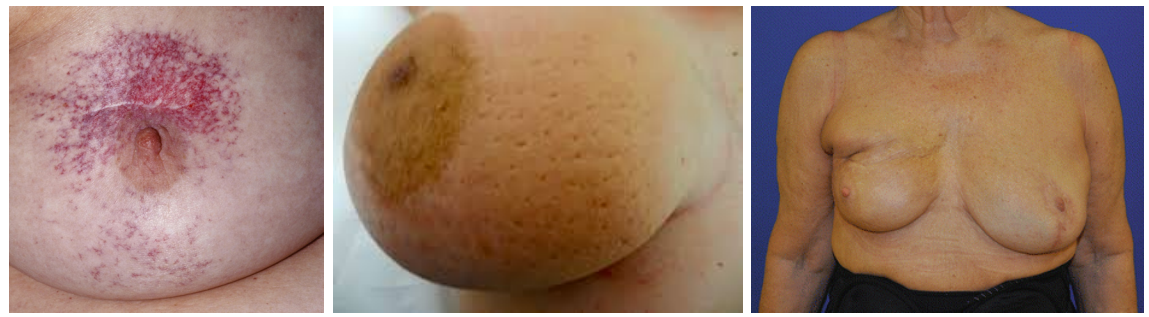


Fig 2 - Radiation-induced breast changes

An association between breast fibrosis and patient age was observed in the boost versus no boost trial[47]. Improved local control was maintained with a boost of 16Gy, even after 20 years, but at the cost of a higher incidence of severe fibrosis (1.8% vs. 5.2%). Sub-analysis per age category demonstrated an inverse association between age and local recurrence risk, whereas the opposite was observed for severe fibrosis, which was more present in the older age categories.

Most robust insight in the relation between fractionation, total dose and aesthetic outcome of the breast came with the UK trials on hypofractionation. The data of the START A trial confirmed the hypothesized α/β for impact on aesthetic outcomes, with an α/β of 3.6Gy for any changes in breast appearance and 2.9Gy for marked change. The estimated α/β for breast induration, breast shrinkage and telangiectasia were estimated respectively 3.1Gy, 4.7Gy and 5.1Gy. Based on these data, the authors calculated a linear relation between breast changes and total dose, with a 5% increase in total dose causing

a 9% increase in the proportion of patients with marked breast change[65]. These results were confirmed after 10-year follow-up and including the results of the START B trial. Cosmesis was similar when comparing 50Gy/25 fractions or 41.6Gy/13 fractions, but improved with hypofractionation applying 39Gy/13 fractions and 40.05Gy/15 fractions, and this as well for breast induration, telangiectasia as for breast oedema[66]. Patient reported outcomes also favoured hypofractionation (15x2,67Gy), with lower hazard ratios for breast hardness, oversensitivity and change in breast or skin appearance[67].

Author, year	Title	Comparison	Results
General			
Clarke, 2005	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	Radiotherapy vs no radiotherapy in ESBC	Excess in (older) radiotherapy regimens of - contralateral breast cancer: HR 1.18 - non-breast cancer mortality HR 1.12 - due to heart disease HR 1.27 - due to lung cancer HR 1.78
Cardiac disease			
Rutqvist, 1992	Cardiovascular mortality in a randomized trial of adjuvant radiation therapy versus surgery alone in primary breast cancer	Radiotherapy vs no radiotherapy	Excess of death due to ischemic cardiac disease in patients with highest cardiac dose (left-sided, cobalt-60 tangential fields): relative hazard 3.2 (7.1% vs 2.3%) but no difference in overall mortality
Cuzick, 1994	Cause-specific mortality in long-term survivors of breast cancer who participated in trials of radiotherapy	Radiotherapy vs no radiotherapy	In breast cancer survivors, no increase in 10y all-cause mortality. Excess of cardiac deaths apparent in both early and more recent trials ($p < 0.001$) but offset by a reduced number of deaths due to breast cancer.
Darby, 2005	Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries	Left- vs right-sided breast radiotherapy	Comparison of women, diagnosed with breast cancer between 1971-2001 (SEER) for ESBC: - 1973-82: cardiac mortality ratio 1.2 <10 years, 1.42 10-14 years and 1. 58 15 years after radiotherapy; - 1983-92: cardiac mortality ratio no difference <10 years and 1.27 10-14 years after radiotherapy - 1993-2001: cardiac mortality ratio no difference <10 years after radiotherapy
Roychoudhuri, 2007	Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study	Left- vs right-sided breast radiotherapy	Comparision of women, irradiated between 1971-88 with cardiovascular mortality at 15y: IHD HR 1.27; all CVD HR 1.59 Comparison of women with left vs right-sided radiotherapy: Cardiovascular mortality at 15y: IHD HR 1.23 and all CVD 1.25

Hooning, 2007	Long-term risk of cardiovascular disease in 10-year survivors of breast cancer	Breast radiotherapy vs general population rates	Comparison of women treated for breast cancer between 1970-1986: - SIR of 1.3 for cardiovascular events - if radiotherapy and chemotherapy: SIR more congestive heart failure (HR 1.85) - smoking and radiotherapy: HR 3.04 (more than additive effect) - for patients with IMNI: treated between 1970-1979: HR 2.55 for AMI and HR 1.72 for congestive heart failure; patients treated after 1979: lower risk for AMI but risk for congestive heart failure and valvular dysfunction remained increased.
Mc Gale, 2011	Incidence of heart disease in 35,000 women treated with radiotherapy for breast cancer in Denmark and Sweden	Left- vs right-sided breast radiotherapy	Comparison of women, diagnosed with breast cancer between 1976-2006 - mean heart dose 6.3Gy left-sided RT vs 2.7Gy right-sided RT - Mortality similar in both groups - Incidence ratio AMI 1.22; angina 1.25; pericarditis 1.61; valvular heart disease 1.54 - Incidence ratios for all heart disease as high for women irradiated after 1990 as for women irradiated between 1976-1989: 1.09 vs 1.08 - Incidence ratios for all heart disease higher in women with IHD diagnosed prior to breast cancer: 1.58 vs 1.08
Henson, 2013	Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer	Left- vs right-sided breast radiotherapy	SEER-based analysis of women diagnosed with breast cancer between 1973-2008: - Women irradiated between 1973-1982: cardiac mortality ratio 1.19 <10y, 1.35 10-14y, 1.64 15-19y and 1.9 20+ years after diagnosis - Women irradiated between 1983-92: cardiac mortality ratio: no evidence for radiation-related cardiac mortality

Darby, 2013	Risk of ischemic heart disease in women after radiotherapy for breast cancer	Population-based case-control study	Population-based case control study in 2168 patients with radiotherapy for breast cancer between 1958-2001 and of which 963 with major coronary event (AMI, coronary revascularization, death from IHD) - mean heart dose 4.9Gy (6.6Gy in left-sided and 2.9Gy in right-sided breast cancer) - increase in rate of MCE linearly 7.4%/Gy with no apparent threshold - absolute increase risk greater in women with preexisting cardiac risk factors
Taylor, 2015	Exposure of the heart in breast cancer radiation therapy: A systematic review of heart doses published during 2003 to 2013	Mean heart doses	Systematic review of cardiac doses reported from studies published between 2003-2013 - Mean heart dose in left-sided breast cancer 5.4Gy, 3.3Gy in right-sided breast cancer - Mean heart dose if no IMNI 4.2Gy - Mean heart dose with tangential fields and breathing control 1.3Gy or lateral decubitus 1.2Gy - Mean heart dose with proton therapy 0.5Gy - Mean heart dose with IMRT 5.6Gy - Mean heart dose with IMNI 8Gy and 9.6Gy (highest dose) if delivered with tangential fields
Chan, 2015	Long-term mortality from cardiac causes after adjuvant hypofractionated vs. conventional radiotherapy for localized left-sided breast cancer	Hypofractionated vs normofractionated radiotherapy	Comparison of women, irradiated for breast cancer between 1990 and 1998: - for left-sided radiotherapy no difference in 15y cardiac mortality (4.8% hypofractionation vs 4.2% normofractionation)

Merzenich, 2017	3D conformal radiotherapy is not associated with the long-term cardiac mortality in breast cancer patients: a retrospective cohort study in Germany (PASSOS-Heart Study)	Left- vs right-sided breast radiotherapy	Comparison of women treated for breast cancer between 1998-2008: - no evidence of tumour laterality on overall mortality in irradiated patients - For cardiac mortality a HR of 0.94 for left- versus right-sided tumours - Diagnosis of cardiac illness prior to breast cancer increased cardiac mortality risk and overall mortality risk
Secondary lung cancer			
Prochazka, 2002	Lung cancer risks in women with previous breast cancer		Comparison of women, diagnosed with breast cancer between 1958-1997: - 5y after radiotherapy increased standardized incidence ratio (SIR) 1.32 with maximum risk after 20 years (SIR 2.53) - higher risk if smoking
Darby, 2005	Long-term mortality from heart disease and lung cancer after radiotherapy for early breast cancer: prospective cohort study of about 300,000 women in US SEER cancer registries	Ipsilateral vs contralateral breast radiotherapy	Comparison of women, irradiated between 1971-2001 (SEER) for ESBC who developed lung cancer: - 1973-82: lung cancer mortality ratio ipsi- vs contralateral lung cancer 1.17 <10 years; 2 10-14 years and 2.71 >15 years after radiotherapy
Berrington De Gonzalez, 2011	Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries	Radiotherapy versus no radiotherapy	SEER-based analysis evaluating secondary cancers attributable to radiotherapy for 15 cancer sites - Highest relative risk for developing lung cancer 15y after radiotherapy: RR 1.62 and in younger age groups (<45y: RR 1.42, 45-59y: RR 1.29, 60-74y: RR 1.20 and > 75y: 1.14)

Henson, 2013	Radiation-related mortality from heart disease and lung cancer more than 20 years after radiotherapy for breast cancer	Ipsilateral vs contralateral breast radiotherapy	SEER-based analysis of women diagnosed with breast cancer between 1973-2008: - Women irradiated between 1973-1982: lung cancer mortality ratio: 1.05 <10y, 2.04 10-19y, 3.87 20+ years after diagnoses - Women irradiated between 1983-92: 1.17 <10y and 1.48 10-19y after diagnosis
Grantzau, 2014	Risk of second primary lung cancer in women after radiotherapy for breast cancer	Lung cancer after radiotherapy vs no lung cancer after radiotherapy	Women with ESBC treated with radiotherapy between 1982-2007 of which 151 developed lung cancer (443 controls): risk related to dose in centreS of secondary lung tumour - mean age of developing lung cancer 54y - median time between radiotherapy and developing lung cancer 12y - 90% of patients with lung cancer after radiotherapy were 'ever smokers' versus 40% of controls - in patients with lung cancer, risk increased with 8.5%/Gy with 17.3% for ever smokers and with 0.6%/Gy for never smokers (but this group was too small for firm conclusions)
Contralateral breast			
Yap, 2002	Sarcoma as a second malignancy after treatment for breast cancer	Radiotherapy vs no radiotherapy	Comparison of patients with sarcoma after breast cancer, comparing 87 patients with radiotherapy and 176 without radiotherapy - low 15y cumulative incidence for sarcoma (0,0032% if radiotherapy vs 0.0023% if no radiotherapy) and for angiosarcoma (0.0009% if radiotherapy vs 0.0001 if no radiotherapy) - if sarcoma within radiation field: 56.8% angiosarcoma vs 5.7% if no radiotherapy - Angiosarcoma is the most prevalent secondary sarcoma after breast RT, occurring mostly in or adjacent to the radiated fields

Hooning, 2008	Roles of radiotherapy and chemotherapy in the development of contralateral breast cancer		Radiotherapy-associated risk for contralateral breast cancer: HR of 1.78 in women younger then 35y and 1.09 in women over 45 years - in patients with radiotherapy and strong family history, the joint effect was greater than the sum of both risks (HR 3.52)
Stovall, 2008	Dose to the contralateral breast from radiotherapy and risk of second primary breast cancer in the WECARE study	Absorbed dose in bilateral vs unilateral breast cancer	Comparison of 708 patients with asynchronous bilateral breast cancer versus 1399 controls (unilateral breast cancer) - Dose on the controlateral breast: Dmean of 1.1Gy - If the mean dose to the contralateral breast exceeded 1Gy, women younger than 40 years had a 2.5-fold higher risk for CLBC than unexposed women, with and excess risk of 1% per Gy - No such risk was observed in women over 40 years
Berrington De Gonzalez, 2011	Proportion of second cancers attributable to radiotherapy treatment in adults: a cohort study in the US SEER cancer registries	Radiotherapy vs no radiotherapy	SEER-based analysis evaluating secondary cancers attributable to radiotherapy for 15 cancer sites - increase in contralateral breast cancer (CLBC) of 0.5% at 10 years, 1.3% at 15 years and 1.6% at 20 years after radiotherapy
Ipsilateral breast toxicity			
Yarnold, 2005	Fractionation sensitivity and dose response of late adverse effects in the breast after radiotherapy for early breast cancer: long-term results of a randomised trial	Different hypofractionation schedules vs normofractionation	Any change in breast appearance occurred in 39.6% (50Gy/25 fractions), 30.3% (39Gy/13 fractions) and 45.7% (41.6Gy/13 fractions) resulted in an α/β 3.6Gy for any breast change For palpable breast induration, an α/β of 3.1Gy was calculated - results were in line with trial predictions.
Hopwood, 2010	Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials	Different hypofractionation schedules vs normofractionation	Comparison between normofractionation (50Gy/25 fractions) and 39Gy/13 fractions or 41.6Gy/13 fractions (START A trial) or with 40Gy/15 fractions (START B trial) - Overall moderate to marked breast changes in 40% of patients and 1/3 of patients had arm and shoulder pain. Breast symptoms and body image concerns reduced over time. Rates of adverse effect were similar in START A trial (50Gy vs. 41.6Gy) and improved with hypofractionation (39Gy in START A and 40Gy in START B trial) compared to 50Gy. - Adverse skin change for 39Gy vs 50Gy: HR 0.63 - for 40Gy vs 50Gy: HR 0.83 - Patient self-rated breast symptoms discriminated 10% difference in randomised dose intensity - No difference in arm/shoulder subscale scores between different regimens, but 1/3 had overall moderate to marked pain in arm and shoulder and 10% experienced moderate to marked arm/hand swelling - Many baseline arm/shoulder symptoms were associated with prior surgery
Haviland, 2013	The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials	Different hypofractionation schedules vs normofractionation	START A trial: moderate or marked breast induration, telangiectasia, and breast oedema were significantly less common normal tissue effects in the 39 Gy group than in the 50 Gy group. Normal tissue effects did not differ significantly between 41.6 Gy and 50 Gy groups. START B trial: breast shrinkage, telangiectasia, and breast oedema were significantly less common normal tissue effects in the 40 Gy group than in the 50 Gy group.

Table 1 - Evidence on toxicity from breast cancer radiotherapy

Factors that influence toxicity

Toxicity in radiotherapy results from the combination of the physical aspects of the irradiation, defined by the volume irradiated (including target as well as off-target tissue) and the related dose distribution/homogeneity, with the radio-biologic aspects, including radio-sensitivity of the irradiated tissue (represented by its α/β ratio), dose per fraction and total dose delivered. These aspects are explored more in detail, as they constitute the theoretical basis for accelerated and partial breast irradiation.

Association between irradiated volume and toxicity

Smaller volumes typically reduce dose to OARs. A dosimetric study on APBI delivered with 3D-CRT indicated an increase of 15% for the mean ipsi-lateral breast dose with every 5mm CTV-PTV increase, a doubling of the mean heart dose and a tripling of the lung dose with 10mm increase in CTV-PTV margins[68].

Regarding ipsilateral breast toxicity, the assumption of an association between toxicity and the volume treated was until recently based on indirect evidence from trials combining different volumes with different treatment schedules or techniques [47, 69]. In the START A trial, a 3.3% increased risk for breast induration was calculated per extra Gy in WBI, in contrast to only 1.05% per extra Gy for the (smaller) boost volume[66].

Direct evidence on the association between dose-volume and aesthetic outcome comes from two recent studies: The IMPORT LOW trial and the Danish Breast Cancer Cooperative Group (DBCG) trial, both comparing partial breast irradiation to WBI with irradiated breast volume as solitary variable. Five-year outcome of the IMPORT LOW trial for a low risk population (age 50 years or older, BCS for unifocal IDC of grade 1-3, pT1-2 ≤ 3cm, pN0-1, R0 ≥ 2 mm) was recently published[70]. Results are promising, with non-inferior local control and superior aesthetic outcomes regarding 'breast appearance' and 'firmness of breast'. The Danish' inclusion criteria were even more stringent and outcomes, presented at ESTRO 36, were as reassuring as for the UK trial[71]. Although both trials seem to pave the way for EB-APBI, volumes were large, up to approaching half-breast irradiation, as investigators chose for an easy implementable supine tangential field set-up with field-in-field IMRT. Alongside robust evidence on the efficacy of PBI, both trials deliver direct proof of the relation between irradiated volume and aesthetic outcome.

Tumourbed delineation

Before shrinking the treated volume, it is important to accurately define the breast tissue at risk. The target volume for APBI can be deducted from recurrence patterns of local failure, predominately located around the primary tumour[45, 46, 72-74], and from microscopic analysis of mastectomized breasts, evaluating the spread of micro-satellites. Holland et al. found tumour satellites in mastectomy specimen beyond 2cm in 14% of cases (figure 3)[43]. At 1cm beyond the tumour margins, micro-satellites where still present in 20% of patients. Vicini et al. support these data: they examined re-resection specimen and found residual disease beyond 15mm of the tumourbed in 9% of cases. In the group with negative resection margins (re-resection because of suspected radiography of specimen), tumour cells were limited up to 10mm from the cavity wall in 90% of cases[44].

As breast is a homogeneous structure, with little anatomic landmarks, guidelines come at help to delineate the tumourbed[75]. Instructions are based on general information (pre-operative imaging, surgical and histo-pathological reports) and on CT-based information: seroma if present, tissue distortion in comparison to the contralateral breast and clips. Although the scar location may bring some information, with the increasing use of onco-plastic surgery and closure distant from the lumpectomy cavity, this landmark can be misleading. In case of full-thickness closure, little if any seroma is left visible on planning-CT.

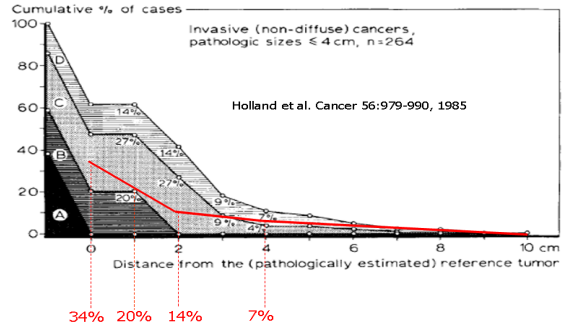


Fig 3 - Subclinical spread of invasive cancer in pathological specimen, A cumulative 34%, 20%, 14% and 7% of the patients had invasive microscopic tumour deposits at distances of respectively 0, 1, 2 and 4 cm from the pathologically estimated resection specimen (modified from Holland[43])

Tissue distortion needs comparison with the contralateral breast, because on CT, post-operative changes cannot be distinguished from glandular tissue. But in case of bilateral surgery or prone positioning, comparison is impossible. The use of clips is informative[48, 49]: these are typically placed in the radial, anterior and posterior cavity walls. However, when clips are placed deeply unto the fascia or when (axillary) haemostatic clips are inserted, clips may lead to large, protracted volumes, away from the initial tumour location and compromising inter-observer delineation conformity. Possible solutions to overcome these obstacles and improve target volume delineation after full thickness closure and with the patient in prone position, are described in publication 1.

Tumourbed margins

In terms of radiotherapy, the target volume consists of the tumourbed, expanded to the clinical target volume (CTV) with a reasonable margin to cover for microscopic tumour cells, as described by Holland et al[43]. Vicini et al. advocate a symmetrical expansion of 15mm[44]. A more precise technique may be to expand the tumourbed with 30mm minus the excision margins[43]. Recommendations on expansion from tumour bed to CTV vary from 0.5-2cm in the literature [76-78]. Bartelink et al suggest an asymmetric expansion, based on pathological margins, to reduce CTV volumes. However, in view of the problem of orientation uncertainty, symmetric expansion of 2cm minus the minimal pathological margin may be a safer option[79].

The impact of fractionation

Sensitivity of cells to fraction dose is described as the ratio of α over β (D=α/β). In this equation, α represents the linear component, and is assumed to result from a single event (DNA double-strand break): the damage is lethal for the cell – the probability to produce lethal damage is proportional to dose. The linear quadratic component β represents sub-lethal damage, with two such events needed to produce cell kill (DNA single-strand break). One sub-lethal damage is proportional to the square of dose. The linear quadratic model (LQ model) assumes that cell-kill consists of these two components α and β, based on the formula $\alpha D=\beta D^2$[80], with the biological effective dose (BED):

The model is applicable for both tumour cells and normal tissue cells. A different α/β is translated into a different sensitivity for radiation dose. The therapeutic window for radiotherapy balances between the impact of a specific dose and fractionation schedule on tumour cell kill and damage to surrounding normal tissue cells (figure 4). When the α/β of a tumour is higher (the α/β of breast cancer cells was previously assumed to be in the range of 10Gy) than the surrounding tissue, low fractions in combination with a high dose are likely to be more effective. In contrast, when the α/β of the tumour and the surrounding tissue are close or similar, hypofractonation with increased dose per fraction but lowered total dose may be more effective and less toxic than normofractionation. An example for breast cancer is given in table 2, comparing the effect on BED and EQD_2 for three standard radiotherapy schedules on different α/βs.

Number of fractions	Dose per fraction (Gy)	Radio-sensitivity (α/β) in Gy					
		10		2.8		4.6	
		BED (Gy)	EQD2 (Gy)	BED (Gy)	EQD2 (Gy)	BED (Gy)	EQD2 (Gy)
25	2	60.0	50	85.7	50	71.7	50
15	2.67	50.7	42.3	78.2	45.6	63.3	44.1
5	5.7	44.7	37.3	86.5	50.5	63.8	44.5

Table 2 – This table illustrates the impact of radio-sensitivity on biologic effective dose (BED) and on equivalent dose compared in 2Gy fractions (EQD_2). For breast tumour cells, an α/β of 10Gy has long been assumed. This is compared to the range of α/β between 2.8Gy and 4.6Gy, the range of breast cancer radio-sensitivity, as deducted from the START trials.

The mechanisms of re-distribution, re-oxygenation, repair and repopulation of cells all contribute to the different reactions of tissue to irradiation. Repair of sub-lethal damage in between fractions reduces the effect of a dose, thus requiring a higher total dose for the same effect if radiation is fractionated. In case of sub-lethal damage (the most important component of tissue with a low α/β), this can be repaired within hours, with completion within 24 hours. However, if sub-lethal damage is added within this period, this can interact to produce lethal damage.

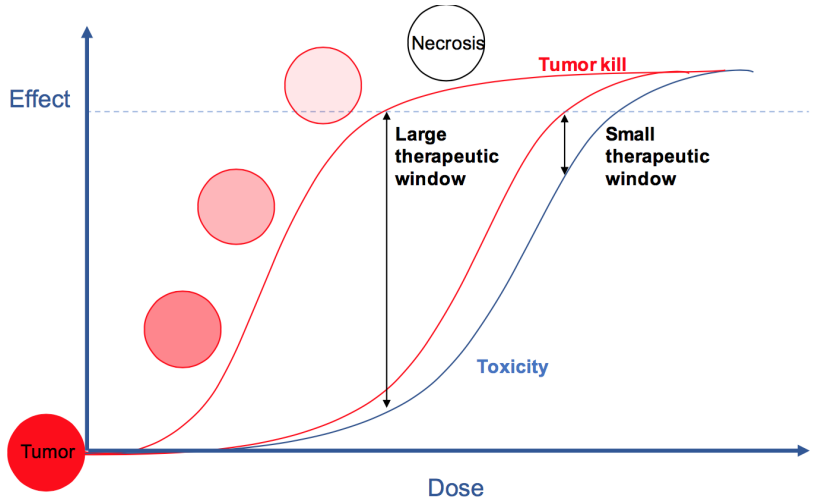


Fig 4 - Therapeutic window of radiotherapy, balancing between tumour kill and sparing of normal tissue. The therapeutic window is defined as the difference between impact of dose and fractionation on the tumour versus normal tissue.

At doses over 5Gy per fraction, the linear quadratic model is less reliable because other systems interfere. In a review of Park et al., the effect of high doses on vascular structures is described. In human tumours, treated with normofractionation, the functional status of the vessels is preserved during the early phase of treatment and only decreases towards the end. Experiments on rodents indicate that doses between 5-10Gy induce mild vascular changes, with severe vascular damage once above 10Gy[81]. Immunologic response and different behaviour of cells in a mixed population may further explain why tumour and normal tissue respond differently than would be expected by the LQ model only. In the high-dose range, the LQ model predicts a bending curve, whereas experiments show a linear relationship between dose and log of surviving cells. As a result, the LQ model overestimates the cell-kill effect of radiation. Such different behaviour may be captured in modified radiobiologic models, better predicting cell-kill effect in the higher dose-ranges. As an example, the Universal Survival Curve, based on the LQ model and a multi-target model, explains how, for higher fraction doses, the equivalent dose depends on the total dose delivered, rather than on the number of fractions (figure 5)[82]

The results of breast hypofractionation are compatible with these theoretic hypotheses. The long-term results of the Canadian and the START trials deliver clinical proof that hypofractionation may be at least equivalent in terms of tumour control, with breast cancer being more sensitive to fraction size than previously assumed[66, 83].

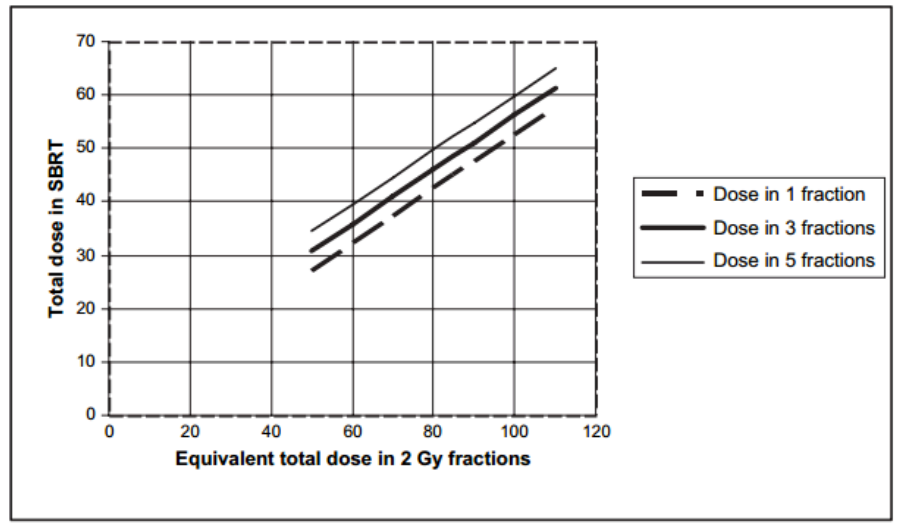


Fig. 5. Graph representing relationships between biologically equivalent dose for stereotactic body radiotherapy (SBRT) and dose for conventionally fractionated radiotherapy. Three stereotactic body radiotherapy fractionated schemes displayed for stereotactic body radiotherapy delivered in one, three, and five fractions).

Fig 5 – Relation between biologically equivalent dose for stereotactic body radiotherapy in 1, 3 and 5 fractions, and dose for conventionally fractionated radiotherapy. Adapted from Park et al.[82]

Higher fraction dose with lower total dose combines this advantage with reduced damage to the surrounding tissues, including breast tissue, heart and the brachial plexus. Although premature, the first results of acceleration to five fractions seem to confirm this, with toxicity predominately related to the total dose[84]. These findings are not contradicted by the adverse outcomes reported in the RAPID trial on twice-daily accelerated partial breast irradiation, where insufficient time in-between fractions may have compromised classical repair of sub-lethal damage[85].

Technical solutions to overcome toxicity

As suggested above, toxicity may be reduced by improving dose distribution within the target volume, by avoiding organs at risk or through adaptation of fractionation and total dose delivered. Several techniques to achieve these goals have already been implemented in daily routine.

Intensity modulated radiation therapy (IMRT)

Clinical application of IMRT started in 1995, initially for brain and prostate cancer, fol-

lowed by head and neck tumours. Implementation of this technique for breast irradiation only started by the end of the nineties[86].

IMRT enables the delivery of concave and inhomogeneous treatment volumes, thus reducing the ratio of normal tissue dose to tumour dose, improves dose homogeneity within the target volume and reduces hot spots. But IMRT tends to be more laborious and thus more expensive than standard radiotherapy, such as a wedged tangential field-technique. The evidence behind the use of IMRT has been described in a review by Veldeman et al., who showed reduced toxicity for various tumour sites[87].

For breast irradiation, two randomized studies using standard fractionation demonstrated that IMRT reduced acute moist desquamation[88] as well as late fibrosis[89]. A 10-year update of the study by Pignol et al. could not demonstrate an impact on chronic pain and aesthetic outcome, but this may be due to the limited sample size. Multivariate analysis however found an association between acute moist desquamation and long-term fibrosis and between acute and chronic pain. Pain significantly impacted patient-reported aesthetic results[90].

In 2013, Mukesh et al. published the results of a RCT, comparing the 5-year results of 1145 patients treated with hypofractionation. If dose constraints were not met (>2cc receiving over 107% of the prescribed dose) patients were randomized between wedged tangential field and IMRT. They found that IMRT resulted in superior cosmetic outcome (OR 0.65) and that worse outcome was further associated with breast volume, baseline surgical results and addition of a boost. Skin telangiectasia occurred significantly less with IMRT (OR 0.57) and was also related to older age, postoperative breast infection, higher breast volume and addition of a boost[91].

IMRT also comes at help in sparing organs at risk. A dosimetric study by Hurkmans et al. compared tangential fields with three-dimensional conformal radiotherapy (3D-CRT) and IMRT and found an absolute reduction of the normal tissue complication probability (NTCP) for the heart of respectively 5.9% to 4% and 2%[92]. Beckham et al. reported improved conformity and dose homogeneity with IMRT versus 3D-CRT in breast radiotherapy including the internal mammary nodes (IMN). Although IMRT reduced the heart and lung volumes receiving high doses, the low dose volume increased with IMRT

[93]. A similar observation was made by Lohr et al. finding lower doses to the left ventricle but an increased mean heart dose with IMRT [94]. Coon et al. reported a benefit with IMRT for cardiac dose in case of unfavourable anatomy [95].

For left-sided breast cancer, the most important volumes exposed to ionizing energy are the left ventricle and the LAD, whereas mean heart dose probably underestimates exposition [96]. Tan et al. suggested relating cardiac dose reporting to the anterior myocardial territory (AMT), which is located close to the left breast. Mean cardiac dose did not differ between tangential field technique and IMRT, but the dose to the AMT and the left ventricle were significantly reduced[97]. Another dosimetric study on the application of multi-leaf collimation for cardiac shielding confirmed lower heart doses, including mean heart dose, but found a compromised CTV coverage in one out of three WBI patients and in one out of ten APBI patients[98].

Breathing techniques and WBI in supine position

It has been demonstrated that breath-hold may significantly reduce heart doses[99]. Several techniques exist, including free breathing gating and voluntary or forced breath-hold. Korreman et al. tested the impact of free breathing, end-inspiratory and end-expiratory gating, deep inspiratory breath-hold (DiBH) and end-expiratory breath-hold on heart and lung dose in 17 patients[100]. Both end-inspiratory gating and DiBH achieved better sparing of heart and lungs, but in left-sided breast cancer, lowest left coronary artery dose came with DiBH. Where the dose to the breast is found relatively insensitive to the effects of breast motion during normal breathing, the internal mammary nodes are not, with a considerable portion receiving dose during normal inhalation [101].

The UK HeartSpare study did not find a difference in dose to normal tissue when active breathing control was compared to voluntary DiBH. Whereas both techniques were found comparable in terms of reproducibility and normal tissue sparing, scanning as well as treatment times were shorter with voluntary breath-hold. Moreover, patients as well as radio-technologists strongly preferred the voluntary technique[102]. Recently, the results of a multicentre study were published: voluntary DiBH was compared to free-breathing 3D-CRT for 93 patients with the heart within the 50% isodose. Breath-hold reduced

mean heart dose from 1.8Gy to 1.1Gy, mean LAD dose from 12.1 to 5.4Gy and Dmax from 35.4 to 24.1Gy. Lung dose also improved[103]. The authors concluded that voluntary breath-hold is effective in sparing the heart and feasible in a multicentre setting.

Breathing techniques and loco-regional irradiation in supine position

Remouchamps et al. performed a dosimetric study on the effect of DiBH, obtained by active breathing control, in women undergoing loco-regional radiotherapy, including the internal mammary chain. Compared to free breathing, DiBH significantly reduced heart and lung doses. They also reported that the combination of IMRT with DiBH resulted in the most optimal combination of dose homogeneity, reduced heart dose and MU's required for dose delivery[104]. This positive effect of active breathing control on heart dose was confirmed by Mast et al. [105] and Swanson et al. [106].

More recently, Pham et al. tested DiBH and free-breathing in volumetric modulated arc therapy (VMAT) versus tangential IMRT for loco-regional radiotherapy[107]. They found no difference in mean heart dose when DiBH was applied, except in those patients where mean heart dose exceeded 6.3Gy.

Prone position

Changing the position of the patient from supine to prone holds several dosimetrical advantages. Prone position can be performed on a flat, horizontal breast-board or on a wedged breast-board, thus maximally exposing the ipsilateral breast to the beams. Gravity induces the breast to fall forward, away from the thoracic wall, lungs and heart. This results in lower doses to the organs at risk[108, 109]. The impact on heart dose however can be attenuated by the systematic displacement of the heart towards the ipsilateral chest wall, shifting the heart into the high-dose region, an effect especially observed in small-breasted patients[110]. As the skin unfolds, build-up of dose in this radio-sensitive region decreases. Prone position also facilitates perpendicular beam entrance which results in a shorter beam travelling distance and helps to improve the ratio of non-irradiated off-target breast tissue over target volume[111]. This comes with improved dose homogeneity and less hot spots.

A UK HeartSpare study compared supine voluntary breath-hold with prone free-breathing on 34 large-breasted patients. Breath-hold resulted in lower mean heart dose (0.4 vs. 0.7Gy) and mean LAD dose (2.9Gy vs 7.8Gy) compared to prone irradiation. They concluded that in large-breasted women, supine voluntary DiBH was superior to prone position without breath-hold[112].

In a publication by Fan et al., prone position for WBI in average sized breasts was compared to supine position. They found lower doses (Dmean, V25 and V20) for the LAD-PRV, the left ventricle, the mean heart dose and for the left lung, all favouring prone position[113].

Prone position in combination with deep inspiratory breath-hold (DiBH)

Applying prone position with DiBH may combine the best of two worlds and has been explored extensively by Mulliez et al (figure 6). End-inspiratory breath-hold was found superior to end-expiratory breath-hold in prone position[114].

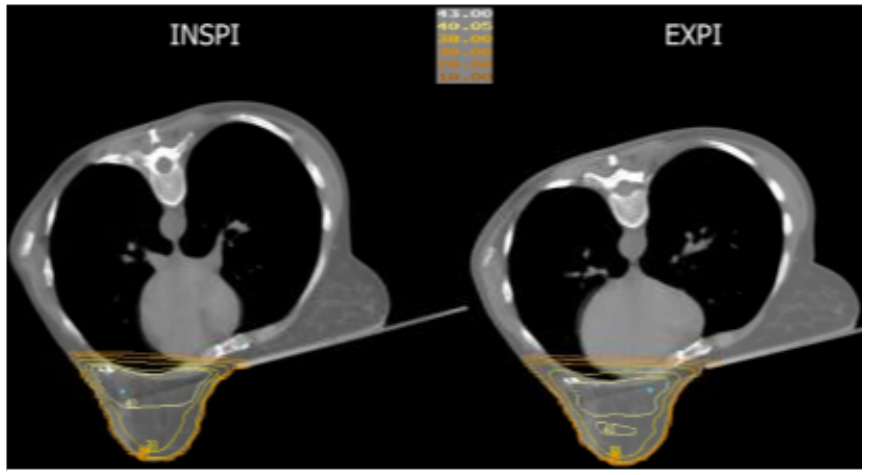


Fig 6 - Combination of prone positioning with end-expiratory versus end-inspiratory breath-hold [114] – by courtesy of T. Mulliez

A dosimetric study compared heart dose in prone with supine position, applying for both voluntary DiBH and shallow breathing. DiBH reduced heart dose in both positions, but the combination with prone position resulted in the lowest dose, while maintaining the advantage of lung sparing. DiBH in prone position is reproducible[115], but requires either larger margins or daily CBCT setup verification to compensate for a higher uncer-

tainty in longitudinal and lateral direction, especially in patients with a higher BMI[116]. Anatomically, prone DiBH was shown to decrease the heart volume by 4.3% and to cause a medial, posterior and caudal heart shift, thus retracting the heart away from the higher isodose-volumes. In comparison to supine DiBH, prone position holds the advantage of minimal to no excursion of the anterior chest wall and breast[117].

CHANGING FRACTIONATION IN ADJUVANT BREAST RADIOTHERAPY

First attempts on hypofractionation in the early 1960s led to increased toxicity compared to normofractionation, as higher fraction doses were not yet compensated for by lowering the total dose. However, together with knowledge on the linear-quadratic model came a better understanding of the radiobiology of fractionation[118]. In combination with an increasing pressure of resource constraints and growing waiting-lists in the 1980s, this led to new trials on hypofractionated breast irradiation in the UK as well as in Canada. First robust evidence came from the large randomized trials of the Ontario Clinical Oncology Group (OCOG) applying 42.5Gy/16fractions and from the UK trial comparing normofractionation with 39Gy/13 fractions and 42.9Gy/13 fractions[65, 119]. Both groups reported excellent tumour control and toxicity profiles. Based on the results from the UK trial, the α/β ratio for change in breast appearance was set at 3.6Gy (CI 1.8-5.4Gy) and the α/β ratio for tumour control at 4Gy (CI 1.0-7.8Gy).

In a next step, the START A trial was initiated to further evaluate the α/β ratio for breast cancer, comparing normofractionation with 41.6Gy or 39Gy in 13 fractions over 5 weeks[120]. To evaluate the Canadian schedule, the START B trial applied 40Gy over 15 fractions in 3 weeks in the experimental arm[121]. Long-term results have been published, and confirmed equivalence for tumour control with less breast change, as well for 40Gy/15 fractions as for 42.5/16 fractions[66, 83]. As a result, both the Canadian and UK schedule are now progressively replacing normofractionation world-wide.

These positive results have paved to way to further increase fraction doses. To overcome the reluctance for radiotherapy in older women, several trials have evaluated the delivery of treatment in 5 weekly fractions and reported excellent toxicity profiles[122-124]. Evidence from a large RCT came from the UK FAST trial, comparing normofractionation with the delivery of 28.5Gy or 30Gy in 5 weekly fractions[9]. At 3 years' median follow-up, 28.5Gy was found milder than 30Gy and comparable to 50Gy. The FAST Trialists' group has taken acceleration

one step further now, and compares delivery of 26 or 27Gy in 5 consecutive days with standard hypofractionation (40Gy/15 fractions). First results on acute toxicity were reported in 2016 and show mild to no acute breast skin toxicity[10] and these findings have been confirmed at three years' follow-up during the recent ESTRO 37 congress (abstract book OC-0595).

Towards accelerated partial breast irradiation

Accelerated partial breast irradiation (APBI) is an intriguing solution to overcome both the obstacles of protracted treatment courses and radiation-induced toxicity to the organs at risk, including heart, lungs, contralateral breast and axilla. By definition, partial breast irradiation shrinks the target to the region deemed most at risk for local recurrence[43, 44, 72]. In combination with evolving evidence on hypofractionation and evidence on the association between irradiated volume and breast-toxicity, this led to the assumption that in ESBC, lower volumes permit higher fraction doses with shorter treatment courses and result in better aesthetic outcomes, without compromising local control or overall survival.

What is the evidence on APBI?

Although APBI has already been implemented in many hospitals, also outside of clinical trials, evidence on the outcome and toxicity of APBI is so far based on short follow-up. Especially for favourable ESBC, difference in tumour control may only become apparent after 5 years.

In the past 15 years, multiple trials on accelerated partial breast radiotherapy have been conducted, with the RAPID, NSABP B39/RTOG 0413, GEC-ESTRO, ELIOT, TARGIT as some of the larger ones [11, 12, 14, 125, 126]. For ESBC with good prognostic characteristics [28, 127], some of these trials reported good to excellent local control [13, 126]. However, in other trials an increase in local recurrences was observed [11, 12], even though these relapses did not impact overall survival. Moreover, in the very favourable subsets of these patient groups, trials on omission of radiotherapy have also reported acceptable LRR[128] and LR[129] with equivalent OS.

An overview of the partial breast irradiation RCTs with five-year median follow-up or longer is listed in table 3.

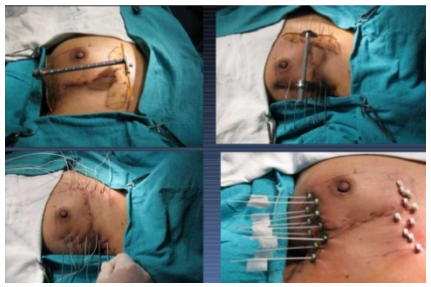
Some remarks need to be made. The superior results on aesthetic outcome from interstitial brachytherapy APBI compared to the control arm, may be explained at least partially by a less representative comparator, applying normofractionation with boost.

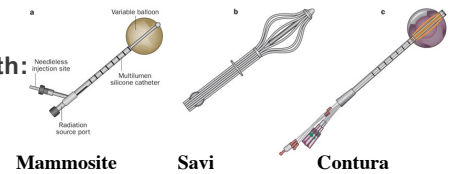
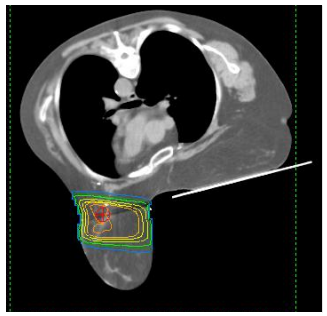
Trials on external APBI report overall good results[13, 130], except for acceleration to a twice daily schedule, as in the RAPID trial, where some authors warn for worse aesthetic outcome after three years[85].

Both the IMPORT LOW trial [70] and the Danish Breast Cancer Group (ESTRO 36) apply hypofractionation for partial breast irradiation and the WBI-group. No difference in local control was reported; difference in aesthetic outcome is small and for the IMPORT LOW trial in favour of volume reduction.

The American Society of Breast Surgeons Mammosite Registry on intraluminal brachytherapy reports relatively good results, but this is an observational study. Two large population-based registries on brachytherapy in the US reported a higher incidence of subsequent mastectomy and complications after brachytherapy[131, 132].

The most paradigm changing evolution could be a shift to a single intra-operative dose delivery for adjuvant breast radiotherapy. However, these techniques, applying intra-operative delivery of either electrons (IOERT) as in the ELIOT trial, or low-energy photons (IORT) as in the TARGIT trial, observe an increase in IBTR rates[11, 12]. In the ELIOT trial, a five-year IBTR of 4.4% was found, compared to 0.4% for WBI, which may to some extent be explained by the impossibility to safely add WBI in case of adverse pathological findings (involved margins or lymph nodes). This illustrates the risks of pre-surgery treatment decisions[133]. IOERT also came with a higher occurrence of fat necrosis. The TARGIT-trial is subject to controversy: 5-year follow up is based on a median follow-up of 2.4years, statistical methodology is contested and the non-inferiority claimed in the pre-pathology-stratum is comparable to IBTR when no radiotherapy is given, at least for the studied very favourable risk group. As WBI has demonstrated to improve the relative relapse risk with two-thirds[4], regardless of risk characteristics, IBTR in case of omission of radiotherapy in this group can be estimated at 3.9% (5-year IBTR was 1.3% in the WBI-arm), which comes close to the 3.3% reported.

Trial Concept Publication	Number of patients	Median follow-up (Range) (months)	Comparators	Technique	Target population	Results
Interstitial Brachytherapy APBI	**Postoperative procedure** **Invasive technique** **HDR or PDR** **Low dose homogeneity** **Specialized expertise needed** **Low dose to surrounding organs**					
BUDAPEST trial Single-centre RCT 2013, Radioth Oncol	Total 258 EBRT WBI 130 Interstitial HDR brachytherapy 128	122 (PBI 18-162 WBI 91-162)	WBI EBRT 25x2Gy PBI: Interstitial brachytherapy 7x5.2Gy or electron beam PBI 25x2Gy	Tumour bed delineation: clip based with 2cm expansion WBI EBRT: Cobalt 6-9MV wedged tangential fields 25x2Gy with boost 8x2Gy (electrons) in 1 patient only. PBI: Interstitial brachytherapy: HDR (Ir192 stepping source) 7x5.2Gy b.i.d. or EB-PBI with 25x2Gy 6-15MeV en face (2cm margin)	pT1 pN0-1mi grade 1-2 non-lobular ESBC, no EIC, R0	5y LR - PBI 4% - WBI 3.3% 10y LR - PBI 5.9% - WBI 5.1% 10y regional relapse - PBI 2.5% - WBI 1.7%
GEC-ESTRO trial Multicentre RCT 2016, Lancet	Total 1184 WBI 551 PBI 622	79 (IQR 70-91)	WBI EBRT 25x2Gy with boost 5x2Gy PBI: multi-catheter brachytherapy, HDR 8x4Gy or 7x4, 3Gy bid or PDR 50Gy at 0.6-0.8Gy/h	WBI: Tangential field 4-10MV in 25-28x1.8-2Gy, followed by electron boost in 5x2Gy, no dose reductions allowed. Target defined on fluoroscopic or CT simulator (not further explained) APBI: Tumourbed delineation: tumourbed of at least 2cm, individually defined. 100% of dose to 90% of target volume. Maximum skin dose restricted to 70% of prescribed dose.	Age ≥40y, lumpectomy for unifocal pTis or pT1-2 (≤3cm) IDC, ILC or DCIS, pN0-1mi, no EIC, ≥2mm uninvolved margin (5mm if ILC or DCIS), no LVSI, if DCIS VNPI <8, no Paget, no skin involvement	5y LR -WBI 0.92% - PBI 1.44% 5y regional recurrence - WBI 0.18% - PBI 0.48% Non-inferiority (increase of LR with 3% at 95%CI)

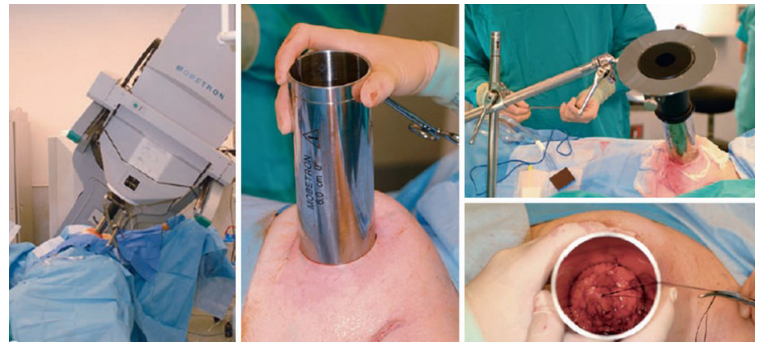
Balloon-based APBI **Partially intra-operative procedure** **Invasive technique** **Mammosite, Contura, Savi, Clearpath:** - **HDR** - **Shielding required** **Axxent:** - **electronic brachytherapy 50kV** - **Conventional walls shield enough** **Low dose to surrounding organs**  **Mammosite** **Savi** **Contura**						
Mammosite registry 2013, Ann Surg Oncol	1449	63	No comparator – observational study	Single–lumen balloon – no specific fractionation		5y-IBTR 3.8%
External beam APBI **Post-operative procedure** **Non-invasive technique** **High dose-homogeneity** **Widely available technique** **Full knowledge of histology, resection margins** **Dose to surrounding organs** 						
SPANISH trial Single centre RCT 2013, IJROBP	Total 102 WBI 51 APBI 51	60 Range not reported	WBI 24x2Gy +/- boost 5x2Gy APBI 10x3,75Gy bid	PTV = same quadrant as primary tumour site Both WBI and APBI by 3D-CRT	Age ≥60y, grade 1-2 unifocal IDC, pT1-2 (≤3cm), pN0. No DCIS, no lobular carcinoma, no EIC, margins >3mm, no postsurgical hematoma >2cm or seroma requiring multiple aspirations.	No LR in both treatment arms
RAPID trial Multi-centre RCT 2013, JCO	Total 2135 WBI 1065 3D-CRT APBI 1070	36 (Range not reported)	WBI 16x2.66Gy or 25x2Gy supine tangential fields with 10Gy boost if indicated. APBI: 10x3,85Gy bid (min. 6h in between fractions) - no boost.	Tumourbed delineation: tumourbed or seroma on CT, including surgical clips, with 1cm margin inside breast tissue (5mm from skin). Addition of 1cm CTV to PTV expansion.	IDC or DCIS treated with lumpectomy, R0, pN0 (cN0 if DCIS), ≥40y, combined tumour size (DCIS + IDC) ≤3cm, unifocal	No publication on tumour control yet

FLORENCE trial Single-centre RCT 2015, EJC	Total 520 WBI 260 APBI 260	60 (IQR 41 - 84 - APBI: 32-84 - WBI: 46-84)	WBI 25x2Gy with boost 5x2Gy APBI 5x6Gy IMRT	Tumourbed based on clips, with 1cm expansion to CTV with 3mm from skin. Addition of 1cm for CTV to PTV. WBI: Tangential field EBRT 25x2Gy followed by electron beam boost 5x2Gy APBI: IMRT with 4 or 5 co-planar fields 5x6Gy 6MV (step and shoot technique) in supine position.	Age >40y, unifocal ESBC pT1-2 ≤ 2.5cm, including DCIS, LVSI, pN0-1. No EIC, R0≥5mm	5y IBTR (LR =true recurrence in index quadrant) -APBI 1.5%, (LR 0, EF 1.5%) - WBI 1.4% (LR 1.4%) 5y LRR - APBI 1.5% - WBI 1.9%
IMPORT LOW trial Multicenter RCT 2017, Lancet	Total 2018 WBI 674 WBI SIB 673 PBI 669	72.2 (IQR 61.7-83.2)	WBI EBRT 15x2,67Gy WBI 15x2.4Gy with SIB 15x2.67Gy PBI 15x2.67Gy	Tumourbed localization either by clips or by postoperative clinical localization, US, MRI or CT. EBRT delivered with FIF IMRT with standard tangential field set up. This included non-target breast tissue medially and laterally of tumourbed in high dose region.	Age ≥ 50y, BCS for unifocal IDC grade 1-3, pT1-2 (≤3cm), pN0-1 (3 nodes or less involved), margin ≥2mm	5y LR - WBI 1.1% - WBI SIB 0.2% - PBI 0.5%

Intra-operative APBI – electrons (IOERT)

Electrons
Intra-operative procedure
- **3-9MeV – 21Gy → 90% isodose at 13-24mm**
- **Depth < 4cm**
- **Delivery time low (30' extra operation time)**
- **Mobilisation of breast tissue to insert protective disc**
- **Mobetron: mobile self-shielded linear accelerator (US, 1997)**
- **Novac/Liac: mobile unshielded linear accelerator (Italy)**

Invasive technique
No knowledge on dose-homogeneity
No knowledge on histology, resection margins
Low dose to surrounding organs



ELIOT trial Single-centre RCT 2013, Lancet	Total 1305 EBRT 654 Mobetron 651	70 (IQR 49.2-92.4)	Mobetron: intra-operative delivery of 21Gy to tumourbed (no complementary WBI) EBRT: 25x2Gy with boost 5x2Gy	WBI with boost	Age 48-75 years, ESBC maximal diameter 2.5cm, suitable for lumpectomy.	5y IBTR: - EBRT 0.4% -Mobetron 4.4% 5y True LR: - EBRT 0.4% - Mobetron 2.5%

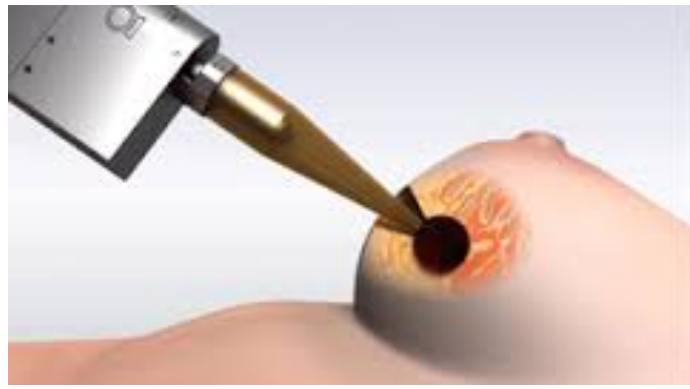
Intra-operative APBI – photons (IORT) **Low Energy X-ray** **Intra-operative procedure** - **50kV – 20Gy → 5-7Gy at 10mm** - **Depth low, RBE high** - **Delivery time 20-45'** - **Thungsten impregnated sheet** - **Conventional walls shield enough** - **Intrabeam: mobile X-ray source (Germany, 1999)** **Invasive technique** **No knowledge on dose-homogeneity** **No knowledge on histology, resection margins but postoperative WBI possible** **Low dose to surrounding organs**						
TARGIT-A trial Multicentre RCT 2014, Lancet	Total 3451 EBRT 1730 Intrabeam 1721 of which 15.2% underwent complementary EBRT	27 (IQR 12-52)	EBRT: conventional EBRT +/- boost (technique not specified) Intrabeam pre-pathology (IORT) or post-pathology (re-opening wound) +/- WBI if unforseen adverse features (margin <1mm, EIC, invasive lobular carcinom) or at the discretion of the centre (margin 1-10mm, N+, LVSI)	EBRT: conventional postoperative EBRT +/- boost Intrabeam followed by EBRT: no EBRT boost	Unifocal IDC (MRI not required), age ≥45y undergoing lumpectomy	5y LR: - EBRT 1.3% - Intrabeam 3.3% Pre-pathology: -EBRT 1.1% - Intrabeam 2.1% Post-pathology: - EBRT 1.7% - Intrabeam 5.4%

Table 3 - Overview of trials on PBI with a median follow-up of at least 5 yearsAbbreviations: WBI = whole breast irradiation; SIB = simultaneously integrated boost; (A)PBI = (accelerated) partial breast irradiation; HDR = High-dose rate; PDR = pulsed-dose rate (brachytherapy); EBRT =external beam radiotherapy; RCT = randomized controlled trial; CTV/PTV = clinical/planning target volume; LR = local recurrence; IBTR = in breast true recurrence; LRR = loco-regional recurrence; CI =confidence interval; IQR = interquartile range; IDC/ILC = invasive ductal/lobular carcinoma; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component; R0 = resection margin free; LVSI = lympho-vascular space invasion; IMRT = intensity modulated radiotherapy; IORT = intra-operative radiotherapy; VNPI = Van Nuys Prognostic Index; MV = megavolt; MeV = mega-electron volt; MRI = magnetic resonance imaging

Who may benefit from APBI?

Both the ASTRO and the GEC-ESTRO groups have published guidelines indicating which patients may safely be treated with APBI and for which indications caution is still warranted or APBI should be avoided (table 4)[26-28]. Bringing these data together with the recommendations of ASTRO and GEC-ESTRO on patient selection, results in an overall limited window of opportunity for APBI, as illustrated in table 5 and graphically represented in figure 7 (information based on breast cancer incidence in Belgium and combined with overall stage distribution, without correction for incidence of stage per age group – features other than tumour size and lymph node involvement were not considered).

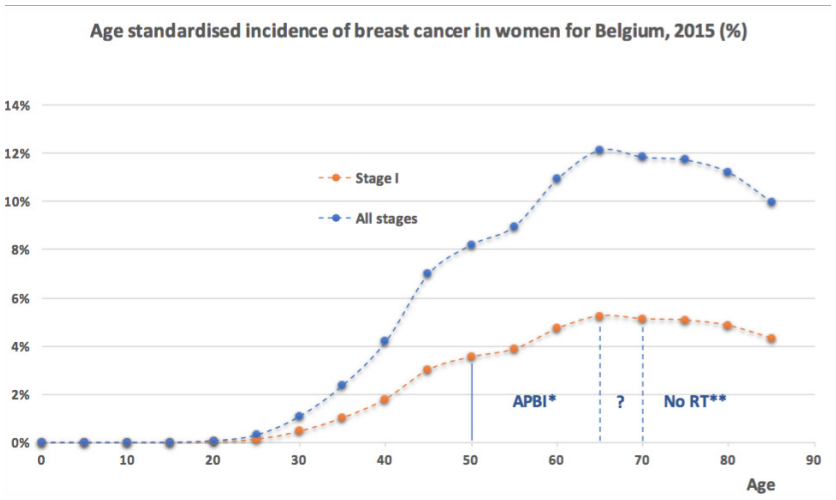


Fig 7 - Graphical illustration of the window of opportunity for APBI (at the condition of favourable characteristics) versus omission of radiotherapy (**Hormone positive, T2 =<3cm, lymph node negative). Percentages are based on breast cancer incidence per age group in Belgium, 2015. At diagnosis, stage I disease is applicable in 43.2% of all breast cancers (global percentage for Belgium, 2015)[2].

		ASTRO - 2009	Update ASTRO - 2017	ASTRO - 2009	Update ASTRO - 2017	ASTRO - 2009	Update ASTRO - 2017	GEC-ESTRO - 2010		
		Suitable - outside clinical trial acceptable		Cautionary - caution and concern applied when considering APBI outside of a clinical trial		Unsuitable - APBI outside of clinical trial not generally considered warranted		Low risk - outside clinical trial acceptable	Intermediate risk - APBI considered acceptable within clinical trial	High-risk: APBI is contra-indicated
Patient factors	Age	≥ 60 years	≥ 50 years	50-59 years	- 40-49 years if all other criteria for "suitable" are met - ≥ 50 years if at least 1 of following factors is applicable	<50	- < 40 - 40-49 if criteria for "cautionary" are not met	≥50	40-50	≤40 years
	BRCA1/2	Not present			NA		Present	NA	NA	NA
Pathologic factors	Tumour size	≤ 20mm			21-30mm		≥30mm	≤ 30mm	<30mm	>30mm
	T stage	T1	Tis or T1	T0 or T2	T2		T3-4	pT1-2	T1-2	pT2 (>3cm)
	Margins	R0 ≥ 2mm			R0 < 2mm		Positive	R0 ≥ 2mm	R0 < 2mm	Positive
	Grade	Any			Any		Any	Any	Any	Any
	LVSI	No			Limited/focal		Extensive	Not allowed	Not allowed	present
	ER status	Positive			Negative		NA	Any	Any	Any
	Multicentricity	Unicentric only			NA		Present	Unicentric	Unicentric	Multicentric
	Multifocality	Clinically unifocal with total size ≤ 2cm		Clinically unifocal with size 2.1-3cm	Multifocality allowed if clinically unifocal with total size 2.1-3cm		Clinically unifocal with microscopically size >3cm of if clinically multifocal	Unifocal	Multifocal (≤2cm of index lesion)	Multifocal (>2cm from index lesion)
	Histology	Invasive ductal or other favorable types			Invasive lobular		NA	IDC, mucinous, tubular, medullary and colloid	ILC	NA
	Pure DCIS	Not allowed	Allowed if all of: - screen-detected - Grade 1-2 - Size ≤2.5cm - R0 ≥3mm	≤ 3cm	Pure DCIS ≤ 3cm if criteria for suitable not fully met	>3cm		Not allowed	Allowed	Allowed
	EIC	Not allowed			≤ 3cm	>3cm		Not allowed	Not allowed	present
	Associated LCIS	Allowed			Allowed	Allowed		Allowed	Allowed	Allowed
Nodal factors	N stage	pN0 (i-,i+)			NA	pN1-3		pN0	pN1i, pN1a (3nodes)	pNx, ≥pN2a (≥4N+)
	Nodal surgery	SN Biopsy or ALND			NA	None performed		SN Biopsy or ALND	SN Biopsy or ALND	Any
Treatment factors	Neo-adjuvant chemo	Not allowed			NA	If used		Not allowed	Not allowed	If used

Table 4 - Overview of the ASTRO[26], updated ASTRO[27] and GEC-ESTRO guidelines[28] for APBI.Abbreviations: NA = not applicable; APBI = accelerated partial breast irradiation; R0/1/2 = resection margins free/microscopically involved/macroscopically involved; LVSI = lympho-vascular space invasion; ER = estrogen receptor; IDC = invasive ductal carcinoma; ILC = invasive lobular carcinoma; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component; LCIS = lobular carcinoma in situ; T-stage = size of tumour; N-stage = lymph node involvement; SN = sentinel node; ALND =axillary lymph node dissection

Age	pN0					
	Hormone positive tumour			Hormone negative tumour		
	T1	T2 (≤3cm)	T2	T1	T2 (≤3cm)	T2 (>3cm)
<50 years	WBI**	WBI	WBI	WBI	WBI	WBI
Between 50 and 65-70 years	Consider APBI*	GEC-ESTRO: consider APBI* Updated AS-TRO: WBI		GEC-ESTRO: consider APBI* Updated AS-TRO: WBI	GEC-ESTRO: consider APBI* Updated ASTRO: WBI	
>65-70 years	Consider no RT	CALGB: WBI PRIME: consid-er no RT		GEC-ESTRO: consider APBI* Updated AS-TRO: WBI	WBI	

*IF SLN or ALND performed, no BRCA 1/2, R0≥2mm, no LVSI, unicentric and unifocal, IDC or favorable subtype (mucinous, tubular, medullary or colloid), no pure DCIS, no EIC and no neo-adjuvant chemotherapy, otherwise WBI

** WBI covers WBI only as well as WBI with sequential boost or SIB.

Table 5 - Combination of GEC-ESTRO and updated ASTRO-guidelines for APBI, combined with evidence from PRIME-trial (age limit 65 years) and CALGB 9343 trial (age-limit 70 years)

HEALTH ECONOMIC EVALUATION - BALANCING COSTS AND EFFECTS

Whereas clinical research investigates the efficacy and effectiveness of new treatments, as described in the former section for accelerated WBI and APBI, the subject of efficiency ('Are new treatment strategies worthwhile from a health economic point of view?) is addressed by health economic evaluations (HEE). With increasing healthcare costs and expenses, in the context of ever tightening budgets, the interest for the balance between costs and effects has been steeply rising over the past 20 years. This can be observed in the increasing yearly number of publications on HEE (figure 8), of which most are based on cost-effectiveness (CEA) or cost-utility (CUA) analysis, techniques that relate the change in cost to the difference in health effects. Such economic exercises within the domain of health care come at help for decision makers in allocating the available resources to strategies that maximise health, decisions which may vary per country and depend on the available health care budget.

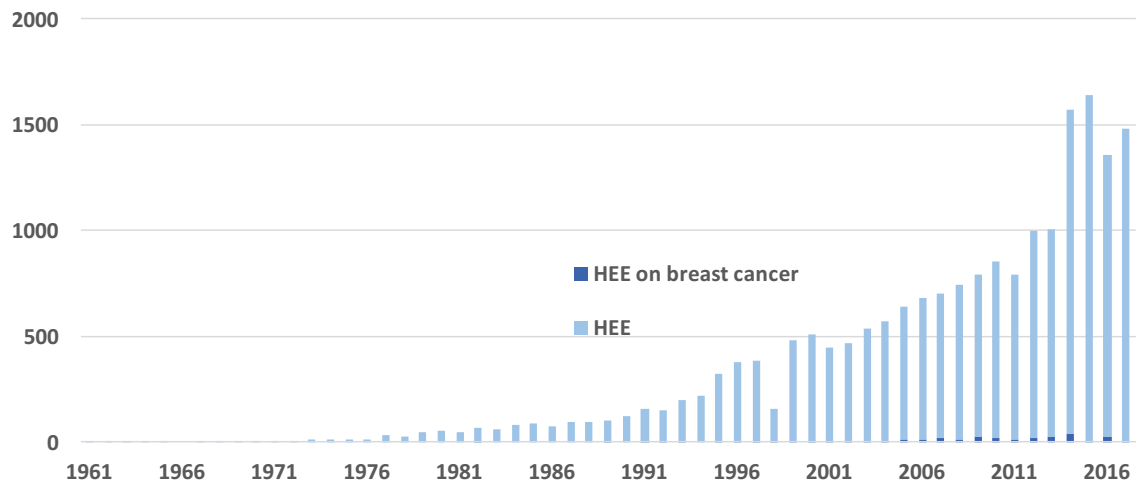


Fig 8 – A steep rise of the INTEREST in health economic evaluation over the past decade can be observed by a simple search in Pubmed). The number of breast cancer related HEE remains however low (dark blue).

Types of health economic evaluations

HEE cover a wide range of approaches, depending on whether both costs and outcomes are evaluated and compared[134]. The mere cost-analysis (CA) of a new intervention,

for example, is less interesting than the approach where the cost of a new intervention is compared with the gold standard, as in cost comparison analysis (CC). In addition, differences in costs may be justified by differences in health effect: a less costly strategy may become less attractive if it impairs survival or quality-of-life (QoL). Hence, increases or decreases in costs only show one part of the equation, and should be evaluated in the light of changes in clinical outcome, as is done in a full HEE.

When the incremental cost is divided by the incremental health effect, this results in an incremental cost-effectiveness ratio or ICER, with in the formula below, y being the new strategy and x the gold standard. This approach is referred to as cost-effectiveness analysis (CEA) or cost-utility analysis (CUA), depending on the health effect used.

$$\text{ICER} = \frac{\Delta\ (\text{Cost y} - \text{Cost x})}{\Delta\ (\text{Effectiveness y} - \text{Effectiveness x})}$$

Health effects represent the effectiveness of a strategy; incremental effects are the additional outcome that can be obtained with a new treatment as compared to the standard. If this effectiveness is expressed in natural units, ideally measured in life-years gained (LYG), then the economic evaluation is referred to as cost-effectiveness analysis (CEA).

However, other measures can be used. To obtain quality-adjusted life-years gained (QALYs), LYGs are multiplied with a factor between 0 and 1, articulating the importance that individuals adhere to a clinical benefit (utility). Such analysis is called a cost-utility analysis (CUA). The term of CEA is more commonly used and often covers both concepts.

Two other HEE techniques are cost-minimization analysis (CMA) and cost-benefit analysis (CBA). A CMA compares the cost of two equally effective strategies. The difference in costs represents the savings that can be obtained if the least costly strategy is applied. In a CBA, health effects are also expressed in monetary units. An overview is given in figure 9.

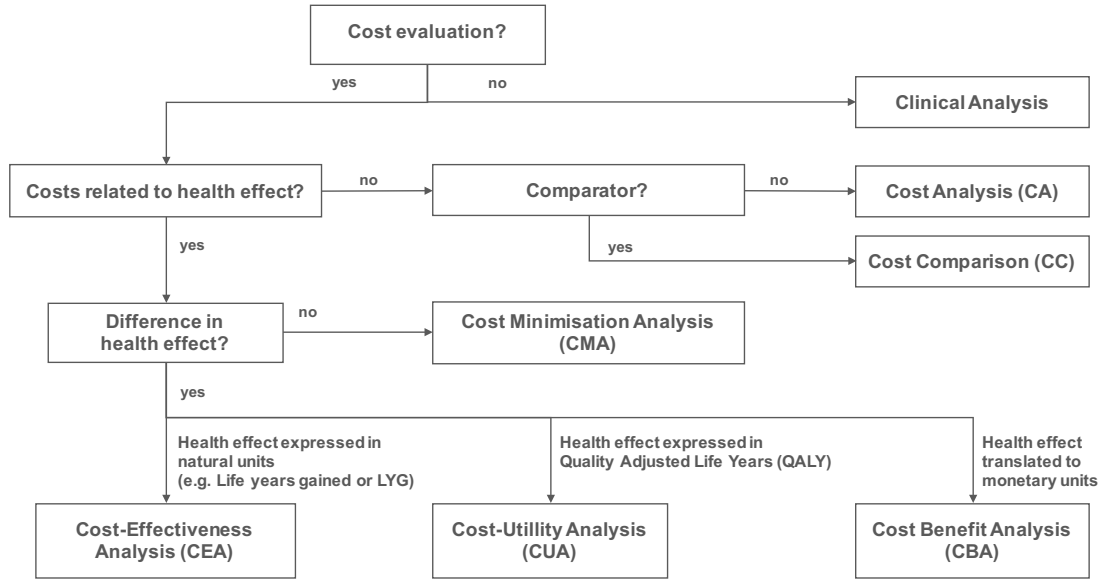


Fig 9: Overview of the different types of HEE, including a decision tree based on comparators and units used.

Defining costs in health economic evaluation

It is important to understand that costs, used in HEE, may take many forms. The difference between direct versus indirect and medical versus non-medical costs is illustrated in figure 10.

Costs incorporate the quantity of the resource used multiplied by the monetary value of a unit. This value can be either the unadjusted market price or the opportunity cost. Although most HEE apply market prices, opportunity cost is a more correct approach. It is the value of a foregone benefit, that cannot be used for a 'best' alternative as the resource is not available anymore[135].

The study perspective determines which costs (and health effects) must be included. Most HEE claim a societal perspective, but, as mentioned in the ISPOR Drug Cost Task Force Report, the term 'societal' is widely misunderstood and misused[136]. A 'health system perspective' would be a more accurate definition, as most HEE apply a payers' perspective based on direct medical costs and expand these with indirect costs. A societal perspective includes all the costs and benefits regardless of who incurs or obtains them, thus avoiding the masking of a cost shift from one to another sector. As an example, wage loss due to sick

leave, may be compensated for by an allowance. Including only the allowance as governmental expenditure would overestimate the cost of working incapacity. Although the narrower 'health system perspective' risks to exclude potential benefits, Drummond states that "it may still lead to very similar decisions once account has been taken of the restrictions on health care expenditure and non-health benefits that are likely to be displaced"[137].

Two methods for cost calculation of interventions are used in HEE: most often, cost inputs are based on reimbursement data or charges claimed by the health-care provider. Reimbursement represents what is paid by the insurer and results from a bilateral negotiation, with different levels of reimbursement per payer. Charges are what the hospital expects to receive for their services and are usually higher than the reimbursement received. The advantage of reimbursement-based cost data relies in its' simplicity. However, these data are rarely representative of the real cost of an intervention. Indeed, as reimbursement is the result of negotiations between health care providers and financing organisations, it can display large regional differences and may be subject to sudden changes, due to budgetary savings.

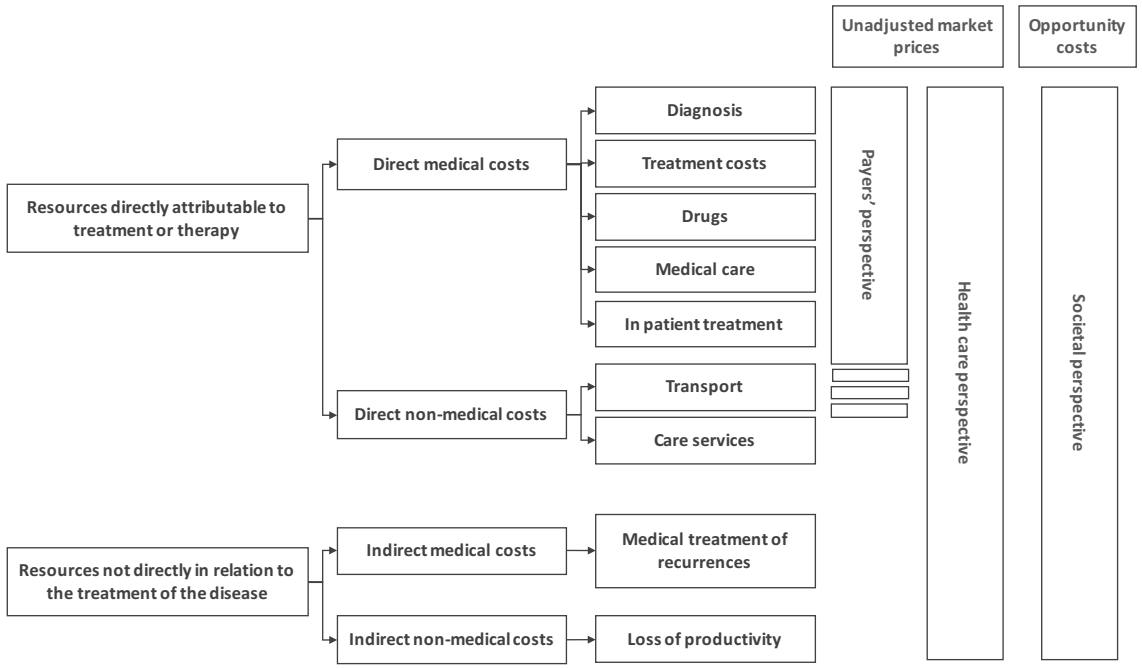


Fig 10: Relation between perspective and types of resource costs.

A more precise method to define the cost of an intervention is calculating the real costs incurred when using resources to deliver a treatment. These resource costs typically include personnel costs (salaries), the investment costs of infrastructure and equipment, consumables, overhead. There are two commonly accepted cost-accounting techniques: micro-costing and activity-based costing (ABC). Micro-costing, a bottom-up approach requiring insight into the time investment of the different resources, is interesting for calculating the cost of specific treatments or process steps, as it multiplies the resources utilized with their related unit costs. The technique of ABC assigns resource costs through the intermediary of the care process activities involved[138]. It is more comprehensive and takes into account the relative weight of indirect resource costs that cannot be directly assigned to the final product, i.e. the treatment. It also provides superior insight into highly variable costs.

From an institutional perspective, reimbursement covering all real costs would signify the most ideal scenario, as no financial risk is carried by the provider. However, from a payers' perspective, the lack of an incentive to economize may lead to inefficient use of health care budgets. Real costs are a dynamic concept, as initially high costs may decrease when learning curves are completed, new strategies change to standard practice, investments are amortized... These uncertainties, together with reimbursement tariffs being straight-forward to use in cost-calculations, may explain why many HEE are reimbursement-based.

Piggyback analyses versus health economic modelling

Although it is well recognized that comparative effectiveness is critical for supporting the appropriate use of more advanced treatments, techniques and technologies, generating these data in radiotherapy remains challenging.

An economic analysis embedded in a clinical trial comparing different treatment strategies is known as a piggyback analysis[139]. In such approach, economic cost data are collected alongside a trial, which in itself is designed to respond the clinical question. Although it may be the appropriate way to measure the economic impact of medical interventions, it is, however, not evident to collect all long-term cost and outcome data necessary to perform the economic evaluation.

Hence, most HEE are based on modelling exercises, with the Markov model as the most frequently used. Such models are based on a predefined series of health states at different time intervals, called cycles. The length of such cycle depends on the nature of the disease and the intervention being evaluated, and could be a month or a year. After each cycle, transition probabilities define how patients move between different health states. Each health state is associated with a cost and, for cost-utility analyses, a utility value. The outcome of such modelling exercise is calculated as the product of the time that the average patient occupies the different health states weighted by the cost and utility of each specific health state (figure 11)[140].

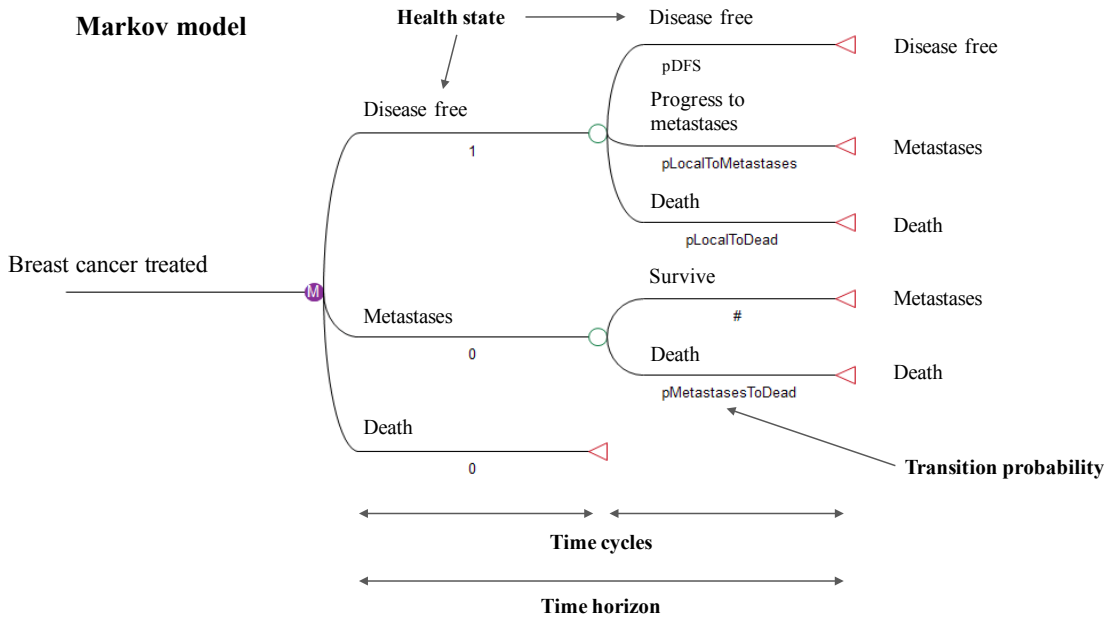


Fig 11 - Markov model decision tree example (adapted from https://www.treeage.com/)

Visualizing the results of an economic evaluation: the cost-effectiveness plane

The results of a CEA or CUA are expressed by the ICER, and can be represented on a cost-effectiveness plane, with the X-axis indicating incremental effectiveness and the Y-axis incremental cost[141]. The different possible situations are illustrated in figure 12. An ICER may result in a positive or a negative figure.

A negative figure indicates the ICER is either dominant (lower cost for improved effectiveness – green quadrant, situation 1) or dominated (higher cost for impaired effectiveness – red quadrant, situation 2). In the former, it is strongly recommended to introduce the new intervention into daily care; in the latter, it should not.

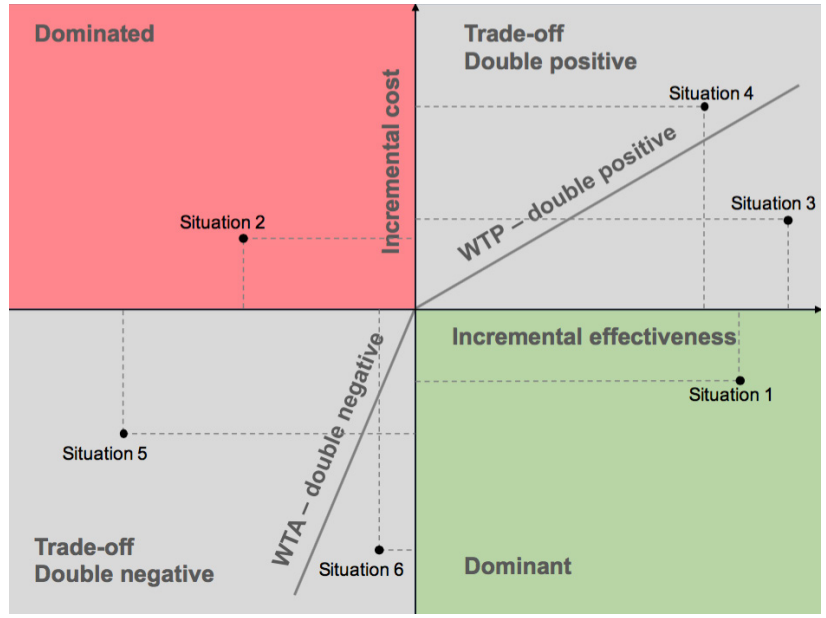


Fig 12 - Cost-effectiveness plane

A positive result indicates a trade-off situation (grey quadrants), with an improved effectiveness for a more expensive treatment as the most common situation (double positive situation, right upper quadrant). Such a result can be compared to a willingness-to-pay threshold, indicating how much a society accepts to pay as incremental cost per LYG or per QALY. This can be a fixed amount (e.g. 20.000-30.000£/QALY or 100.000$/QALY as applied by respectively the UK and the US) or a variable or undefined amount, as is the case in Belgium[142]. If no fixed amount is defined, factors such as the innovative character or need of a new intervention, the available health care budget or the availability of alternative interventions are additionally taken into consideration to guide decision-making. In these trade-off situations, society aims at a maximal gain in effectiveness for minimal extra cost. In figure 12, situation 3 would be considered as an acceptable strategy, whereas situation 4 may be considered too costly.

A less frequent situation is the trade-off where a new strategy costs less, but comes with a loss in effectiveness (double negative situation). In this case, the focus will shift to minimal loss in effectiveness for a maximal reduction in cost. Hence, in case of a double negative situation, a high cost reduction for a minimal loss in health effect would be preferred, which is the opposite of the double positive right upper quadrant. In the illustration, situation 5 may therefore be regarded inacceptable whereas situation 6 could be considered acceptable.

Handling uncertainty in health economic evaluation

To address the inherent uncertainties of a HEE, uncertainty analysis is applied. This technique assumes an acceptable range in costs or outcomes and evaluates the impact ranges have on the final cost-effectiveness result. In one-way sensitivity analysis, each variable is evaluated separately. Probabilistic sensitivity analysis (PSA) varies different variables at the same time through the means of a Monte Carlo simulation, running hundreds to thousands of times. The result of such exercise can be visualized as a cloud, located over the cost-effectiveness plane (figure 13).

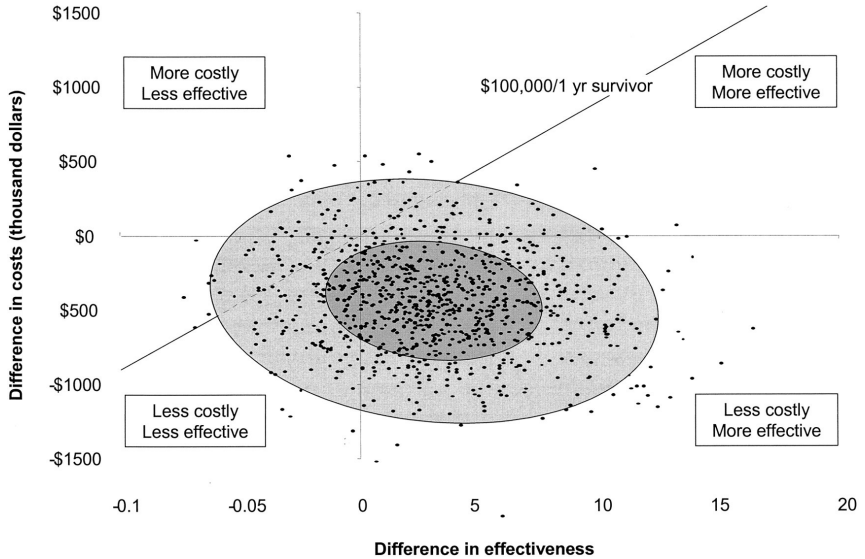


Fig 13 – Visualisation of Monte Carlo based PSA (1000 simulations) with the example indicating that the new intervention is most probably less costly and more effective than the comparator. Ellipses represent 50% and 95% confidence intervals. Illustration from D. Angus et al. Pediatrics, 6/12/2003[143]

Heterogeneity takes into consideration the impact the chosen base case may have on the cost-effectiveness results. The impact of heterogeneity may be explored through the

means of scenario analysis, recalculating cost-effectiveness if a different population (e.g. age, social status, sexe…) or indication (e.g. tumor stage, co-morbidity…) is chosen. Even in the absence of such analysis, heterogeneity should be discussed, to avoid inappropriate generalization of the cost-effectiveness results.

Quality in health economic research

The results of a HEE exercise, and ultimately whether they will be suitable to guide health care decision-making, strongly depend on the validity of the input data and on the model used. In 2012, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) published a report on 'good research practices' emphasizing the importance of transparency on the models used and validity of the input data sources[144]. To improve conformity and quality in HEE reporting, the Consolidated Health Economic Evaluation Reporting Standards or CHEERS' consensus was published, a checklist containing 24 items indispensable for evaluating the validity and reliability of a HEE[145].

It cannot be overstressed that, as for clinical research, high-quality and valid HEE data is indispensable. Only in the presence of such data, correct decisions can be made about which new health care interventions to grant reimbursement, and which interventions conversely are too expensive for society to introduce in daily clinical practice.

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OBJECTIVES

Purpose of my research

As described in the introduction of my PhD, breast cancer radiotherapy has a well-defined place in the multidisciplinary treatment of breast cancer. It has been proven to be effective, with proportional gains in local control and overall survival being grossly stable across tumour stages and clinical indications. All in all, post-operative radiotherapy halves the risk of any first recurrence and for each 4 local relapses averted, one life can be saved.

Yet, in contrast, the absolute gains in local control and survival do vary significantly across tumour stages and clinical indications. Consequently, in the more favorable situations of ESBC, it is often questioned - by the patient or the referring specialist - whether the benefits anticipated are sufficient to run the risk of toxicity and to subject the patient to the burden of cumbersome travels to and from the hospital. This is especially the case for the elderly breast cancer patient, a patient population that is not only important, but is still on the rise. In this context, the long-standing paradigm of normofractionated whole breast irradiation is clearing the field for the newer approaches of acceleration and partial breast irradiation. Both have the aim to reduce the cost of breast cancer radiotherapy, in terms of toxicity, of patient burden as well as in budgetary terms.

Before considering new health care interventions for introduction in daily clinical care, evidence must be generated, not only from a clinical, but also from a health economical perspective. In an indication as frequent as post-operative radiotherapy for breast cancer, the judicious selection of the most appropriate treatment strategy for each specific clinical situation, is not only deemed to improve the care to the individual patient, but also allocate the scarce health care resources and budget in the most efficient way.

Based on these considerations, the central purpose of my research was to examine the feasibility, toxicity and economic impact of accelerated breast cancer radiotherapy, with the aim to provide the best outcome to each individual patient, at the lowest cost from a clinical as well as an economical perspective.

Before considering the introduction of partial breast irradiation in our standard approach of prone breast radiotherapy, the first question to tackle was how to safely reduce the treated volume and ascertain accuracy in tumourbed delineation. This was investigated in a feasibility study evaluating interobserver variability and dosimetric impact of a geometrical approach to target volume delineation.

Based on the equivocal findings of this study, and with the ambition to reduce treatment burden beyond the confines of low risk indications only, a prospective phase 2 trial exploring the safety of acceleration to 5 fractions in all indications for adjuvant breast radiotherapy, including thoracic wall and lymph node irradiation, was conducted in an elderly patient population.

Health economic evaluations have the aim to support healthcare decision-making on the introduction of new, often costlier, treatment strategies in daily practice. In order to do this correctly, the health economic information must be valid and of high quality. To assess the validity of the available evidence, economic evaluations on different types of breast cancer radiotherapy, retrieved by a systematic literature review, were subjected to a qualitative and quantitative analysis and a new method of quantification was explored.

In a subsequent exercise, the available evidence on cost and cost-effectiveness of different strategies in adjuvant breast radiotherapy was assembled. Despite the pitfalls inherent to HEE, some conclusions could be drawn on the efficiency of new schedules and treatment techniques within this domain.

SCOPE OF THESIS IN FOUR OBJECTIVES

Objective 1:

Partial breast irradiation: is it feasible in prone position?

Evaluation of a practical approach to obtain precise and accurate target volume delineation for accelerated partial breast irradiation in prone position.

Objective 2:

Accelerated radiotherapy: can it be extended beyond partial breast irradiation, without increasing acute toxicity?

Evaluation if accelerated breast irradiation may safely be expanded to a broader population of elderly patients with early as well as locally-advanced stage breast cancer.

Objective 3:

Health economic evidence of post-operative breast radiotherapy: is it valid?

Evaluation of the quality of the available health economic evidence on post-operative breast radiotherapy, and its validity to guide health care decision-making.

Objective 4:

Post-operative breast radiotherapy: what are its cost and cost-effectiveness?

Evaluation of the available health economic evidence on post-operative breast radiotherapy regarding the balance between costs and effectiveness of different techniques and fractionation schedules.

DESCRIPTION OF THE SCIENTIFIC WORK PERFORMED

Publication 1 – External partial breast irradiation in prone position: how to improve accuracy? – Acta Oncologica (accepted)

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Authors: [1]Chris Monten, [1]Liv Veldeman, [1]Katrien Vandecasteele, [1]Luiza Oltéanu, [1]Werner De Gersem, [1]Tom Vercauteren, [1]Thomas Mulliez, [2]Rudy Van Den Broecke, [2]Herman Depypere, [1]Wilfried De Neve, [1]Yolande Lievens
[1]Department of Radiation Oncology, Ghent University Hospital, Belgium
[2]Department of Obstetrics and Gynaecology, Ghent University Hospital, Belgium

Running title
Accuracy in prone partial breast irradiation

Key words
Radiotherapy; breast cancer; prone position, target volume delineation

Abstract

Introduction In view of the limited incremental benefit between whole breast irradiation (WBI), accelerated partial breast irradiation (APBI) and omission of radiotherapy in favourable early stage breast cancer (ESBC), APBI can only be justified if it combines adequate target coverage with the lowest achievable toxicity. Interobserver exercises demonstrated the difficulty of precise target delineation, especially in prone position; information on accuracy is even scarcer. We tested the impact of inserting an additional indicatorclip, marking the depth of the tumour in the breast, and the added value of a preoperative CT in treatment position on precision and accuracy.

Materials and methods In 12 patients, tumour bed delineation was performed by 4 radiation oncologists, with $CTV_{standard}$ (clinical target volume) based on standard delineation guidelines, CTV_{clip} resulting from a 1-2cm symmetrical expansion with the indicatorclip as centre and CTV_{clip_CT} expanding from the midpoint between the indicatorclip and preoperative gross tumor volume (GTV) as centre. Precision was measured as the mean pairwise Jaccard index (JI_{pairs}) between observers, accuracy as the mean overlap between GTV and respective CTVs.

Results JI_{pairs} was 0.38 for $CTV_{standard}$, 0.75 for CTV_{clip} and 0.59 for CTV_{clip_CT}. Overlap rate of GTV with CTVs was respectively 0.48, 0.67 and improved further to 0.88 for CTV_{clip_CT}. High-dose coverage of GTV (D95 and D90) improved with an indicatorclip, but the most optimal result was reached when preoperative CT was added.

Conclusion If EB-APBI in prone position is aimed for, an indicatorclip intended to mark the depth of the tumour increases the probability of accurate target coverage, but cannot entirely replace the added value of a preoperative CT in treatment position. Avoiding the cost and effort of such CT implies a risk of missing the target., especially when small volumes are aimed for. Increasing target volumes to reduces this risk, questions the concept of APBI.

INTRODUCTION

Adjuvant radiotherapy is an evidence-based part of breast conserving therapy, improving local control and overall survival[1]. These advantages however come at the cost of radiation toxicity as well as burdensome treatment courses. In answer to these obstacles, accelerated partial breast irradiation (APBI) was introduced for early stage breast cancer (ESBC), with acceleration to address the problem of protracted schedules and reduced target volumes to avoid the potential consequences of high fraction doses in terms of aesthetic outcome. At the same time, smaller volumes would facilitate sparing of the surrounding organs at risk (OAR). Previous trials on adjuvant breast radiotherapy already indicated a relation between irradiated volumes and aesthetic outcome of the breast, and direct proof came recently with the IMPORT-LOW trial[2-4]. This trial, along with others, also suggested that APBI is a safe alternative to whole breast irradiation (WBI) while reducing toxicity[5-8]. However, a maximum of 5 years' follow-up may be too short to draw definitive conclusions, especially in case of favourable ESBC, where differences in survival only start to emerge afterwards [1, 9]. An even more radical solution to patient burden and toxicity was tested in the CALGB 9343 and the PRIME trial, omitting radiotherapy in favourable subgroups[10, 11]. Although both trials reported an adverse impact on respectively loco-regional and local control, overall survival was equivalent[10, 11]. The limited incremental benefit between WBI, APBI and omission of radiotherapy indicates that APBI can only be justified if it combines adequate local control, hence adequate target coverage, with the lowest achievable toxicity.

The IMPORT-LOW trial evaluated hypofractionated straight-forward tangential-beam field-in-field IMRT for partial breast irradiation (PBI) as a robust and widely implementable technique, and results indicated equivalence for tumour control and overall survival between PBI and WBI[4]. However, the concept of partial breast is challenged in this trial, as beam set-up resulted in high-dose delivered to off-target breast medially and laterally from the tumourbed, including part of the axilla for targets located in the upper part of the breast. Delivering high dose to up to half the breast may also explain why difference in aesthetic outcome was altogether limited.

In EB-APBI, prone position may help tackling volume and toxicity issues: it reduces the latero-lateral beam travelling distance and increases the antero-posterior diameter, both resulting in reduced high-dose volumes compared to supine position[12]. These dosimetric advantages however come at the cost of increased uncertainty in target delineation, most pronounced in the antero-posterior direction[13]. Interobserver delineation exercises have demonstrated the difficulties of tumourbed delineation, even in supine position with seroma present. Clips come at help, but not all clips are relevant, some are even misleading (figure 1). Addressing this uncertainty with larger target volumes would forego the primary goal of APBI, volume-reduction.

In search of combining precision (high interobserver conformity) with accuracy (high probability of primary tumour coverage) in prone position and after full thickness closure (FTC), we tested in an interobserver exercise the impact of inserting an additional indicatorclip, intended for marking the depth of the tumour in the breast. To test accuracy, the resulting postoperative CTVs were compared with the GTV on preoperative CT in treatment position. Tangential-beam APBI using intensity modulated radiotherapy (IMRT) was compared with three-beam IMRT to evaluate the relevance of accuracy and the dosimetric impact of beam set-up on low- as well as high-isodose volumes.

Material and methods

Following local Ethics Committee approval of the study, seventeen patients with histologically confirmed clinical stage I-II breast tumours (cT1-2 cN0), candidate for tumourectomy, signed informed consent and were enrolled between May and December 2014. Patient, tumour and treatment characteristics are listed in table 1. Five patients were excluded after preoperative CT because of switch to supine position: in one patient, multi-centricity necessitated mastectomy and in four a positive sentinel node was found, requiring lymph node dissection and irradiation. In the 12 remaining patients, the tumour was visualized by harpoon in eight patients with non-palpable tumours and by contrast in four patients with palpable tumours.

The pre-operative CT scan was performed on a large bore Toshiba CT, one day before tumourectomy and following the standard image acquisition protocol (120kV, 70mAs, 3-5mm slices). Patients were installed in prone position on the breast board [23]. Contrast-enhancement was performed with 100cc IV Visipaque (2cc/sec, scanning started

100-120sec after start of injection). Tattoos were applied to help ensuring the same position on postoperative planning CT.

Surgeons were requested to insert clips according to the following protocol: incision and localization of the tumour in the breast with insertion of a 9mm large titanium "indicatorclip" in the cavity wall at the depth of the 'resection lump', to indicate antero-posterior tumour location as precisely as possible. Following excision of the tumour, usual "cavity wall" clips (6mm, titanium), including a deep "pectoral fascia" clip, were placed according to routine practice. FTC was performed in all patients, none underwent oncoplastic surgery. Four to five weeks after tumourectomy, patients underwent a planning CT-scan in the same position and under the same conditions as preoperatively, but without contrast.

Delineation was performed by four experienced in-house radiation oncologists using version 9.8 of the Pinnacle Treatment Planning software. For $CTV_{standard}$, volumes were delineated on the planning CT-scan according to existing guidelines, aided by pre-operative information (including surgical and histological reports and preoperative imaging but not the preoperative CT in treatment position)[24].

For CTV_{clip}, the indicatorclip was located on simulation CT and symmetrically expanded from the centre with a 20mm radius[21, 22], minus the minimal surgical margin (maximally 10mm). Expansion was limited to the skin, shrunk with 5mm, and excluded the thoracic wall. No other volume corrections were allowed.

The preoperative CT in treatment position was only then fused with the simulation CT, the primary tumour was delineated as GTV and a CTV_{clip_CT} was calculated by Gratis, an in house developed vector-based planning system[25], as an automatic expansion from the calculated midpoint between clip and preoperative GTV.

Mean distance between centres of volumes (dCoV) and mean of pairwise volume comparisons, using the Jaccard formula (JI_{pairs}), were calculated to evaluate inter-observer variability of CTVs. Pairwise comparison avoids the influence of the number of observers on the final results[14]. Overlap coefficient (OC) was calculated as the ratio of the preoperative GTV falling within the CTVs. Distance between indicatorclip and preoperative

location of the tumour and between CTVs and OARs were calculated with Gratis.

Finally, APBI treatment plans were created per delineation technique, prescribing 28.5Gy in 5 fractions to the PTV (CTV + 5mm, excluding skin minus 5mm and thoracic wall) with dose fall-off from 28.5Gy to 20Gy in a surrounding rim of 1cm. A 2- and a 3-beam set-up with IMRT were applied, with identical gantry and collimator angle per patient, and couch rotations for the 3-beam set-up (15° and 340°).

Results are reported as means with 95% confidence intervals. The Wilcoxon signed rank test was used to compare the delineation techniques, Friedman's 2-way test when more than 2 results are compared. Significant difference was assumed when a confidence level of 95% was reached with an alpha-error of 5%.

Results

Results are listed in table 2 and 3. Volumes were small, but symmetric expansion resulted in somewhat higher volumes for CTV_{clip} compared to standard delineation, due to larger laterolateral and cranio-caudal diameters and despite smaller antero-posterior diameter. Low mean dCoV for CTV_{clip}, indicates good recognisability of the indicatorclip. This led to a high JI_{pairs} for CTV_{clip} compared to $CTV_{standard}$ (0.75 versus 0.38, p=0.003). When adaptation of the centre was allowed for CTV_{clip}, JI_{pairs} decreased to 0.59, reflecting a lower agreement on delineation of the GTV, for which a mean dCoV of 7mm was found (1mm if contrast-located versus 10mm if harpoon-located, p=0.03).

Overlap coefficient of GTV with CTVs as a proxy for accuracy, was better for indicatorclip-based delineation than for standard delineation (0.67 versus 0.48, $p<0.05$) and improved even further to 0.88 when information of the preoperative CT was added.

Distance of CTVs to heart and ipsilateral lung was not significantly different for both delineation techniques.

Dosimetric characteristics are listed in table 3. Coverage of GTV (D95) increased with clip-based delineation, and further improved after adding of the preoperative CT. The

risk of relevant underdosing was estimated by the number of patients with 95% of the GTV receiving less than 95 and 90% of the prescribed dose. Standard delineation resulted more often in severe underdosing or fails then clip-based expansion; the risk increased with 3- beam set-up, as downside of sparing off-target breast tissue from high dose. Heart and ipsilateral lung dose did not differ significantly (mean heart D2 0.8-1Gy and ipsilateral lung V10 0.2-0.3Gy).

Discussion

Conformity exercises demonstrate that even in controlled circumstances, precision of tumour bed delineation in breast cancer is low: breast tissue is a homogeneous structure with little reference points for localization. When prone position is applied, the antero-posterior diameter of the breast increases and landmarks for delineation change. Tissue distortion is a radiological sign, indicating high-density regions (glandular tissue and oedema) versus fat tissue. In supine position, (a)symmetry between left and right breast may to some extent help to differentiate between oedema and glandular structures, but not in prone position, where compression of the contralateral breast on the breast board precludes this comparison. Indirect tumour bed localizers such as clips, seroma or tissue distortion do not always correlate with preoperative imaging. Although they indicate the surgical trajectory, tunneling upon the pectoral fascia may lead to unnecessarily large irradiated volumes, close to lungs and heart, thus losing the advantages of prone position and partial breast irradiation[15]. The omission of 'irrelevant clips' may solve this, however at the cost of lower interobserver conformity, even if preoperative mammography is available[16]. As already suggested by Kirby et al., surgeons plays an important role and should be informed on the implication of clips on irradiated volumes[17]. Insertion of a minimum of 5-6 clips is recommended, but re-resections may accidently remove such clips. Kirova et al. found that preoperative CT (supine position) mainly corrected for left-right discrepancy in tumourbed delineation. According to Verhoeven et al., this does not translate into a better jaccard index[18]. However, with folding of the breast over the thoracic wall, antero-posterior uncertainty is reduced by natural borders.

Daily practice confirms this target uncertainty. In case of PBI, geographical miss of the region at risk is not corrected for by the whole breast component. In view of above mentioned results on delineation conformity, and before starting a trial on EB-APBI in prone position, this feasibility trial was conceived for evaluating how to improve precision and accuracy in tumourbed delineation. Recognisability of the marker was good and resulted in an interobserver conformity for CTV_{clip} comparable to preoperative exercises[19]. Overlap rate of GTV with CTV_{clip} compared to $CTV_{standard}$ improved with 40%, indicating increased accuracy, even if based on 'blind' expansion from this indicatorclip only. Fusion of images with the preoperative CT in treatment position further enhanced overlap rates, be it at the cost of interobserver conformity, which decreased to 0.59. This can be explained by discrepancy in GTV delineation, especially after harpoon-localization.

The dosimetric impact of delineation uncertainty was tested in a planning exercise. When a third beam was added, high-dose volumes decreased and low-dose volumes increased. Although GTV coverage, represented as the dose received by 95% of the volume, did not differ significantly between delineation strategies or beam set-ups, the GTV D95 receiving less than 95% and even more pronounced, 90% of the prescribed dose, occurred far more often with standard delineation. Reducing high-dose volumes by adding a third beam comes at the cost of a higher probability to miss the target. More importantly, delineation based on clips, seroma and tissue distortion only may be misleading. It may seem paradoxical that underdosing still occurred even after adding the preoperative CT. However, CTV_{clip_CT} was based on a straightforward expansion from the midpoint between clip and preoperative GTV. Such a situation is illustrated in figure 2.

The results invite debate: first, what is the risk of clips inserted randomly in the cavity walls, potentially marking an irrelevant part of the surgical trajectory? Introduction of at least 5 clips improves delineation precision, but may not translate into accuracy. A preoperative MRI may correct for misleading clip location, but is rarely available. Large high-dose volumes reduce uncertainty, but undermine the concept of APBI.

The most intriguing question is how accurate we need to be. In ESBC, omission of radiotherapy has little to no impact on survival[10, 11]. The main goal of radiotherapy in this favourable cohort relies in prevention of relapses, but in favourable breast cancer, radiotherapy has only a limited benefit on local control[1]. Moreover, patients may relapse despite WBI. Where surgeons' results are exposed in pathological reports, target miss in

radiotherapy is obscured by the low recurrence probabilities of ESBC. Do low relapse rates justify additional imaging for improving target coverage when APBI is aimed for, or can we allow a more liberal approach, either by increasing the volume to compensate for uncertainty or by accepting the odds of failure? If target coverage is the primary goal, large volumes will do, but WBI would bring even more security for an overall small cost in toxicity. If reduction of toxicity and improvement of aesthetic outcome are pursued, dedicated preoperative imaging seems needed to avoid fails in target coverage. The introduction of an indicatorclip may suffice to improve boost-delineation, but is in our view an insufficient compromise for APBI.

A preoperative CT in treatment position does come at a cost. If APBI is aimed for, introducing this additional step into the treatment process requires an optimal coordination between the radiology, surgery and radiotherapy departments. In only 70% of the patients enrolled in our study the preoperative images could be used for target delineation, which is lower than the 86% of fusible (supine) CT-scans observed by Boersma et al[16]. Censoring was in all cases due to upstaging of the disease. Upstaging has also been reported in the TARGIT trial and ELIOT trial. Pre-operative imaging may be redundant if APBI is replaced by WBI, but not useless, as upstaging will often require a tumourbed boost.

Some additional cautionary remarks must be made. As tumour spread is not spherical and can be located eccentrically in the resection specimen, Bartelink et al. have suggested asymmetric application of histopathologic resection margins for expansion to CTV[20]. However, in view of the disappointing results of a breast specimen orientation exercise by Molina et al., symmetric expansion minus the minimal margin was estimated a safer option[21]. Asymmetrical expansion may further reduce CTV_{clip} volumes, but potentially at the cost of accuracy. The impact of an indicatorclip and preoperative imaging was only tested in prone position, and cannot be translated to supine. The number of patients was kept low intentionally, as this was only a feasibility trial exploring the prerequisites for safe EB-APBI. Non-palpable tumours were located by harpoon instead of contrast, which in retrospect increased uncertainty. With small tumours being the primary indication for APBI, combining both techniques could have brought additional insight in the value of harpoon-based GTV localization. The study was single-centre. All observers were familiar with tumourbed delineation based on standard guidelines, not with the new procedure, including fusion with preoperative CT for GTV delineation. However, increased experience would probably have further favoured the experimental arm.

In conclusion, if EB-APBI in prone position is aimed for, an indicatorclip clearly intended to mark the depth of the tumour increases the probability of covering the primary tumour location, but cannot entirely replace the additional value of a preoperative CT in treatment position. Avoiding the cost and effort of such a preoperative CT, implies accepting a risk of missing the target, especially when small volumes are aimed for. Increasing target volumes may reduce this risk, but questions the concept of APBI. With shorter treatment schedules and lower costs of EB-APBI compared to WBI[22], adding a preoperative CT may be considered a marginal expenditure for improving accuracy.

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Conflicts of interest

L. Oltéanu, W. De Gersem, T. Vercauteren, T. Mulliez, T. Van Den Broecke, H. Depypere and Y. Lievens have nothing to disclose. W. De Neve reports grants from Think pink and from Kom Op Tegen Kanker, during the conduct of the study.

TABLES

Table 1: Patient, tumour and treatment characteristics.

	Included patients									
Localizer	**Patient**	**Histology**		**Clinical diameter (mm)**	**Pathological diameter (mm)**	**Minimal margin (mm)**	**Chemo therapy**	**Number of clips**	**Deep clip?**	**Distance tumour/thoracic wall ³ 3cm?**
Contrast	**1**	**NST**	**2**	**10**	**11**	**3**	**No**	**5**	**yes**	**yes**
	2	**NST**	**3**	**27**	**30**	**10**	**Yes**	**4**	**yes**	**yes**
	5	**Pl_lobul**	**2**	**13**	**14**	**4**	**No**	**5**	**yes**	**yes**
	8	**NST**	**1**	**12**	**8**	**3**	**No**	**3**	**yes**	**no**
	3	**Lobular**	**1**	**9**	**5**	**4**	**No**	**5**	**yes**	**no**
	4	**NST**	**2**	**6**	**11**	**4**	**No**	**5**	**yes**	**yes**
	6	**NST**	**3**	**16**	**18**	**0**	**No**	**4**	**no**	**yes**
Harpoon	**7**	**NST**	**2**	**7**	**10**	**4**	**No**	**4**	**yes**	**no**
	9	**NST**	**1**	**12**	**8**	**7**	**No**	**1**	**no**	**yes**
	10	**NST**	**1**	**3**	**5**	**3**	**No**	**1**	**no**	**yes**
	11	**NST**	**2**	**8**	**8**	**1**	**No**	**4**	**no**	**yes**
	12	**Lobular**	**2**	**12**	**1**	**3**	**No**	**6**	**no**	**no**

Abbreviations: NST = non special type (invasive ductal type). Pl_lobul = Pleiomorph lobular carcinoma

Table 2: Comparison of delineation methods following standard guidelines versus a delineation based on an indicatorclip only or in combination with a preoperative CT in treatment position.

	Measurements Mean (CI_{95})	**GTV**	**$CTV_{standard}$**	**CTV_{clip}**	**CTV_{clip_CT}**
	Volume (cc)	**2.1 (0.5-3.7)**	**17.0 (11.4-22.4)**	**29.1 (22.0-36.1)**	**29.0 (22.0-36.1)**
Precision	**CI_{pairs}**	**0.47 (0.47-0.60)**	**0,38 (0,32-0,44)**	**0,75 (0,61-0,89)**	**0.59 (0.52-0.65)**
Accuracy	**OC (GTV vs CTV)**	**-**	**0.48 (0.31-0.66)**	**0.67 (0.43-0.91)**	**0.88 (0.81-0.96)**

Table 3: Dosimetric results comparing different delineation methods and beam set-up.

Mean (CI_{95})	Standard guidelines		Clip based		Clip & preoperative CT	
	2 beam	3 beam	2 beam	3 beam	2 beam	3 beam
Breast volume (cc)	787,6 (518.7-1056.5)					
Off target breast volume (mean, cc)	603.2 (369.8-836.5)		588.7 (349.8-836.5)		707.6 (419.4-995.7)	
GTV D95 (mean, Gy) p = NS	24.7 (20.0-29.3)	24.5 (20.4-28.6)	26.1 (23.1-29.2)	25.1 (21.2-29.0)	27.7 (25.9-28.7)	27.7 (27.0-28.4)
GTV D95 < 95% dose (number of pt)	4	5	2	5	2	2
GTV D95 < 90% dose (number of pt)	4	5	2	3	1	1
Breast tissue < 20Gy (mean, %) p<0.05	74,4 (70.8-78.0)	77.4 (73.4-81.4)	69.8 (63.9-75.8)	72.6 (66.9-78.3)	71.3 (64.9-77.8)	73.8 (67.0-80.5)
Breast tissue <5Gy (mean, %) p<0.05	61.3 (55.8-66.8)	54.5 (48.3-60.6)	58.7 (50.0-67.3)	54.2 (46.1-62.2)	59.1 (50.5-67.7)	54.3 (45.3-63.8)

FIGURES

Figure 1: Illustration of situation with non-informative postoperative clips.

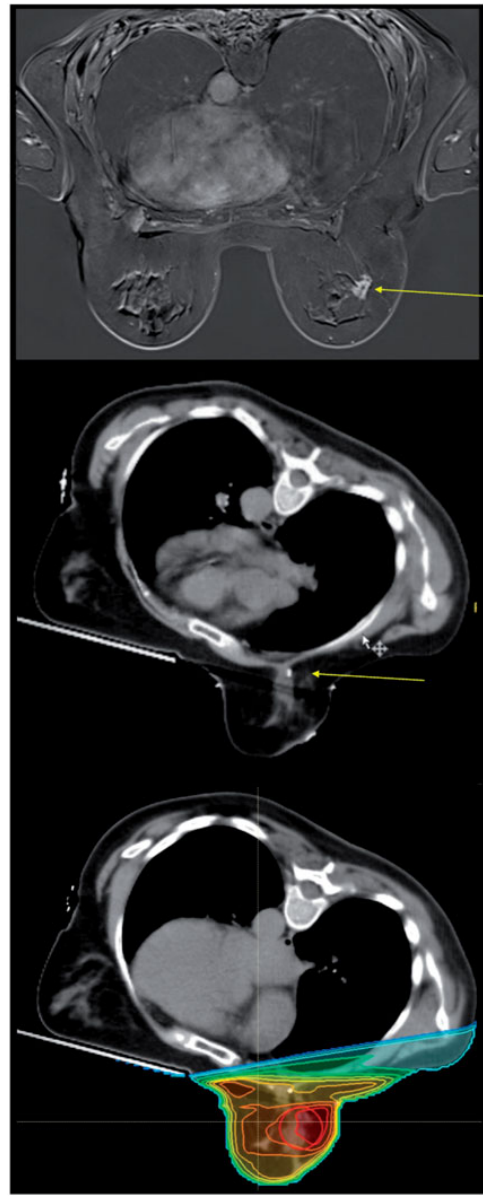
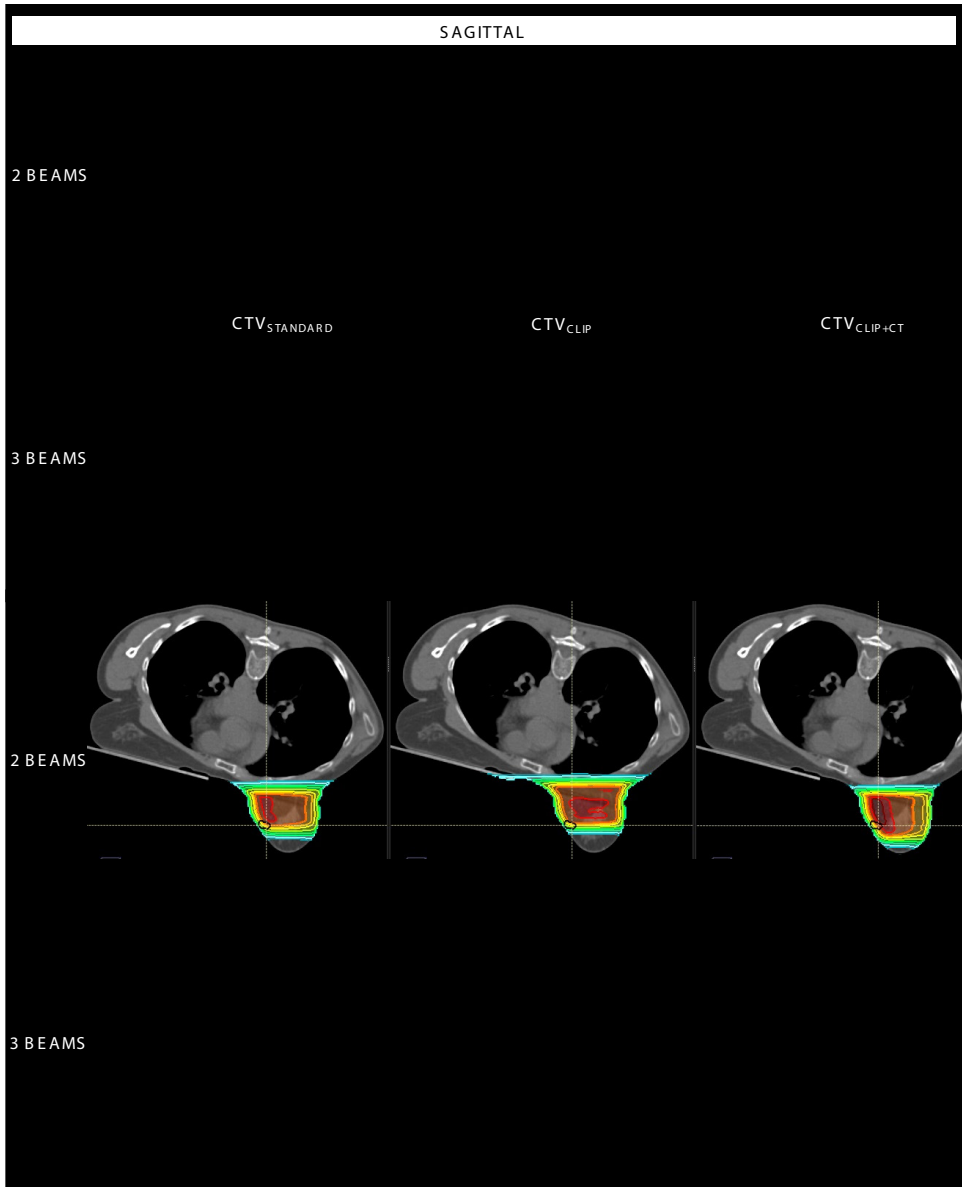


Illustration of a patient with preoperative MRI indicating a tumour location distant from the thoracic wall. However, on postoperative simulation CT all clips were located close to the thoracic wall. For tumourbed delineation (WBI plan with SIB) none of the clips were enclosed. Abbreviations: WBI – whole breast irradiation; SIB – simultaneously integrated boost

Figure 2: Illustration of dosimetry in a worst-case GTV-coverage



Dosimetry in patient with despite a pT1a tumour (1mm diameter), the worst coverage result of GTV (black), which is located very medially and more peripherally in the breast than estimated by clips and tissue distortion. Two additional resection specimen had been excised perioperatively, on CT only one clip was left behind. A CT-slice including the GTV is chosen for illustration. In this patient, CTVstandard and CTVclip did not overlap with GTV (distance between indicatorclip and GTV was 23mm), whereas an overlap ratio of 0.67 was reached for CTVclip_CT. GTV D95 is respectively 17.7Gy, 16.5Gy and 20.6Gy for 2-beam set-up and 20.0Gy, 11.9Gy and 24.8Gy for 3-beam set-up.

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Publication 2 –

Highly Accelerated Irradiation in 5 Fractions (HAI-5): Feasibility in Elderly women with early or locally advanced stage breast cancer. Published.

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Authors: Chris Monten, MD[1]; Yolande Lievens, MD, PhD[1]; Luiza Ana Maria Olteanu, MSc[1]; Leen Paelinck, PhD[1]; Bruno Speleers[1]; Pieter Deseyne, MD[1]; Rudy Van Den Broecke, MD, PhD[2]; Wilfried De Neve, MD, PhD[1]; Liv Veldeman, MD, PhD[1]
[1]Department of Radiation Oncology, Ghent University Hospital, Belgium
[2]Department of Obstetrics and Gynaecology, Ghent University Hospital, Belgium

Running title
Accelerated breast irradiation in elderly women

Key words
Radiotherapy; breast cancer; tumour bed delineation

Abstract

Rationale More than 50% of breast cancer cases occur in women aged 65 years or more. Adjuvant radiotherapy improves local control and overall survival, but is often omitted in older women because of concerns over treatment burden or logistical obstacles, even in poor prognostic groups. Accelerated radiotherapy might be an alternative to overcome these obstacles, at the condition of technical feasibility and acceptable toxicity in this frailer patient population.

Research question In this prospective phase I-II trial, we investigated the safety and feasibility of delivering external beam radiotherapy in 5 fractions to the breast or thoracic wall, including boost and/or lymph nodes if needed.

Methods Ninety-five patients aged 65 years or more, referred for adjuvant radiotherapy, were treated in 5 fractions over 12 days with a total dose of 28.5Gy/5.7Gy to the breast or thoracic wall and, if indicated, 27Gy/5.4Gy to the lymph node regions and 32.5Gy/6.5Gy-34.5Gy/6.9Gy to the tumour bed. The primary endpoint was clinically relevant dermatitis (≥ grade 2).

Results Mean follow-up time was 5.6 months and mean age was 73.6 years. Clinically relevant dermatitis was observed in 11.6% of patients and only occurred in breast irradiation with boost (17.5% grade 2-3 versus 0% in the no-boost group). Although doses were high, treatment delivery with IMRT was swift, except for complex treatments including lymph nodes where single-arc VMAT was needed to reduce beam-on time.

Conclusion Accelerated radiotherapy in 5 fractions was technically feasible and resulted in low acute toxicity. Clinically relevant erythema was only observed in patients receiving a boost, but still at an acceptable rate.

Implications/application Although the follow-up is still short, the results on acute toxicity after accelerated radiotherapy were encouraging. A 5-fraction schedule is well tolerated in the elderly and may lower the threshold for radiotherapy in this population.

Introduction

Breast cancer is the most frequent cancer type worldwide: with an incidence of 1,677,000 cases annually it represents 11.9% of all cancers diagnosed[1]. Along with an evidence-based indication for radiotherapy of 87%, it is the cancer type with the highest radiotherapy needs globally. Radiotherapy plays an important role in local control, but also improves survival[2-4]. Whereas optimal access to radiotherapy is a precondition to obtain these clinical benefits, substantial gaps in radiotherapy access exist, not only in low- and middle-income countries where lack of resources may be the dominating factor, but even in regions with a higher welfare such as Europe, Canada and Australia[5-8]. In these countries, other barriers may determine the observed underutilization, of which age is a well-recognized one[9]. Hence, where advanced age is associated with lower stage and more favorable prognostic outcomes, survival is paradoxically worse compared to younger cohorts, as many patients go undertreated due to factors such as co-morbidity, physician's bias, cost and psychosocial issues[10-12].

In 2007 the International Society of Geriatric Oncology (SIOG) published guidelines recommending patients over 70 years be treated according to standard guidelines, with exceptions for cases with significant co-morbidity or low functional status[13]. However, radiotherapy, chemotherapy and hormonal therapy continue to be offered less frequently to patients of advancing age, resulting in higher mortality for early stage breast cancer[14, 15].

Although increase of co-morbidity and frailty is a gradual process, no uniform age threshold can be found for the decline in adherence to treatment guidelines, suggesting a psychological trigger rather than purely physiological considerations[12]. The most negative effect on overall survival and disease-specific survival is observed for radiotherapy[16, 17], especially in hormone receptor negative breast cancer, where omission of radiotherapy results in higher numbers of deaths from breast cancer than from cardiovascular disease, even in the age group over 80 years[18].

Living far from radiation facilities or having insufficient insurance coverage are established obstacles to receiving radiotherapy[19-21]. Yet, even in countries with adequate social security and wide availability of radiotherapy facilities, uptake decreases with age[9]. Although radiotherapy treatment for breast cancer has moved towards hypo-fractionation as the new gold standard, older patients still remain reluctant to undergo radiotherapy.

For elderly patients with very early stage breast cancer, single fraction intra-operative techniques may lower the threshold of access to radiotherapy[22, 23] or radiotherapy can even be omitted[24, 25]. This is not the case in locally advanced stages or when poor prognostic characteristics are present[25, 26] and whole breast irradiation (WBI) or thoracic wall irradiation (TWI) along with lymph node irradiation (LNI) are indicated. In these cases, accelerated delivery in 5 fractions may overcome resistance to adequate loco-regional treatment, provided it does not come at the cost of higher toxicity in this frail subset of the population. External beam radiotherapy (EBRT) for WBI in 5 fractions has been tested in several studies, yet little remains known about acceleration for TWI, or in case lymph nodes should be included or a boost added[27-31].

In preparation for a randomized controlled trial comparing 5 to 15 fractions over 10 or 15 days, a phase I-II study was performed, including all breast cancer stages in women of 65 years of age and over.

This paper reports on the feasibility of accelerated radiotherapy to the breast, thoracic wall and lymph nodes and on the first clinical results, more specifically on acute toxicity.

Materials and Methods

Patient selection

All female patients of 65 years or older, referred for adjuvant radiotherapy after breast cancer surgery – breast-conserving or mastectomy - were offered the study protocol and included after signing the informed consent, approved by the ethics committee of our institution. The exclusion criteria were the need for bilateral breast irradiation or re-irradiation, or the need for boost after mastectomy.

Image acquisition

Patients were simulated on a large bore Toshiba CT, with intravenous injection of contrast (Visipaque, 100cc) in case of LNI and if not contra-indicated. Prone positioning was offered if WBI +/- simultaneously integrated boost (SIB) without LNI was prescribed[32]. TWI and LNI were performed in a supine position.

Target volumes and doses

Target volumes and organs at risk (OARs) were delineated according to standard guidelines[33-35]. If the ratio of positive over resected lymph nodes was below 40%, LNI included axillary level 2-4. If 40% or more of resected lymph nodes proved pathologically invaded by tumour, level 1 was added to the target[36]. The internal mammary chain was never included. Target doses were prescribed at the D50, and consisted of 28.5Gy/5.7Gy for WBI or TWI and 27Gy/5.4Gy for the lymph node regions. If indicated according to our hospital's guidelines, a SIB of 32.5Gy/6.5Gy was delivered and increased to 34.5Gy/6.9Gy in case of positive resection margins (Figure 1).

Equivalent doses in 2Gy fractions were calculated using an α/β ranging between 2.8-4.6Gy[37-40] for breast tumour and breast toxicity, resulting in an EQD2 range of 44.5-50.5Gy for the breast or thoracic wall (5x5.7Gy) and 54.7-63Gy for the boost dose (5x6.5Gy). For cases with involved margins, the resulting EQD2 for the boost was 60.1-69.7Gy.

For the lymph node regions, a compromise was chosen between a high enough dose for tumour control and avoidance of any brachial plexopathy. With an α/β of 1.5Gy, a schedule of 27Gy/5.4Gy results in an EQD2 of 53.2Gy, far below the limit of 66Gy and below the maximum doses reported for stereotactic radiotherapy[41-43]. Applying the α/β of 2.8-4.6Gy, lymph node dose resulted in an acceptable EQD2 of 40.9-46.1Gy for breast tumour control.

Planning parameters and treatment techniques

The optimal irradiation plan was calculated using software developed at Ghent University Hospital (GUH) and integrated into the GRATISTM 3D-planning system (developed by G.W. Sherouse). Treatment was delivered with step and shoot intensity-modulated radiotherapy (IMRT). For WBI administered in the prone position, tangential field-IMRT (TF-IMRT) was sufficient to obtain qualitative dosimetry. In the supine position, multi-beam-IMRT (MB-IMRT) was used to increase dose homogeneity and to reduce dose to the OARs[44]. SIB always required MB-IMRT (or volumetric modulated arc therapy - VMAT), in some cases with non-coplanar beams. MB-IMRT or VMAT was used in cases involving LNI to obtain adequate coverage of the breast, boost and lymph nodes, without the need for field matching. Simultaneous delivery of the prescribed dose to all target volumes was chosen to avoid any risk of overlap, especially in the region of the brachial plexus.

VMAT was preferred over IMRT and concatenated into one or two arcs when MB-IMRT resulted in a high number of gantry positions with a long beam-on time. This method reduced the delivery time of simultaneously 5.7Gy, 5.4Gy and 6.5Gy from 8-12 minutes to 3-4 minutes per fraction. Breath-hold for left-sided prone irradiation has not yet been introduced, because a longer bream-on time in patients with compromised mobility and reduced breath-hold capacity had not been tested before accrual started.

The dose was prescribed to the planning target volume (PTV, 7mm margin from CTV). For the OARs, the constraints of Benedict et al.[41] were respected for heart, lungs, ribs, esophagus, trachea and brachial plexus. A V20 with normofractionation was translated to a V13<20% (α/β of 2-3Gy)[45] to avoid acute pneumonitis in the ipsilateral lung. Contralateral breast doses were kept as low as possible, but in cases of conflict between heart/lung dose versus contralateral breast, the heart was given priority for these elderly patients. In LNI cases, the brachial plexus was contoured in order to have correct estimates of the doses delivered to the plexus[35].

Treatment delivery schedule

Radiation treatment was delivered over 12 days, on week days only, with an interval of at least one day between 2 fractions (e.g. Tuesday – Thursday – Monday – Wednesday – Friday). Each fraction was preceded by CBCT positioning verification.

Outcome evaluation

Dermatitis was evaluated using the CTCAE v.4.03 toxicity score, with measurement before, during and 2-4 weeks after radiotherapy. Desquamation was scored as none, dry or moist. Edema, pain, pruritus and fatigue were also registered. The worst score registered for each item was reported. Determination of the time point for evaluation of acute toxicity was based on evidence from the Fast-Forward Trial, describing highest prevalence of grade 2-3 toxicity at 1-4 weeks after the start of treatment[29].

Long-term follow-up in the radiotherapy department was limited to 6 months in the first year and every twelve months thereafter in order to limit the additional burden of consultations in this specific patient group.

Statistics

The population was divided into two independent strata for sample size calculation – one without and one with LNI.

The Wilson Confidence Interval for binomial proportion was applied, a 2-sided exact method for power analysis, using the "SAS Power and Sample Size" routine. To obtain a conditional probability of 95% with an alpha-error of 0.05, a total of 50 patients was needed in the WBI-only group and 45 patients in the LNI included group, allowing for 10% drop out.

Acceleration was considered acceptable if acute moist desquamation stayed below 20% for the "no LNI" group and 35% for the "LNI" group.

A stopping rule was included, discontinuing recruitment in the 'LNI' arm if EMG-confirmed radiation induced brachial plexopathy (RIBP) would occur in 2 of the first 10 patients, or in 3 patients overall.

Results

Patient characteristics

Ninety-five patients were included in this analysis. Characteristics of patients, tumour and treatment are described in Table 1. Mean age was 73.6 years, with 65% of patients above 70 years. Two patients had not reached 65 years at the time of inclusion. The mean follow-up time was 5.6 months.

Forty-five percent of patients were diagnosed with early (stage I) breast cancer, 35% with stage II and 20% with stage III or locally-advanced. Poor prognostic subtyping was found in 45% of patients, with 9.5% 'triple negative' and 35.8% Luminal B type. Hormone-negative disease was found in 17 patients (17.9%), of whom 7 did not receive any chemotherapy. In 16 patients HER2 was amplified. In 6 of these patients Trastuzumab was not started. Seventy-eight patients tested positive for ER and/or PR, two of whom did not receive any anti-hormonal therapy. Because the population was limited to patients referred for adjuvant radiotherapy, no data can be derived on percentage of indications for whom radiotherapy was omitted.

One patient with triple-negative advanced stage breast cancer died due to loco-regional recurrence and distant metastasis, diagnosed 6 months after radiotherapy. All other patients remained without relapse.

Overall, prone irradiation was an option in 54 patients (WBI without LNI) of whom 37 (11 above 75 years) were amenable to prone positioning.

Dosimetric results

Good accordance of planning to dosimetry constraints was found except for TWI and LNI, where underdosing of D95 of PTV was observed. Results including doses to target and to OARs are reported in Table 2. In the 22 left-sided WBI patients, a reduction of heart dose and ipsilateral lung dose was observed for prone versus supine, without use of any breath-holding technique ($p < 0.001$, Mann-Whitney U test). The boxplot distribution is shown in Figure 3.

Heart and ipsilateral lung dose increased significantly when LNI was applied. For the ipsilateral lung, Dmean increased from 1.5Gy without LNI ($p < 0.001$) to 5.3Gy with LNI, and the V13Gy from 2.9% to 15.1% ($p < 0.001$). In left-sided treatment, Dmean for the heart increased from 1.3Gy without LNI to 2.2Gy with LNI ($p < 0.001$) and heart D2 similarly increased from 7.1Gy to 14.2Gy ($p <0.001$).

Acute toxicity

Grade 3 dermatitis was observed in one patient (WBI + SIB + LNI in supine position) who developed a small zone of moist desquamation in the inframammary fold shortly

after radiotherapy. A second patient developed an intense grade 2 dermatitis, covering the entire breast. In all other patients, grade 2 dermatitis was less pronounced.

As dermatitis and desquamation were uncommon, we aggregated grades into a subclinical group (grade 0-1) and a clinical group (grade 2-3) before evaluating the impact of variables on the occurrence of acute toxicity. Applying Fisher's exact test, no statistically significant relation could be found between patient, tumour and treatment characteristics and toxicity, except for boost versus no boost (17.4% vs. 0%, p=0.01). Clinically relevant toxicity occurred only in the group with boost (Figure 2, Table 3).

No symptoms indicating RIBP have been registered so far, but the follow-up time is still very short.

Discussion

Undertreatment in the older population impacts local control and disease free survival, especially in the intermediate and high risk groups[16, 18]. Acceleration to 5 fractions in less than 2 weeks may possibly overcome resistance to adjuvant radiotherapy. However, the feasibility and safety of accelerated treatment need validation before applying these schedules beyond clinical trials. Since many patients present with advanced tumour stages, this trial was conceived to test acceleration for all indications, including SIB, TWI and LNI.

In 2005, Ortholan et al. reported on weekly hypofractionated WBI (71.5%) and TWI (28.5%) in 150 patients above 70 years[27]. In 73.5% of patients, no dermatitis was observed and it was limited to grade 1 and grade 2 in 18.6% and 9.4% respectively. These results are superior to our trial (52.6% of grade 1 dermatitis for WBI and TWI combined) despite a comparable WBI vs. TWI ratio. Our shorter delivery time may have impacted toxicity. However, toxicity scales differed, with possibly an upward shift of faint erythema towards grade 1 with the CTCAE toxicity scale. By comparison, the FAST Forward Trial switched from RTOG to CTCAE toxicity scale during the trial, with similar results for CTCAE-scored grade 1 toxicity compared to our trial (63% and 58% grade 1 dermatitis for 27Gy/5.4Gy and 26Gy/5,2Gy respectively)[29, 46].

Kirova et al. (2009) retrospectively compared an accelerated weekly schedule (32.5Gy/6.5Gy) with normofractionation in elderly patients and reported reassuring loco-regional control and cause-specific survival[28]. Groups were not equally balanced for age, performance status, tumour size or presence of lymph node dissection, disfavoring the accelerated schedule. LNI and boost were limited to the normofractionation group. Nevertheless, five-year results were equivalent. A worse cause-specific survival at 7 years did not depend on the treatment schedule. Only lymph node status, hormonal receptors and mitotic index were retained as independent prognostic factors. RTOG acute toxicity scores were similar for both groups.

A retrospective analysis of acceleration to five fractions by Rovea et al. (32.5Gy/6.5Gy or 30Gy/6Gy weekly) showed no toxicity in 71.8% and grade 1 in 22.6% of patients with only 6.1% clinically relevant dermatitis, lower than in our breast-only subgroup (14.8%) but again these were scored with the RTOG/EORTC toxicity criteria[31].

In the FAST-Forward Trial delivery was accelerated to 5 days, with WBI delivered daily in 5x5.2Gy or 5.4Gy. RTOG grade 3 acute toxicity appeared in 5.6-9.8% of patients (26-27Gy) and CTCAE grade 3 toxicity in 2.4-0% respectively. These results are in line with our findings (1.1% grade 3 toxicity). Grade 1 and 2 dermatitis were 63% and 27% respectively, which is comparable to our 53.7% and 14.8% in the WBI +/- SIB group.

In our study, overall acute toxicity remained low (11.6% clinically relevant dermatitis) and was limited to patients with SIB. Only one patient developed moist desquamation, located in the inframammary fold. Using a strict interpretation of the CTCAE criteria, this is a grade 2 toxicity, as the inframammary fold can be categorized as 'skin fold'. The region did not correlate with a 'hot spot' but with the location of tangential beam incidence resulting in skin scraping and loss of dose build-up.

Older patients referred for radiotherapy often present with locally-advanced breast cancer, needing LNI. IMRT or VMAT permit simultaneous delivery of different doses with avoidance of field overlap. In 2000, Johansson reported on long term RIBP after hypofractionation for breast cancer. His analysis showed higher doses to the brachial plexus than intended due to positioning problems. Ten years earlier, Powell compared hypofractionation 45Gy/3Gy with 54Gy/1.8Gy using a 3- or 4-field technique[42, 47]. Both reported that

larger daily fractions (3-4Gy) to doses of 44-54Gy were associated with RIBP. Whereas Johansson clearly described overlap problems leading to unwanted high total doses, Powell seemed confident that this is not possible with a 4-field technique. RIBP is described as a slow process over a latency period of 1 to 4 years, continuing even after 5 years[48]. So far no RIBP occurred in our study, but the results are still very preliminary[49]. Although 27Gy/5.4Gy is gentler in terms of BED and EQD2 (α/β = 1.5-2Gy), follow-up with active questioning for sensory or motor nerve damage will further screen for RIBP[50].

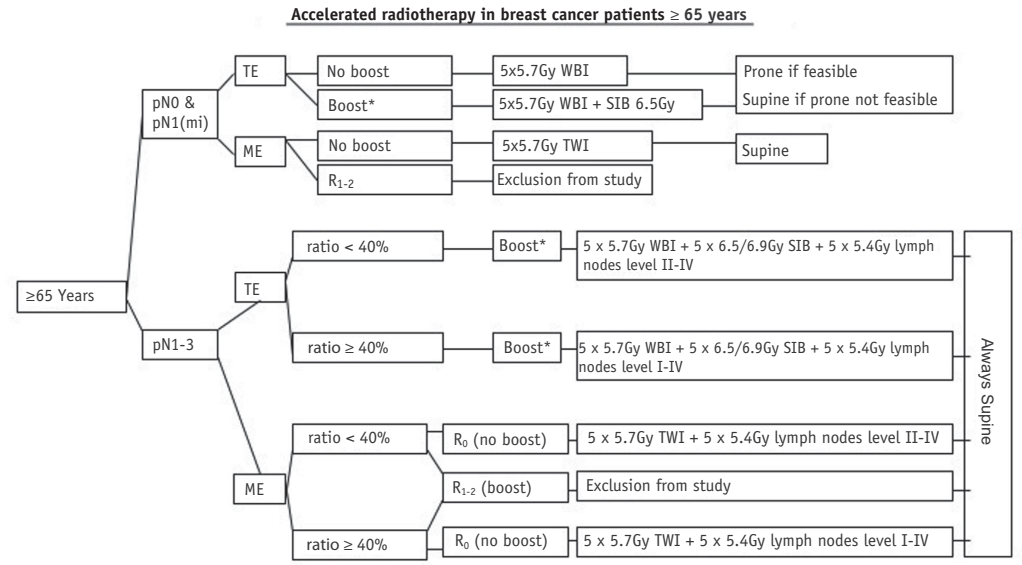
Dosimetric results were satisfying. For left sided irradiation including LNI, the heart Dmean of 1.8Gy stayed far below the dose reported in a recent review, describing a Dmean 5.6Gy for this situation[51]. Breath-hold techniques to further lower heart dose were not yet introduced because this has not yet been validated technically.

This feasibility trial precedes a randomized trial that will compare efficacy and toxicity of 5 versus 15 fractions. Tumour bed boost dose will be lowered in the upcoming trial in answer to the observed increased toxicity in the boost group.

In conclusion, accelerated delivery of adjuvant radiotherapy for breast cancer in 5 fractions is feasible and does not appear to increase acute toxicity compared to published data on normo- or moderate hypofractionation. The effects on loco-regional control and chronic toxicity will be further analyzed in a planned randomized controlled trial comparing 5 with 15 fractions.

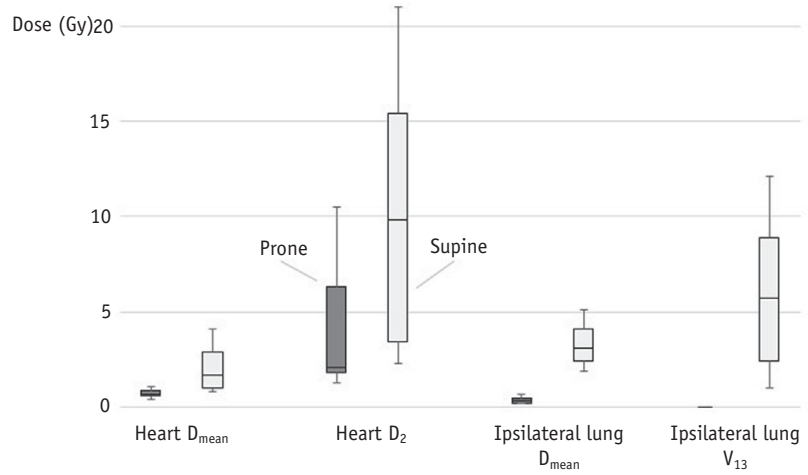
FIGURES

Figure 1: Inclusion flowchart



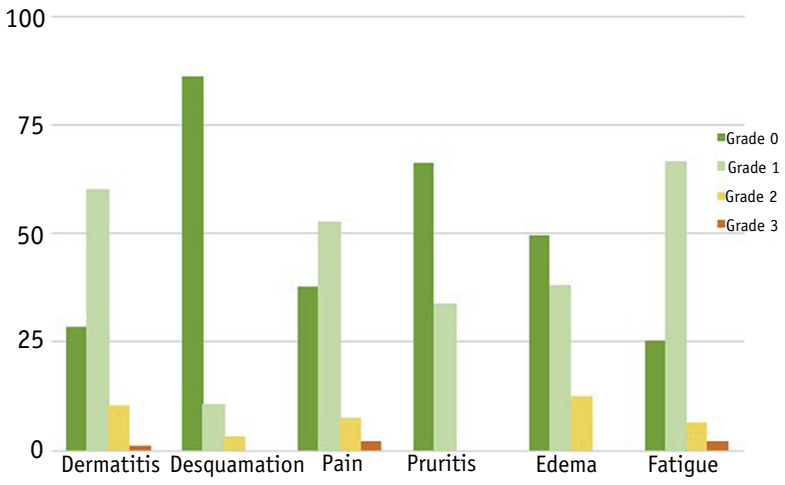
In-house decisional tree for target and dose prescription in accelerated schedule. Inclusion is based on hospital guidelines for adjuvant radiotherapy.

Figure 2: Boxplot illustrating the effect of position on heart and lung dose



Prone positioning significantly reduced heart and lung dose. The boxplot illustrates the mean, minimum, maximum, 25% and 75% doses to heart (Dmean and D2) and ipsilateral lung (Dmean and V13) for patients with left sided WBI +/- SIB (no LNI), treated in prone (n=11) or supine (n=11) position. For the ipsilateral lung, the maximum percentage of volume receiving 13Gy (V13Gy) was 0.6% in prone (to small for visualization).

Figure 3: Toxicity



Highest grade toxicity occurring during treatment or in the first weeks after radiotherapy (percentage).

TABLES

Table 1: Patient and tumour characteristics

Characteristic	n	%
Patient characteristics (n = 95)		
Age category (y)		
≤70	33	34.7
71-75	24	25.3
76-80	25	26.3
81-85	10	10.5
≥86-90	3	3.2
Tumor characteristics		
Histology		
Ductal type	78	82.1
Lobular type	13	13.7
Mucinous	3	3.2
Mixed ductal–lobular	1	1.1
ER status		
Positive	76	80
Negative	19	20
PR status		
Positive	71	74.7
Negative	24	25.3
Tumor stage		
Stage I (T1N0 or N1mi)	43	45.3
Stage II (T1N1, T2N0-1, T3N0)	33	34.7
Stage III (T3N1, T1-3N2, T4N0-3)	19	20
IHC subtype		
Luminal A (ER and/or PR pos, Ki67 <14%)	34	35.8
Luminal B (ER and/PR pos, Ki67 >14%)	34	35.8
Luminal Her2 (ER and/or PR pos, HER2 pos)	10	10.5
HER2 (ER neg, HER2 pos)	6	6.3
Triple negative	9	9.5
Unknown	2	2.1

Abbreviations: ER = estrogen receptor; IHC = immunohistochemistry; pos = positive; PR = progesterone receptor.

Table 2: Dose characteristics for target and OARs

No LNI	Prone				
	WBI - SIB				
	Number of patients		n = 32		
	Dosimetric parameters	D_{mean} (Gy)	D_{95} (Gy)	D_2 (Gy)	V_{13} *(%)*
	Total dose	29.6 (28.9-31.1)	27.7 (27.1-28.5)	33.1 (32.5-34.2)	NA
	Heart*	0.8 (0.4-1.8)	NA	4.5 (1.3-20.0)	NA
	Ipsilateral lung	0.6 (0.2-1.9)	NA	NA	0.6 (0-5.7)
	WBI - No SIB				
	Number of patients		n = 5		
	Dosimetric parameters	D_{mean} (Gy)	D_{95} (Gy)	D_2 (Gy)	V_{13} (%)
	Total dose	28.6 (28.6-28.7)	27.5 (27.2-27.7)	29.9 (29.7-30.1)	NA
	Heart*	-	-	-	-
	Ipsilateral lung	0.8 (0.3-1.5)	NA	NA	1.3 (0-4.1)
	Supine				
	WBI - SIB				
	Number of patients		n = 13		
	Dosimetric parameters	D_{mean} (Gy)	D_{95} (Gy)	D_2 (Gy)	V_{13} (%)
	Total dose	29.6 (29.2-30.3)	27.6 (27.1-28.3)	33.3 (32.8-33.8)	NA
	Heart*	1.9 (0.8-3.1)	NA	11.1 (2.3-22.8)	NA
	Ipsilateral lung	3.3 (1.9-6.1)	NA	NA	7 (1.0-22.1)
	WBI - No SIB				
	Number of patients		n = 4		
	Dosimetric parameters	D_{mean} (Gy)	D_{95} (Gy)	D_2 (Gy)	V_{13} (%)
	Total dose	28.6 (28.4-28.8)	27.4 (27.0-27.8)	30 (29.7-30.1)	NA
	Heart*	1.2 (1.0-1.4)	NA	3.8 (3.4-4.1)	NA
	Ipsilateral lung	3.3 (3.1-3.4)	NA	NA	7.2 (4.7-9.4)
	TWI - No SIB				
	Number of patients		n = 2		
	Dosimetric parameters	D_{mean} (Gy)	D_{95} (Gy)	D_2 (Gy)	V_{13} (%)
	Total dose	28.5 (28.4-28.8)	27.1 (26.6-27.5)	30.2 (30.0-30.4)	NA
	Heart*	-	NA	-	NA
	Ipsilateral lung	3.2 (2.7-3.7)	NA	NA	8.3 (7.0-9.5)
LNI	Supine				
	WBI - SIB				
	Number of patients		n = 18		
	Dosimetric parameters	D_{mean} (Gy)	D_{95} (Gy)	D_2 (Gy)	V_{13} (%)
	Total dose	29.4 (28.9-30.1)	27 (22.3-28.1)	32.9 (30.5-34.4)	NA
	Heart*	2 (0.9-3.1)	NA	12.9 (3.4-22.2)	NA
	Ipsilateral lung	5.3 (3.0-7.3)	NA	NA	15 (5.3-22.8)
	TWI - no SIB				
	Number of patients		n = 21		
	Dosimetric parameters	D_{mean} (Gy)	D_{95} (Gy)	D_2 (Gy)	V_{13} (%)
	Total dose	28.6 (28.1-29)	26.6(22.1-27.6)	30.5(30.0-31.2)	NA
	Heart*	2.4 (1.1-3.7)	NA	15.1(3.8-26.0)	NA
	Ipsilateral lung	5.4 (2.9-7.0)	NA	NA	15.2 (4.2-23.3)

Abbreviations: LNI = lymph node irradiation; NA = not applicable; SIB = simultaneously integrated boost; TWI = thoracic wall irradiation; WBI = whole-breast irradiation.

Values are mean results (range) of planning target volume dose, heart doses for left-sided treatment only (*), and ipsilateral lung dose and lung volume receiving 13 Gy.

Table 3: Toxicity results

	Prone				Supine			
	SIB		No SIB		SIB		No SIB	
Group	Grade 0-1	Grade 2-3	Grade 0-1	Grade 2-3	Grade 0-1	Grade 2-3	Grade 0-1	Grade 2-3
No LNI								
WBI	27 (84.4)	5 (15.6)	5 (100)	0	10 (76.9)	3 (23.1)	4 (100)	0
TWI	-	-	-	-	-	-	2 (100)	0
With LNI								
WBI	-	-	-	-	15 (83.3)	3 (16.7)	-	-
TWI	-	-	-	-	-	-	21 (100)	0

Abbreviations as in Table 2.

Incidence by number (percentage) of highest-grade dermatitis (Common Terminology Criteria for Adverse Events version 4.03) during or in the first weeks after radiation therapy in relation to target and positioning.

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Publication 3 –
A systematic review of health economic evaluation in adjuvant breast radiotherapy: quality counted by numbers – Accepted

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Authors: Chris Monten[1], Liv Veldeman[1], Nick Verhaeghe[2], Yolande Lievens[1]
[1]Ghent University Hospital, Radiation Oncology Department, Ghent, Belgium
[2]Ghent University, Department of Public Health, Ghent, Belgium

Running title
Quality of HEE in adjuvant breast radiotherapy

Key words
Health economic evaluation, Breast cancer, Radiotherapy, Cost effectiveness analysis, Cost comparison, Quality evaluation

Abstract

Background Evolving practice in adjuvant breast radiotherapy inevitably impacts healthcare budgets. This is reflected in a rise of health economic evaluations (HEE) in this domain. The available HEE literature was analysed qualitatively and quantitatively, using available instruments.

Methods HEEs published between 1/1/2000 and 31/10/2016 were retrieved through a systematic search in Medline, Cochrane and Embase. A quality-assessment using CHEERS (Consolidated Health Economic Evaluation Reporting Standards) was translated into a quantitative score and compared with Tufts Medical Centre CEA registry and Quality in Health Economic Studies (QHES) results.

Results Twenty cost-effectiveness analyses (CEA) and thirteen cost comparisons (CC) were analysed. In qualitative evaluation, valuation or justification of data sources, population heterogeneity and discussion on generalizability, in addition to declaration on fund-

ing, were often absent or incomplete. After quantification, the average CHEERS-scores were 74% (CI 66.9-81.1%) and 75.6% (CI 70.7-80.5%) for CEAs and CCs respectively. CEA-scores did not differ significantly from Tufts and QHES-scores.

Conclusion Quantitative CHEERS evaluation is feasible and yields comparable results to validated instruments. HEE in adjuvant breast radiotherapy is of acceptable quality, however, further efforts are needed to improve comprehensive reporting of all data, indispensable for assessing relevance, reliability and generalizability of results.

Introduction

In adjuvant breast radiotherapy, the past two decades brought important treatment changes: the use of hypofractionation in the context of breast-conserving treatment has been established[1, 2] and new techniques and technologies for per- and postoperative irradiation were introduced such as intensity-modulated radiotherapy (IMRT), partial breast irradiation and intra-operative radiotherapy approaches[3, 4]. Breast cancer being the second most common cancer type worldwide[5] and the most frequent indication for radiotherapy[6, 7], such evolutions will inherently have an impact on healthcare budgets.

Indeed, increasing possibilities in medicine typically come with increasing costs and put healthcare budgets under strain[8]. Healthcare policy deals with allocation and re-allocation of the available financial means, according to the principles of communicating vessels – each expenditure precludes expenses in other healthcare domains. The methodology applied to analyse if new interventions or strategies are worthwhile from an economic point of view, is referred to as health economic evaluation (HEE). Not surprisingly, the interest for HEEs has increased considerably over the last decades, as can be observed by a simple PubMed search, showing an evolution from a few HEE publications annually in the seventies until over 1500 per year today. HEE encompasses different techniques and concepts. In short, whereas cost comparison (CC) is limited to the costs of standard versus new strategies, cost-effectiveness analysis (CEA) relates a change in costs (i.e. incremental cost) to the difference in health effects, expressed in natural units such as life years gained. In case of a cost utility analysis (CUA), the difference in health effect is expressed as quality adjusted life years gained. The perspective of HEE indicates from which viewpoint costs are calculated (provider, payer, patient or society). The type of costs can be based on the real costs of the resources used (materials, labour activities, infrastructure, overhead…) or on reimbursement or charges.

Transparency of reporting is a fundamental element to evaluate quality, reliability, relevance and generalizability of HEE results. To address this question, quality checklists guide researchers as well as editors towards qualitative HEEs. The 'Drummond', the 'British Medical Journal' and the 'Consensus on Health Economic Criteria' checklists are well-known instruments for qualitative evaluation[9-11]. In 2013, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force published the

Consolidated Health Economic Evaluation Reporting Standards statement (CHEERS), with the objective to further standardize reporting of economic evaluations[12]. Although not intended for quantification, its structure predisposes to ranking, as has been undertaken for the first time by Mangham-Jefferies et al.[13]. In contrast, the Quality of Health Economic Studies (QHES) and Tufts Medical Centre scores are instruments intended and validated for quantitative benchmarking[14, 15].

We performed a qualitative and quantitative evaluation of HEE publications focusing on adjuvant breast radiotherapy, retrieved through a systematic literature review. CHEERS was used for quality evaluation and subsequently applied as a quantitative scoring system, of which the results were compared with Tufts and QHES evaluation. This article reports on the results of this qualitative and quantitative evaluation and comparison, and describes remaining shortcomings and methodological questions in the available literature of HEE in adjuvant breast radiotherapy.

Materials & Methods

Systematic literature review

A systematic literature review was performed, according to PRISMA guidelines (2009, www.prisma-statement.org). Medline, Embase and Cochrane libraries were searched for publications on HEE in adjuvant breast radiotherapy, published between 1/1/2000 and 30/11/2016. A detailed description of the search strategy can be found in appendix 1.

After removal of duplicates, titles were screened for referral to either economic aspects or adjuvant breast cancer irradiation. Subsequent abstract screening was based on presence of both aspects. Final selection required comparison of different radiotherapy strategies in adjuvant breast cancer, specifying radiotherapy cost either as a result of a real costing exercise or of reimbursement/charges. Only original articles and health technology assessments were included and underwent full manuscript review. When publications were based on the same set of resource input data, the most relevant paper was selected for final evaluation. Conference abstracts, reviews and position papers were excluded. Bibliography of the selected publications was hand-searched to complete the database.

Qualitative evaluation

The CHEERS checklist is a 24-item checklist, used to improve reporting quality in health economic research[12]. All 24 items were checked per article by two observers (YL and CM). In case of disagreement, a consensus was reached through discussion. To improve uniformity of interpretation, the same criteria were re-evaluated in a cross-sectional way, going through all articles per item. For the articles on CC, evaluation was limited to the 13 relevant items (appendix 2).

Quantitative evaluation

Tufts and QHES scores were obtained for quantitative benchmarking of articles on cost-effectiveness. Tufts scores were extracted from the Tufts Medical Centre CEA registry[16], an inventory of over 5500 CEAs on diseases and treatments. Besides a summary of topic, method and results, it contains a subjective assessment about overall quality of the analysis, reflected as a score between 1 (low quality) and 7 (high quality).

The QHES is a dichotomous scoring system, again only intended for cost-effectiveness analysis and based on 16 items, allocating a score 0 (not fulfilled) or 1 (fulfilled) per item[14, 15]. Each score is multiplied by a weight, varying between 1 and 9, to obtain a total score on 100 points. An intermediate appreciation is not allowed, even though several criteria cover different sub-items or request appreciation of the content. To address this interpretational problem, responsible for inter-observer differences[17], the QHES score was defined twice per article: first only accepting the item as 'fulfilled' if all sub-items were met, to obtain a minimum score. For the maximum score, 'fulfilled' was applied if at least one of the sub-items was met. The midrange of minimum and maximum score was used as a proxy for multi-observer evaluation.

To compare Tufts and QHES results with the qualitative CHEERS evaluation, CHEERS was translated into a quantitative score. Because each item focuses on one single aspect, equal weights were allocated, with a score '2' if complete, '1' if partially respected and '0' if applicable but not mentioned. This method corresponds to the scores of respectively 1, 0.5 and 0 as proposed by Mangham-Jefferies et al., who also accorded an equal weight to all items[13].

Resulting scores of the three instruments were then transformed into percentages to allow comparison.

Statistical analysis

Instruments were compared using the paired, non-parametric Wilcoxon rank test for continuous variables. A significance level of .05 was maintained to calculate confidence intervals.

Results

Systematic review

Overall, 9356 titles were found, yielding 7217 publications after removal of duplicates, 104 after screening titles and abstracts. Thirty-eight articles were excluded because of conference paper, abstract or editorial. Main reason for exclusion of articles on the final list, was 1) only total breast cancer cost, encompassing screening, diagnosis, surgery and/or systemic therapy (14 articles), 2) no explicit cost methodology (8) and 3) general radiotherapy cost on different types of cancer (4). The CONSORT diagram is illustrated in figure 1.

An overview of the selected publications is to be found in appendices 3 and 4. Twenty out of the 33 publications represented a full economic evaluation, examining both costs and effectiveness (CEA) or utilities (CUA), for the purpose of readability conjointly referred to as CEA[18-37]. The other 13 publications were CCs, looking only into the financial aspects of the alternatives, not the effectiveness[38-50].

The majority of articles compared different radiotherapy techniques or fractionation schedules (n=19), being normo- versus hypofractionation and/or intra-operative techniques, or the cost implication of IMRT. Eleven articles evaluated the effect of additional radiotherapy (adjuvant radiotherapy or not (n= 8), boost or no boost (n=2), complementary internal mammary field (n=1)) and two compared photon- with proton-therapy. A final article compared the cost of breast conserving therapy, including radiotherapy, over three different reimbursement systems.

Qualitative evaluation

A visual representation of the fulfilment of the CHEERS criteria and a ranking of completeness of the items can be found in figure 2a-b for CEAs, in figure 3a-b for CCs.

Treatment comparators were always described. However, the number of fractions, relevant information in the context of radiotherapy costs, was unclear in three papers[25, 26, 29]. In four papers, all based on SEER data, a combination of various schedules resulted in the reported costs[37, 38, 40, 50]. For accelerated partial breast irradiation (APBI), covering multiple techniques, in three out of nine papers it was unclear whether single- or multi-lumen balloon brachytherapy was used[25, 26, 39].

Only in five CEAs, measurement and valuation of preference-based outcomes was either reported directly, based on a systematic review or a motivated selection[18, 22, 24, 35, 36]. The other CEAs referred to the source of utilities used, without justifying the selection. An almost similar observation was made for the clinical outcomes, where 11/20 CEAs based outcomes on specific studies, without conducting a systematic review or justifying the choice made[19, 21, 25-31, 34, 37].

Regarding the cost inputs, currency was always mentioned, but in one article the reference year could not be found[47] and in one only after thorough searching[36]. In the CEAs, discounting percentages were usually mentioned (17/20), but only 2 articles justified the chosen percentages[24, 36].

Except for 3 publications[27, 29, 34], all CEAs included one-way and/or probabilistic sensitivity analysis. Heterogeneity however, a potential source of uncertainty, was described in only half of CEAs[18, 21-24, 28, 31, 33, 36, 37].

Three elements of discussion (study findings, fit in with literature and limitations) were present in most publications. Generalizability however, was discussed in only 6/20 CEAs[25, 31, 32, 35-37] and 4/13 CCs[43, 47-49].

Quantitative evaluation

Tufts scores were available for 14 CEAs and resulted in an average score of 72.4% (CI 64.1-80.8%). Average QHESmidrange score was 75.2% (CI 67.8-82.6%), with 57.3% (CI 46.8-67.9%) for QHESmin and 93% (CI 87.6-98.4%) for QHESmax. CHEERS quantification resulted in an average of 74.0% (CI 66.4-81.6%) for CEA and 75.6% (CI 70.7-80.5%) for CC. Statistical pairwise comparison between CHEERS, QHESmidrange and Tufts scores did not result in significant differences (figure 4), whereas QHESmin and QHESmax did differ significantly (p-values <0.05).

Discussion

In order to support decision-making in healthcare, evidence on cost and cost-effectiveness of new interventions and technologies needs to be reliable and of good quality, in other words, based on a transparent methodology, traceable sources and a justifiable selection of data inputs. Different instruments evaluating the quality of HEEs have been developed, evolving in the CHEERS Consort statement, a comprehensive checklist incorporating the most essential elements required for transparent reporting. Since its publication in 2013, over 34 review articles in different medical domains evaluated adherence of HEEs to the CHEERS checklist.

A quality review may serve two objectives: it may be intended to select publications that meet a minimal standard before being accepted for publication or before including results in a review. In addition, it may be intended for signalling shortcomings, indicating what elements are underreported and where and how to improve quality.

In radiotherapy, such a qualitative review of CEAs has previously been performed by Barbieri et al. in different tumour types (breast, prostate, colorectal and head & neck cancer), evaluating compliance to the NICE reference case and UK-specific criteria[51]. They signalled absence of a systematic review for data selection, of a methodology for preferences of outcomes and of probabilistic sensitivity analyses as important obstacles for quality. A similar exercise has been done by Nguyen et al., who reviewed the quality of CEAs in radiotherapy for a variety of tumours[52]. Evaluation was limited to a selection of data abstraction variables, based on the CHEERS guideline, while the Tufts' score was used for qualitative benchmarking. Although reporting improved with time, they concluded that even in more recent years there was still room for awareness, especially concerning the reporting of funding or conflict of interest (COI), discounting, the choice of a time horizon and the application of multivariate and probabilistic sensitivity analysis.

Quality review of the selected publications in our study revealed some recurrent shortcomings.

As already signalled by Nguyen et al.[52], a declaration of COI and funding sources in the domain of HEE is important to avoid all doubt on bias. Although journals have become stricter on the subject, a declaration on funding is often lacking, whereas declarations on COI are more often present. This discrepancy may be explained by the presumption that a negative declaration on COI encompasses both topics. However, explicit statements would avoid all doubt.

Similar to the findings of Barbieri et al.[51], definition of the origin of data, including clinical outcome, costs and especially preferences of outcome, needs far more attention. Selective data input and analysis may bias outcomes, potentially resulting in misleading information and jeopardizing valid decision-making on the allocation of limited health care resources. Hence, in the absence of a systematic review, the choices made should at least be clearly motivated.

Most articles contained a sensitivity analysis, at least to some extent. The topic of heterogeneity however, analysing the impact of the population chosen on the final results, is rarely discussed. This seems connected to the recurrent neglect of generalizability in the discussion. CEA-results are at risk to be considered as 'evidence of cost-effectiveness' of a specific intervention, although a different indication or modified base case may completely change the picture.

A surprising finding was the lack of clarity on the radiotherapy fractionation schedules. If analysis is based on large-scale data such as registries or claim-based data sets, the advantage of these real-world data may come at the cost of loss of specificity regarding

indications and acts performed[53]. Most articles however compare specific strategies. In those cases, a clear description of fractionation as well as radiotherapy technique is strongly advisable because both influence costs, as well in a reimbursement[39] as in real cost-based setting[49, 54].

To avoid arbitrariness, a quantitative evaluation with acceptable thresholds may be superior to a purely qualitative approach. Policy makers sometimes adopt such a strategy, frequently extended with country-specific requirements, as listed on the ISPOR website (https://www.ispor.org/PEguidelines/index.asp). Quantitative benchmarking is often extracted from the Tufts Medical Centre CEA registry. These Tufts scores are based on a subjective appreciation, and no information is provided on how scores are precisely obtained.

A second tool, the QHES checklist, is a validated quantitative instrument. This checklist does not permit intermediate scores although several items consist of various sub-items and combine transparency evaluation (formal presence of data) with quality appreciation (appropriateness of choices made). As a consequence, QHES-results are observer-dependent[17]. Averaging out interpretative differences by increasing the number of observers may remediate this problem, but such a solution results in a high workload. As an alternative, we applied a least and a most strict interpretation of 'fulfilment' of the items, and used the midrange of the respective results for comparison with the other instruments.

The CHEERS checklist was not intended for quantitative benchmarking. However, its structure predisposes to quantification, as has been confirmed repeatedly after the first exercise by Mangham-Jefferies et al.[13, 55-69]. Most of these CHEERS-based quality reviews of HEEs implemented a score for 'partially respected' to overcome the problem of incompleteness and accorded an equal weight to each item. Regarding weights, one may question if every item is of a similar importance, from completeness of title over reporting of data sources to uncertainty analysis.

Another question regarding CHEERS is whether its use can be extended to the evaluation of CCs. For the moment, no checklists dedicated to CC evaluation exist. For our evaluation, it seemed reasonable to adopt the CHEERS for quantification of CC quality, excluding 11 items related to effectiveness outcome or modelling.

A last unsolved question is the threshold. Ofman et al. proposed three categories for QHES evaluation, with high quality for scores over 75%, medium quality between 50 and 75% and low quality below 50%[15]. The same threshold has been adopted for quantitative CHEERS evaluations[58, 60, 61, 63-65, 67]. Plumpton et al. even applied a threshold of 85% for high quality[69]. Although practicable, such thresholds remain arbitrary.

In the present study focusing on adjuvant breast radiotherapy, quantification of quality with CHEERS resulted in an average score of 74% for CEAs and 75.6% for CCs. If a threshold of 75% would be applied, only 6 out of 13 CCs and 13 out of 20 CEAs would be considered reliable and of good quality. A minimal threshold of 50% (medium quality) was met by all CCs and almost all CEAs whereas the stricter 'Plumpton' threshold (85%) was attained by only 4 CCs and 4 CEAs. Similar numbers would be obtained with both validated quantitative instruments.

Possible limitations of our study are related to the unsolved questions raised above and to the limited number of observers performing the evaluation. Consequently, this exercise cannot be interpreted as a validation of CHEERS for quantitative benchmarking, neither as a confirmation of the use of this instrument for CCs. Nevertheless, the extension of CHEERS guidelines to quantitative benchmarking of CEAs as well as CCs seems feasible. Moreover, comparison to other validated quantitative instruments did not result in significant differences. A critique may be that transparency is a prerequisite, not a substitute for model validity[70]. Therefore, it remains advisable to evaluate HEE not only on transparency, but to also critically appraise the quality of the sources and models used. More particularly, the validity of the model itself as well as the appropriateness of the results in the own health economic environment should be considered, to ascertain reliability and generalizability of the results.

In conclusion, quantitative CHEERS evaluation is feasible and yields comparable results to validated instruments. For HEE in adjuvant breast radiotherapy, the quantitative evaluation of reporting transparency typically reached an acceptable threshold of medium to high quality. Thresholds are however arbitrary and may result in loss of granularity. This was illustrated by the qualitative evaluation, which showed that some items like data sources, population heterogeneity and sensitivity analysis, essential for reliable cost-effec-

tiveness results, could benefit from more transparent reporting and justification of choices. A combination of quantitative and qualitative evaluation of HEE is indispensable for assessing relevance, reliability and generalizability of the results, hence to support valid decision-making on the allocation of the scarce health care resources.

Conflict of interest statement

This research was supported by a grant (Klinisch Onderzoeks Fonds) from Ghent University Hospital.

FIGURES

Figure 1: Consort diagram

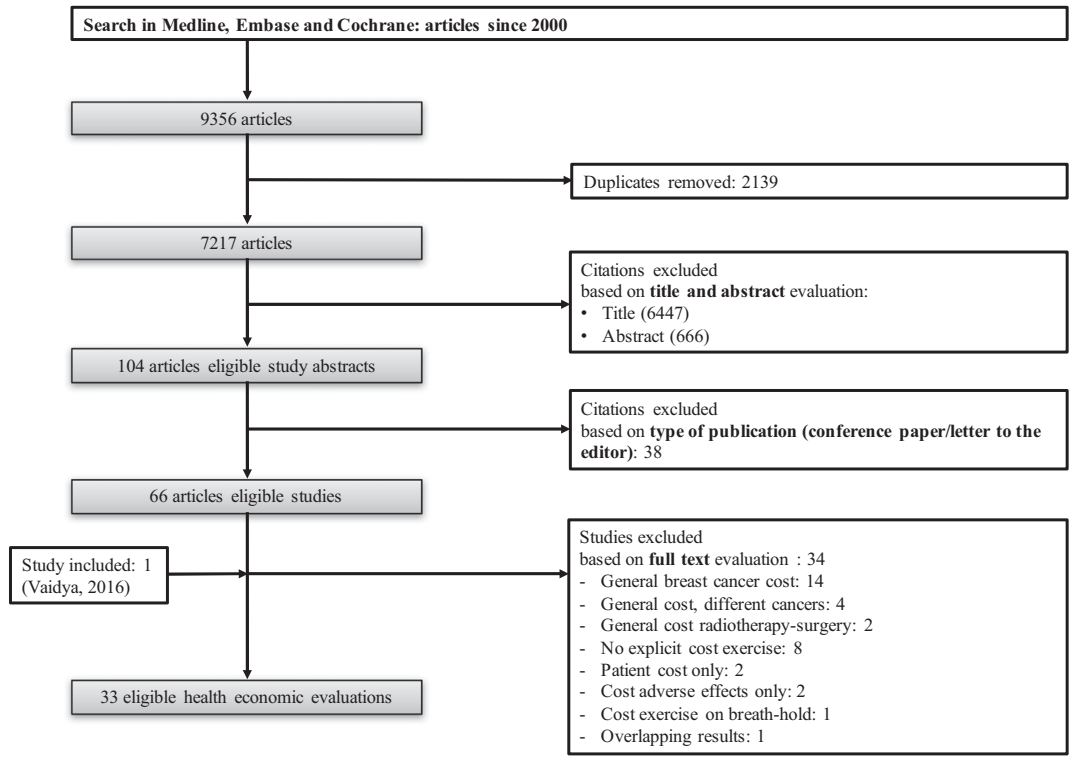


Figure 2: Overview of qualitative evaluation of cost-effectiveness analyses using CHEERS checklist, per article (left) and per item (right).

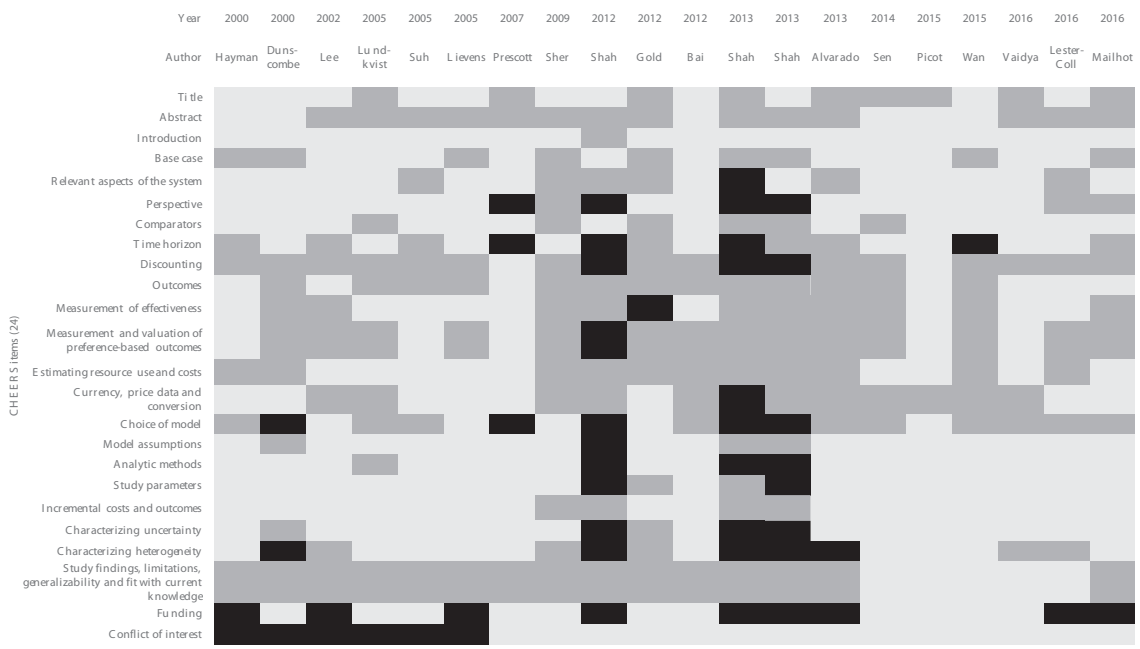
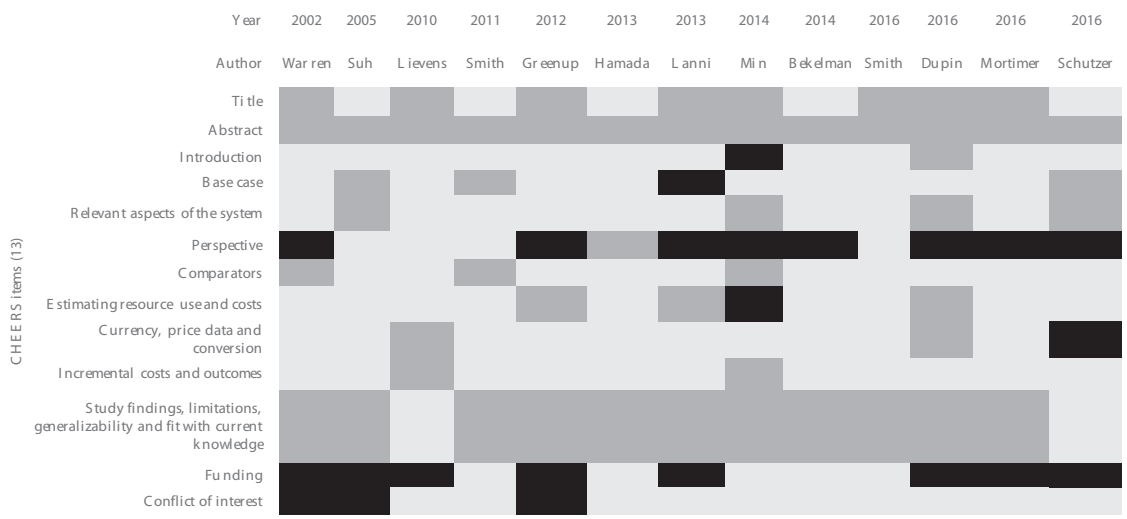


Figure 2a (left): Visual representation of the 24-item CHEERS evaluation applied on the 20 selected CEAs.

Fig 2b (right): Ranking of completeness of sub-items. Same code was applied as in fig 2a. High percentages of 'partially respected' indicate either presence of requested elements without justification (items 9, 15, 12, 11, 13…) or presence of some elements, but not all (items 22, 2, 14…). The items 'funding' and 'conflict of interest' are either 'complete' or 'not mentioned', with a worse score for funding as this is probably not always explicitly separated from the conflict of interest declaration

representation of the 24-item CHEERS evaluation applied on the 20 selected CEAs.

Figure 3: Overview of qualitative evaluation of cost comparisons using CHEERS checklist, per article (left) and per item (right)



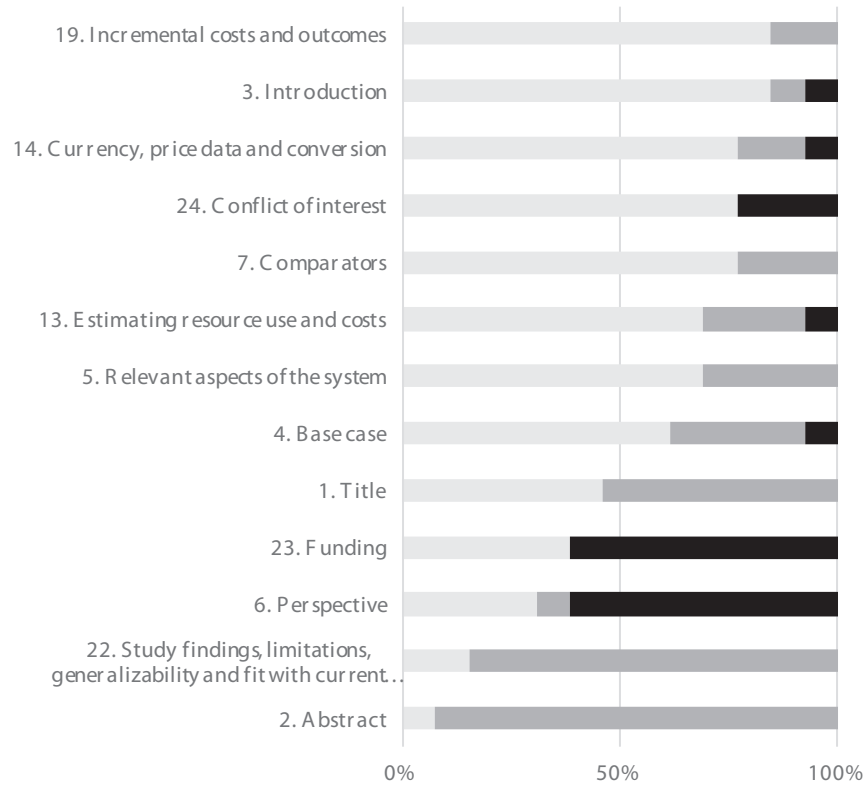
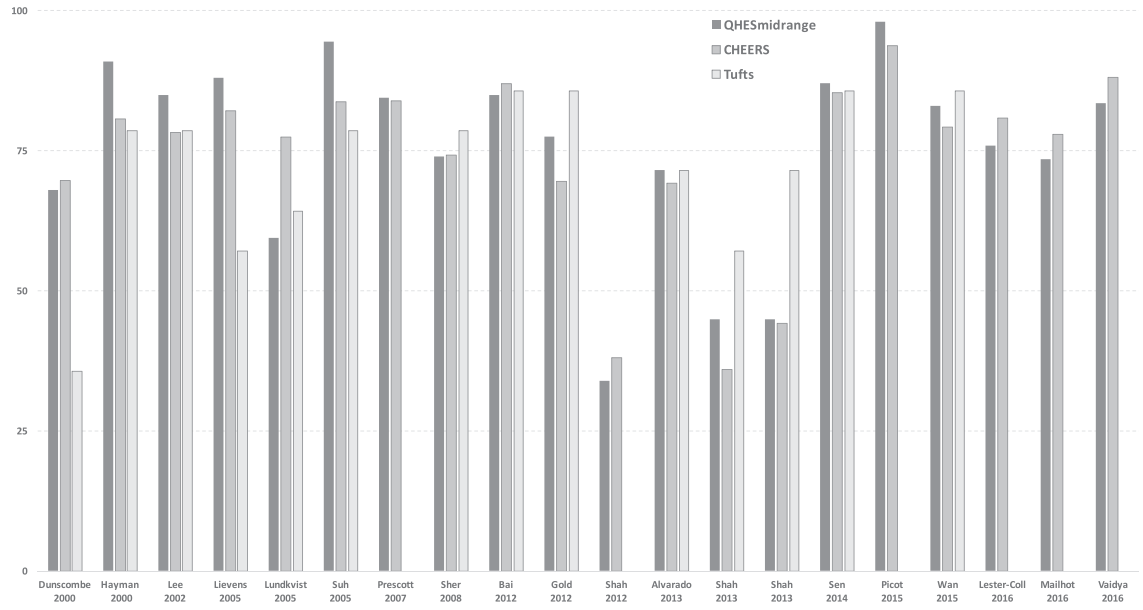


Figure 3a (left): Visual representation of the CHEERS, applied on the 13 selected CCs and limited to the items relevant for cost comparison.

Figure 3b (right): Ranking of completeness of items for CC. Same color codes were applied as in figure 3a. The items 'perspective' and 'funding' were missing most frequently. Item 2 'abstract' and 22 'discussion' consist of several sub-items. As a result, these items are often only partially respected.

Figure 4: Comparison of CEA-scores for CHEERS, $QHES_{midrange}$ and Tufts



Statistical comparison (paired Wilcoxon rank test) of CHEERS with Tufts and QHESmidrange scores did not result in a significant difference between instruments (QHESmidrange vs. Tufts: p=0.7; QHESmidrange vs. CHEERS: p=0.3; CHEERS vs. Tufts: p=0.8). Scores per article are illustrated in percentages to allow comparison. Tufts scores were available for 14 out of 20 CEA. Dark grey = QHESmidrange, medium grey = CHEERS, light grey = Tufts.

APPENDICES

Appendix 1: Search strategy according to PRISMA guidelines

PICOS
Participant: Breast cancer **Intervention**: radiotherapy (adjuvant) **Comparator**: radiotherapy or no radiotherapy **Outcome**: cost or effectiveness ***Study design****: economic analysis (cost comparison, cost effectiveness, cost utility)*
Embase
'radiotherapy'/exp OR radiotherapy OR 'radiation'/exp OR radiation OR 'irradiation'/exp OR irradiation AND ('cost'/exp OR cost OR costs OR economic OR economical OR effectiveness OR benefit) AND ('breast'/exp OR breast) AND ([article]/lim OR [article in press]/lim OR [review]/lim OR [short survey]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [humans]/lim Emtree: 'breast cancer'/exp OR 'breast cancer' AND ('radiotherapy'/exp OR 'radiotherapy') AND ('health economics'/exp OR 'health economics')
Pubmed
("radiotherapy"[MeSH Terms] AND "Costs and Cost Analysis"[Mesh]) AND "Breast Neoplasms"[Mesh]) OR (((radiotherapy[Title/Abstract] OR radiation[Title/Abstract] OR irradiation[Title/Abstract]) AND (Cost[Title/Abstract] OR costs[Title/Abstract] OR economic[Title/Abstract] OR economical[Title/Abstract] OR effectiveness[Title/Abstract] OR benefit[Title/Abstract])) AND breast[Title/Abstract]) AND ("2000/01/01"[PDAT] : "3000/12/31"[PDAT])
Cochrane
Search Name: Cochrane_CEA_word and MeSH combined Description: ID Search Hits #1 radiotherapy:ti,ab,kw or radiation:ti,ab,kw or irradiation:ti,ab,kw (Word variations have been searched) 25548 #2 benefit:ti,ab,kw or cost:ti,ab,kw or economic:ti,ab,kw or economical:ti,ab,kw or effectiveness:ti,ab,kw (Word variations have been searched) 167655 #3 Breast:ti,ab,kw (Word variations have been searched) 28316 #4 #1 and #2 and #3 722 #5 MeSH descriptor: [Costs and Cost Analysis] explode all trees 24985 #6 MeSH descriptor: [Breast Neoplasms] explode all trees 9949 #7 MeSH descriptor: [Radiotherapy, Adjuvant] explode all trees 993 #8 #5 and #6 and #7 9 #9 #4 or #8 722

Appendix 3: Overview of CHEERS and QHES questionnaires.

CHEERS	Weight	QHES	Weight
1. Identify the study as an economic evaluation, or use more specific terms such as "cost-effectiveness analysis" and describe the interventions compared	**1**	Was the study objective presented in a clear, specific, and measurable manner?	7
2. Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses) and conclusions	**1**	Were the perspective of the analysis (societal, third-party payer, etc.) and reasons for its selection stated?	4
3. Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decision	**1**	were variable estimates used in the analysis from the best available source (ie. RCT - best, Expert opinion-worst)?	8
4. Describe characteristics of the base-case population and subgroups analyzed including why they were chosen	**1**	If estimates came from a subgroup analysis, were the groups pre-specified at the beginning of the study?	1
5. State relevant aspects of the system(s) in which the decision(s) need(s) to be made	**1**	Was uncertainty handled by: 1) statistical analysis to address random events; 2) sensitivity analysis to cover a range of assumptions?	9
6. Describe the perspective of the study and relate this to the costs being evaluated	**1**	Was incremental analysis performed between alternatives for resources and costs?	6
7. Describe the interventions or strategies being compared and state why they were chosen	**1**	Was the methodology for data abstraction (including value health states and other benefits) stated?	5
8. State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate	1	Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted 3-5%) and justification given for the discount rate?	7
9. Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	1	Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8
10. Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	1	Were the primary outcome measures for the economic evaluation clearly stated and were the major short term, long term and negative outcomes included?	6
11a. Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	1	Were the health outcomes measures/scales valid and reliable? If previously tested valid and reliable measures were not available, was justification given for the measures/scales used?	7

11b. Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data	1	Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear transparent manner?	8
12. If applicable, describe the population and methods used to elicit preferences for outcomes	1	Were the choice of economic model, main assumptions and limitations of the study stated and justified?	7
13a. Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	**1**	Did the author(s) explicitly discuss direction and magnitude of potential biases?	6
13b. Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	**1**	Were the conclusions/recommendations of the study justified and based on the study results?	8
14. Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate	**1**	Was there a statement disclosing the source of funding for the study?	3
15. Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended	1		
16. Describe all structural or other assumptions underpinning the decision-analytic model	1		
17. Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (eg half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	1		
18. Report the values, ranges, references and if used, probability distribution for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended	1		

19. For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios	**1**
20a. Single study-based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective)	1
20b. Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	1
21. If applicable, report differences in costs, outcomes or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	1
22. Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	**1**
23. Describe how the study was funded and the role of the funder in the identification, design, conduct and reporting of the analysis. Describe other nonmonetary sources of support.	**1**
24. Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations.	**1**

Items in bold were only used for cost comparison evaluation. Weights per item to obtain a total score are indicated.

Appendix 3: Overview of the characteristics, comparators and scores of the 20 publications on cost-effectiveness analysis.

Publication				Comparison		HEE characteristics		Scores		
Year	**Author**	**Title**	**Country**	**Type**	**Specific comparators**	**Perspective**	**Type of costing**	**CHEERS**	**QHES**	**Tufts**
2000	Hayman	Cost-effectiveness of adding an electron-beam boost to tangential radiation therapy in patients with negative margins after conservative surgery for early-stage breast cancer	USA	Additional RT	BCT +/- boost (8 fractions)	Societal	Reimbursement	80,7%	91,0%	78,6%
2000	Dunscombe	A cost-outcome analysis of adjuvant postmastectomy locoregional radiotherapy in premenopausal node-positive breast cancer patients	Canada	Additional RT	Lymph node irradiation	Institutional	Real cost	69,8%	68,0%	35,7%
2002	Lee	Decision-Analytic model and cost-effectiveness evaluation of postmastectomy radiation therapy in high-risk premenopausal breast cancer patients	USA	Additional RT	Lymph node irradiation	Payers	Reimbursement	78,2%	85,0%	78,6%
2005	Lundkvist	Economic evaluation of proton radiation therapy in the treatment of breast cancer	Sweden	Proton vs. photon	BCS + EBRT (25 fractions)	Societal	Real cost	77,5%	59,5%	64,3%
2005	Suh	Cost-effectiveness of radiation therapy following conservative surgery for ductal carcinoma in situ of the breast	USA	Additional RT	BCS +/- EBRT (30 fractions)	Societal	Reimbursement	83,8%	94,5%	78,6%
2005	Lievens	Economic consequence of local control with radiotherapy: cost analysis of internal mammary and medial supraclavicular lymph node radiotherapy in breast cancer	Belgium	Additional RT	Lymph node irradiation	Institutional - including patient cost	Real cost	82,2%	88,0%	57,1%
2007	Prescott	A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.	UK	Additional RT	BCS +/- EBRT (15 fractions)	Payers	Reimbursement	83,9%	84,5%	N/A
2008	Sher	Partial breast irradiation versus whole breast irradiation for early-stage breast cancer: a cost-effectiveness analysis	USA	Technique/ fractionation	EBRT (10 or 15 fractions) vs. APBI-ML (10 fractions)	Payers	Reimbursement	74,3%	74,0%	78,6%

2012	Shah	Cost-effectiveness of 3-Dimensional conformal radiotherapy and applicator-based brachytherapy in the delivery of accelerated partial breast irradiation	USA	Technique/ fractionation	EBRT vs. IMRT vs. APBI-SL vs. APBI-ML (10 fractions)	Payers	Reimbursement	38,0%	34,0%	N/A
2012	Gold	Cost effectiveness of new breast cancer radiotherapy technologies in diverse populations	USA	Technique/ fractionation	EBRT (10 or 25 fractions) vs. APBI-Mammosite (10 fractions)	Societal	Reimbursement	69,6%	77,5%	85,7%
2012	Bai	Economic evaluation of radiotherapy for early breast cancer after breast-conserving surgery in a health resource limited setting	China	Additional RT	EBRT (25 or 30 fractions)	Societal	Reimbursement	87,0%	85,0%	85,7%
2013	Shah	Evaluating radiotherapy options in breast cancer: does intra-operative radiotherapy represent the most cost-efficacious option?	USA	Technique/ fractionation	IORT (1 fraction) vs. EBRT (10 or 25 fractions) vs. IMRT (10 fractions) vs. APBI-SL or APBI-ML or APBI-IS (10 fractions)	Societal	Reimbursement	35,9%	45,0%	57,1%
2013	Shah	Cost-efficacy of acceleration partial-breast irradiation compared with whole breast irradiation	USA	Technique/ fractionation	EBRT (10 or 28 fractions) vs. IMRT (10 or 28fractions) vs. APBI-SL or APBI-ML or APBI-IS (10 fractions)	Societal	Reimbursement	44,3%	45,0%	71,4%
2013	Alvarado	Cost-effectiveness analysis of intraoperative radiation therapy for early stage breast cancer	USA	Technique/ fractionation	IORT (1 fraction) vs. EBRT (15 or 33 fractions)	Payers	Reimbursement	69,2%	71,5%	71,4%
2014	Sen	Examining the cost-effectiveness of radiation therapy among older women with favorable-risk breast cancer	USA	Additional RT	BCS only vs. BCS + EBRT or IMRT (mix of fractions) or APBI-IS (10 fractions)	Payers	Reimbursement	85,4%	87,0%	85,7%
2015	Picot	The intrabeam photon radiotherapy system of the adjuvant treatment of early breast cancer: a systematic review and economic evaluation	UK	Technique/ fractionation	IORT (1 fraction) vs. EBRT (15 fractions)	Payers	Real cost	93,8%	98,0%	N/A
2015	Wan	Subgroup economic evaluation of radiotherapy for breast cancer after mastectomy.	China	Additional RT	Lymph node irradiation	Societal	Reimbursement	79,2%	83,0%	85,7%
2016	Vaidya	An international randomised controled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving sugery for women with early-stage breast cancer (the TARGIT-A trial)	UK	Technique/ fractionation	IORT (1 fraction) vs. EBRT (15 fractions)	Payers	Reimbursement	88,1%	83,5%	N/A

2016	Lester-Coll	Cost-effectiveness assessment of lumpectomy cavity boost in elderly women with early stage estrogen receptor positive breast cancer receiving adjuvant radiotherapy	USA	Additional RT	BCT +/- boost (8 fractions)	Payers	Reimbursement	80,8%	76,0%	N/A
2016	Mailhot	Establishing cost-effective alllocation of proton therapy for breast irradiation	USA	Proton vs. photon	Cardiac toxicity with photon vs. proton therapy (28 fractions)	Societal	Real cost	78,0%	73,5%	N/A

Abbreviations: RT: radiotherapy; BCS: breast conserving surgery; BCT: breast conserving therapy (BCS + RT); EBRT: external beam radiotherapy; IMRT: intensity modulated radiotherapy; IORT: intra-operative radiotherapy; APBI: accelerated partial breast irradiation; SL: single-lumen; ML: multi-lumen; IS: interstitial; N/A: if Tufts score not available

Appendix 4: Overview of the characteristics, comparators and scores of the 13 publications on cost comparison.

Publication				Comparison		HEE characteristics		
Year	**Author**	**Title**	**Country**	**Type**	**Specific comparators**	**Perspective**	**Type of costing**	**Score**
2002	Warren	Costs of Treatment for elderly women with early-stage breast cancer in Fee-for-Service settings	USA	Additional RT	ME vs. BCS + RT (type and number of fractions not specified)	Societal	Reimbursement	66,6%
2005	Suh	A cost comparison analysis of partial versus whole-breast irradiation after breast-conserving surgery for early-stage breast cancer	USA	Technique/ fractionation	EBRT (10 or 16 or 25 or 30 fractions) vs. IMRT (10 or 30 fractions) vs. APBI-Mammosite or APBI-IS (10 fractions)	Societal	Reimbursement	73,3%
2010	Lievens	Hypofractionated radiotherapy: Financial and economic consequences	Belgium	Technique/ fractionation	EBRT (5 vs. 13 vs. 15 vs. 16 vs. 25 vs. 30 fractions)	Institutional	Real cost	77,8%
2011	Smith	Adoption of intensity-modulated radiation therapy for breast cancer in the united states	USA	Technique/ fractionation	EBRT vs. IMRT (number of fractions not specified)	Payers	Reimbursement	89,1%
2012	Greenup	Cost comparison of radiation treatment options after lumpectomy for breast cancer	USA	Technique/ fractionation	EBRT (9 vs. 20 vs. 30 fractions)	Payers	Reimbursement	67,8%
2013	Hamada	Cross-national comparison of medical costs shared by payers and patients: a study of postmenopausal women with early-stage breast cancer based on assumption case scenarios and reimbursement fees.	Japan	Different reimbursement systems	EBRT 25 fractions - patient and payers' cost in Germany, UK vs. Japan	Societal	Reimbursement	93,9%
2013	Lanni	A cost comparison analysis of adjuvant radiation therapy techniques after breast-conserving surgery	USA	Technique/ fractionation	EBRT vs. IMRT (10 or 16 or 28 or 33 fractions) vs. APBI-SL or APBI-ML (10 fractions)	Payers	Reimbursement	65,2%
2014	Min	Hypofractionated radiation therapy for early stage breast cancer: outcomes, toxicity and cost analysis	USA	Technique/ fractionation	EBRT (4 vs. 16 vs. 25 fractions)	Payers	Reimbursement	57,4%
2014	Bekelman	Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013	USA	Technique/ fractionation	EBRT (15 vs. 25 fractions in endorsed vs. permitted population)	Payers	Reimbursement	89,2%

2016	Smith	Cost and complications of local therapies for early-stage breast cancer	USA	Technique/ fractionation	ME +/- reconstruction vs. BCS +/- RT (type and number of fractions not specified)	Payers	Reimbursement	94,3%
2016	Dupin	Evolution des pratiques médicales d'hypofractionnement en radiothérapie pour cancer du sein et impact économique	France	Technique/ fractionation	EBRT (5 vs. 15 vs. 16 vs. 25 fractions)	Payers	Reimbursement	60,4%
2016	Mortimer	Use of hypofractionated post-mastectomy radiotherapy reduces health costs by over $2000 per patient: An Australian perspective	Australia	Technique/ fractionation	EBRT (15 vs. 25 fractions)	Payers	Reimbursement	79,4%
2016	Schutzer	Time-driven activity-based costing: a comparative cost analysis of whole-breast radiotherapy versus balloon-based brachytherapy in the management of early-stage breast cancer	USA	Technique/ fractionation	EBRT (20 or 30 fractions) vs. APBI-ML (10 fractions)	Institutional	Real cost	67,9%

Abbreviations: RT: radiotherapy; BCS: breast conserving surgery; ME: mastectomy; EBRT: external beam radiotherapy; IMRT: intensity modulated radiotherapy; APBI: accelerated partial breast irradiation; SL: single-lumen; ML: multi-lumen; IS: interstitial

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Publication 4 –
Adjuvant breast radiotherapy: how to trade-off cost and effectiveness?

Ref: Radioth Oncol (RO-D-17-01015)

Authors: Chris Monten[1], Yolande Lievens[1]
[1]Ghent University Hospital, Radiation Oncology Department, Ghent, Belgium

Running title

Evidence on cost and cost-effectiveness in adjuvant breast radiotherapy

Key words

Health economic evaluation; Breast cancer; Radiotherapy; Cost effectiveness analysis; Cost comparison; IORT; Hypofractionation; Accelerated partial breast irradiation; Post-mastectomy radiotherapy

Abstract

Introduction: The introduction of new fractionation schedules and techniques for adjuvant breast radiotherapy has been followed by health economic evaluations (HEE) comparing the efficiency of these new strategies. This overview assembles the available evidence and evaluates to what extent HEE-results can be compared.

Methods: Based on a systematic literature review of HEEs from 1/1/2000 to 30/10/2016, all cost comparison and cost-effectiveness analyses comparing different adjuvant breast radiotherapy approaches were analyzed. Costs were extracted and converted to Euro 2016 and costs per QALY were summarized in cost-effectiveness planes.

Results: Twenty-four publications are withheld, comparing different fractionation schedules and/or irradiation techniques or evaluating the value of adding radiotherapy. Normofractionation, IMRT and interstitial as well as intraluminal techniques are important cost-drivers. Highest reimbursement costs come from the US, but may overestimate the real-cost. Whereas cost-effectiveness of hypofractionation seems evident, the results of APBI are less unequivocal. Intra-operative radiotherapy and external beam APBI seem the most cost-effective APBI techniques for favourable risk groups, but WBI is superior in terms of health effect and omission of radiotherapy in terms of costs.

Discussion: In conclusion, although comparison of CC and CEA is inherently based on many uncertainties and assumptions, HEE-based evidence can guide decision-making to tailor-made strategies, allocating the optimal treatment in terms of effectiveness as well as efficiency to the right indication.

Introduction

Excellent survival results in early and locally advanced breast cancer allowed to change the treatment paradigm in breast cancer therapy from maximizing cure to awareness for long-term toxicity, quality of life and treatment burden[1].

An evolution from normofractionation to shorter, hypofractionated schedules was made possible through growing evidence on the radio-biologic aspects of breast cancer, indicating a higher sensitivity to fraction dose than originally assumed[2-5]. These schedules have further evolved into extremely accelerated schedules[6, 7]), and in combination with knowledge on the recurrence patterns of breast cancer and new technological capabilities, have paved the way for accelerated partial breast irradiation (APBI)[8-17].

In health care, the development of evidence is built on three core questions, evaluating efficacy, effectivity and efficiency of new approaches[18, 19].

Efficacy research – can it work? – is confined to the rules of a trial, with strict intake criteria, follow up of compliance and complications and quality check of the providers' interventions. This question has been answered for most of the above-mentioned approaches, although for APBI, be it with post-operative external, intra-operative of peri-operative dose delivery, longer follow up is still awaited[13-15, 17, 20].

The question on effectivity – does it work? – evaluates if results can be repeated in a real-world setting, under less ideal circumstances. This can be provided by observational research, based on large-scale databases[21]. As an example, a Medicare-based analysis compared brachytherapy-based APBI with standard whole breast irradiation (WBI) for overall survival, complications and mastectomy rates. It found equivalence for survival, but an increase in complications and subsequent mastectomies[22].

But even if a new approach proves effective, additional expenses in health care must be worthwhile, most certainly from the perspective of health-care payers. This evaluation of efficiency is explored in health economic evaluations (HEE), with cost comparisons (CC) inventorying the cost difference of new strategies versus the gold standard, whereas

cost-effectiveness evaluations (CEA) compare this incremental cost to incremental health effects. In HEE, health effects are expressed in natural units, ideally in 'life years gained' (LYG) or in quality adjusted life years gained (QALY), factoring in the importance that individuals assign to purely clinical gains. Whereas CCs give a mere representation of the cost, be it resource costs, reimbursement figures or charges, CEAs provide a more complete analysis with the ultimate aim to define whether its implementation is financially acceptable from a societal perspective. Such societal acceptance can be translated in a 'willingness-to-pay' (WTP), indicating how much a society is prepared to pay per LYG or per QALY. This can be a fixed amount, depending on the economic status of a country, or variable, depending on factors such as the societal impact, the illness burden or the innovative nature of the technology[23].

Even with reassuring and robust evidence, implementation of new approaches can be slow, as is observed for hypofractionation[24-29] or on the contrary, can anticipate the evidence, as for APBI, where the need for reassuring long-term results on intra-operative and balloon-based APBI has not impeded its wide-spread application, within but also outside of clinical trials[30, 31]. The answer to this paradox may at least to some extent be ascribed to the conflicting economic impact of these techniques between different stakeholders.

This paper aims at providing a comprehensive overview of the published literature on costs and cost-effectiveness of hypofractionated and accelerated breast radiotherapy, based on a systematic review of the literature. Comparability of data is ascertained by applying monetary conversions, categorization is performed for different radiation techniques and fractionation schedules.

Materials and methods

Publications on HEE of adjuvant breast radiotherapy, published between 1/1/2000 and 31/10/2016, were retrieved through systematic literature review in Medline, Embase and Cochrane databases. The methods are described in a previous publication[32]. From this series, only publications focusing on the cost and cost-effectiveness of adjuvant whole breast irradiation (WBI), post-mastectomy radiotherapy (PMRT) or partial breast irradi-

ation (PBI) were withheld for comparison. Publications were excluded if results could not be related to the specific radiotherapy cost (e.g. if including surgery or systemic therapy cost) or to specific techniques or fractionation schedules (e.g. in large database evaluations, as in SEER analyses, based on global charges over different techniques and fractionation schedules).

Comparison of treatment cost

Cost data were extracted from both CCs and CEAs. Direct radiotherapy costs per technique and fractionation schedule are presented, excluding non-medical and indirect costs. The published costs are inflated to the year 2016 (for one article that did not mention a reference year, 2015 was assumed, based on publication date), according to the country-specific Consumer Price Indices (http://fxtop.com/en/inflation-calculator.php) and then converted to Euro, using available conversion factors (www.xe.com/currencytables). Because monetary values are subject to fluctuations, the 31st January of 2016 was chosen as reference date.

Comparison of cost-effectiveness

Data were derived from the CEA publications. Incremental cost-effectiveness is defined as the incremental cost of a new intervention compared to the standard, and divided by the incremental health effect between both interventions, also referred to as incremental cost-effectiveness ratio (ICER)[33]. If incremental health effect is based on LYG, it results in a cost-effectiveness analysis (CEA). A cost-utility analysis (CUA) is based on QALY, with health effects weighted by the utilities adhered to each possible health state. The term CEA often covers both definitions. For reasons of readability, we further use the more common term of cost-effectiveness, even if QALYs are applied.

For the incremental costs, the same technique of inflation and conversion to Euro-2016 was applied as described above. Only ICERs based on QALYs are presented in this publication.

Results

Comparison of treatment cost

Twenty-four publications are withheld, 4 based on real-cost exercises [34-37] and 20 on reimbursement[26, 38-56] (table 1).

WBI or PMRT are delivered with external beam radiotherapy (EBRT) or more specifically, intensity-modulated radiotherapy (IMRT) and costs are available for normofractionated schedules, with or without a boost (25-35 fractions for EBRT; 28-33 for IMRT) and hypofractionated schedules (EBRT 11-20 fractions; IMRT 16 fractions).

APBI is delivered with EBRT (APBI-EBRT 4-10 fractions) or IMRT (APBI-IMRT 10 fractions), with single-fraction intra-operative radiotherapy (IORT), with post-operative interstitial brachytherapy (APBI-IS) or with balloon-based brachytherapy, applying a single- or a multi-lumen balloon-technique (APBI-balloon, further subdivided in either APBI-SL or APBI-ML). Postoperative intraluminal partial-breast techniques all apply 10 fractions. Two articles, included in the APBI-EBRT group, report the cost of EBRT in 5 fractions for WBI[35, 55].

Overall, 81 radiotherapy costs are extracted from these publications, of which 69 are based on reimbursement and 12 on real costs. An overview of the published costs, expressed in € for 2016, can be found in table 1; aggregated data per treatment category (technique and fractionation schedule) and per cost type are presented in figure 1. Unsurprisingly, costs increase with the number of fractions, especially when IMRT is applied. Post-operative intraluminal strategies also lead to higher costs. In contrast, the cost of IORT remains low over different reimbursement systems (UK and US-data available), comparable to the cost of APBI-EBRT.

Regional and time-bound factors influence costs. On average, hypofractionated and normofractionated EBRT cost almost twice as much in the US than elsewhere (respectively 7,609€ and 11,316€ versus 3,649€ and 6,670€). Large variability is also observed within the US healthcare system itself: the reimbursement of APBI-IS ranges from 11,709€ to

20,276€; the same goes for balloon-based brachytherapy, with APBI-ML ranging from 13,453€ to 24,141€. From 2011 on, reimbursements drop with almost 25%.

The number of real-cost calculations per radiotherapy technique is too low to draw firm conclusions. Overall, real-life costs seem lower than reimbursement, except for IORT, where reimbursement seems to align with real-cost (figure 1). However, when costs and reimbursement are compared within the European setting, the opposite goes, with real-life costs exceeding the reimbursement in several countries (table 1).

Comparison of cost-effectiveness

Fourteen publications were analysed on cost-effectiveness results (table 2). A fifteenth CEA was not withheld, because aesthetic outcome was used as health effect, hampering comparison with the recommended effects of LYGs and QALYs[53]. Cost-effectiveness results are illustrated in figure 2, comparing the cost-effectiveness of radiotherapy versus no radiotherapy in different age- and risk-groups[34, 38, 40, 41, 43, 52, 54] and figure 3, comparing different fractionation schedules and radiotherapy techniques (either APBI compared to WBI or inter-comparison of different APBI-techniques)[36, 42, 44, 47, 49, 50, 56] on cost-effectiveness planes[57].

When comparing radiotherapy with no radiotherapy in different age- and risk-groups (presence or not of lymph nodes in earlier stages breast cancer) (figure 2), the addition of radiotherapy after breast-conserving surgery or mastectomy always results in an increase in health effect, but at a higher cost, most explicit for IMRT and normofractionated schedules. One study evaluated the effect of PMRT in older women, and calculated a decreasing effect for equal costs with increasing age, hence a higher ICER for older age groups[52]. A similar observation is made in the CEA of the PRIME-trial, evaluating the effect of WBI in older women with favourable breast cancer. These results demonstrate a minor improvement of health effect at a non-negligible cost, questioning the efficiency of radiotherapy in this target population[41].

Two studies evaluated the addition of radiotherapy in lymph node positive indications. Bai et al. calculated an acceptable ICER for WBI in lymph-node negative as well as

positive patients, with the higher incremental cost for pN0 versus pN+ outweighted by an even higher incremental effectiveness for pN0, resulting in a superior ICER for this subgroup. Wan et al. analysed the pN+ group and found a significantly lower ICER for PMRT when the number of lymph nodes involved was limited to maximally three. This was based on a lower cost for the pN1-3 subgroup together with improved effectiveness compared to 4 or more lymph nodes[43, 54].

The cost-effectiveness of APBI versus WBI is spread over the four quadrants of the diagram, with a concentration of results in the left-lower quadrant, indicating reduced expenses at the cost of a lower benefit (figure 3). Expensive techniques as balloon-based brachytherapy are dominated by WBI, even if compared to normofractionation. The results of IORT are scattered over 3 quadrants, with disagreement in utility (Picot and Shah calculate reduced QALYs for IORT compared to WBI, whereas Alvarado and Vaidya report better QALYs) and disagreement in cost (Picot refers to the CEA by the manufacturer Zeiss, indicating a higher cost for IORT whereas he himself calculates almost no cost difference; in contrast, Shah, Alvarado and Vaidya report lower costs with IORT)[36, 47, 49, 56].

Discussion

HEE on the cost and cost-effectiveness of adjuvant breast radiotherapy covers a vast landscape of fractionation schedules and techniques. Evidence is available from several geographic regions (US, Europe, Canada, Australia and Asia). The reviewed publications either evaluate the effect of additional radiotherapy versus no radiotherapy or compare different fractionation schedules and/or techniques, varying from single-fraction intra-operative APBI to 35-fraction WBI or PMRT. Although most cost data are reimbursement-tariffs, some are based on real-cost calculations.

All evaluations on the cost-effectiveness of additional radiotherapy in specific age and risk groups result in an increased health effect for radiotherapy, be it at an additional cost. Apart from the IMRT-arm in Sen's publication[52], incremental costs, even with normofractionation in the investigational schedule, systematically remain below 10,000€. However, in combination with varying QALYs gained, these relatively acceptable incre-

mental costs result in a wide range of ICERs. The ICERs calculated by Wan, Bai, Lee and Dunscombe remain between 1,000€ to 30,000€/QALY, with incremental costs outweighed by relatively high incremental outcome. However, the CEA of protracted fractionation schedules in elderly women by Sen et al. combines high incremental costs with limited gains in health effects, resulting in ICERs between 37,188€/QALY to 232,479€/QALY when IMRT is applied. A similar conclusion can be drawn for the ICER of adjuvant EBRT-30 for DCIS[39]. The PRIME-study, evaluating hypofractionated WBI in the breast-conserving setting, is an extreme example: although the incremental costs are a mere 2,800€, combined with the very limited gain in health effect of 0.0075 QALYs, results in an ICER of 370,445€/QALY[41].

This result invites to debate. Clearly, an ICER of over 370,000€/QALY is not acceptable, even if the sensitivity analysis, excluding 4 outliers, resulted in significantly different costs and effects and reduced the ICER by a factor of three. The outcomes, however, remain the main issue. Although in the CEA effects were based on a median follow-up of 15 months, which is very short in favourable breast cancer treated with adjuvant Tamoxifen, outcomes remained excellent in both arms. As even the five-year outcomes of the PRIME-trial revealed no differences in overall survival or loco-regional control, this analysis approaches a cost-minimisation study, where in the absence of incremental effects, the lowest cost (no treatment) should be favoured[58]. In addition, seeing the good results of omission of radiotherapy in favourable risk groups, this 'no-treatment-arm' may be a relevant comparator for future APBI trials.

Other trials, however, do not support this: the comparable CALGB 9343-trial, evaluating omission of radiotherapy in a seemingly more favourable risk group (women over 70 years with T1N0 breast cancer), reported an 8% increase in loco-regional relapse at 10 years [59]. If a similar long-term effect would have been observed in the PRIME trial, different costs and QALYs would probably have impacted the ICER.

The results for APBI-techniques are widely spread-out over the cost-effectiveness plane. Some techniques come at increased costs, even when compared to normofractionation (balloon-based APBI and interstitial APBI). Other techniques are less costly (IORT, APBI-EBRT, APBI-IMRT). Most publications compare these new strategies with normofractionation. However, in line with growing evidence on hypofractionated and even accelerated WBI and its lower costs, shorter fractionation schedules may again be a more valuable comparator. Effectively, Picot and Vaidya only report a marginally lower cost when IORT is compared to hypofractionation.

Except for two publications (Vaidya and Alvarado assume an increased QALY with IORT), QALYs slightly decrease with APBI. If such a loss in health effect – however limited – is esteemed acceptable in return for lower costs or patient burden, the rationale to preferentially compare APBI to no radiotherapy for prognostic favourable indications, is further substantiated.

The ICERs in the upper-right quadrant of the cost-effectiveness plane require a trade-off in acceptable supplementary expenses per QALY, decisions that are typically made on the basis of willingness-to-pay thresholds, varying from country to country and being all or not explicit[60]. In contrast, ICERs located in the lower-left quadrant represent possible budgetary savings by sacrificing QALYs. As a result, higher ICERs are more favourable in this quadrant, as they indicate either higher gains in costs or lower loss in health. In contrast to the willingness-to-pay thresholds for the upper-right quadrant, no thresholds are available to support decision-making in lower-left situations.

When looking at these results, and considering whether they are applicable in the own health care environment, several caveats must be kept in mind.

First it should be acknowledged that a large discrepancy is observed for real-cost estimations versus reimbursement data. However easy to use, reimbursement is only a surrogate for costs[61]. Based on the available data, for IORT, real-life costs and reimbursement seem well-aligned. In contrast, the cost calculation by Schutzer et al. results in a much lower cost for EBRT and balloon-based brachytherapy than the US reimbursement tariffs[37] whereas the activity-based-costing exercise by Lievens et al. suggests that reimbursement in most European countries underestimates the real-life cost of EBRT[35]

Secondly, although real-life costs may seem more relevant than reimbursement, heterogeneity of costing exercises makes results difficult to compare: different models for real-cost

calculation are used with a variety of cost inputs and computing various cost outputs[62]. The large differences in incremental costs for IORT between Picot et al. and the manufacturer Zeiss, illustrate this heterogeneity[36]. In addition, even if a uniform template is used for cost calculation, heterogeneity of personnel salaries and time investment, infrastructure cost, equipment use and overhead cost will lead to a range of results, as demonstrated in a Belgian multi-centre time-driven activity-based-costing exercise[63].

Thirdly, costs - and more importantly - reimbursements, are strongly influenced by region and time. The large differences between US reimbursement versus other countries support this regional effect. And although inflation may to some extent correct for time-bound differences, it does not neutralize the effect of reimbursement renegotiations.

In addition, not only costs but also health effects may be subject to selection bias. The controversies in the literature on the results of the TARGIT-trial demonstrate how arguable clinical outcomes can be. When using QALYs, this heterogeneity is further magnified by an even larger uncertainty regarding utilities[64, 65].

A last remark concerns the perspective used. All articles adopt a payers' perspective, extended to a societal perspective when non-medical costs are included. However, other stakeholders, like patients and caregivers, play a role in the choice of treatment strategies[29, 66]. Different perspectives may lead to very different results. For example, if a radiation department would consider adopting hypofractionation as standard therapy, they would compare the reimbursement received with the departmental costs of normo- versus hypofractionation. If reimbursement of hypofractionation would be lower than its cost and thus jeopardize income, hard evidence may not overcome this financial hurdle related to the need of radiotherapy departments to function within an economic reality. This virtual example may at least partially explain the slow implementation of hypofractionation world-wide.

In conclusion, although comparison of CC and CEA is inherently based on many uncertainties and assumptions, some conclusions can be drawn. Substituting normo- by hypofractionation reduces healthcare costs for a comparable health-effect. Addition of radiotherapy, even in favourable risk groups, improves QALY, but comes at a cost. ICERs may become acceptable if shorter fractionation schedules are adopted. The results for APBI are more controversial, especially for IORT, where longer follow-up and relevant comparators may eventually settle its place within the landscape of adjuvant breast radiotherapy.

All in all, the one-disease-one-treatment paradigm no longer prevails: whereas different strategies have proven effectiveness, an evolution to tailor-made allocation of the most efficient radiotherapy option could be facilitated if evidence from cost-effectiveness research where more systematically implemented.

Table 1: Overview of costs converted to €, 2016, per publication.

Publication		Setting		Technique and fractionation							
Author Year	**Title**	**Country**	**Original monetary unit Ref year**	**IMRT (25-33)**	**EBRT (13-20)**	**IMRT (16)**	**AP-BI-EBRT (4-10)**	**APBI-IM-RT (10)**	**IORT (1)**	**APBI-IS (10)**	**APBI-SL (10)**	**AP-BI-ML (10)**
Reimbursement-based calculations												
Lee 2002	Decision-Analytic model and cost-effectiveness evaluation of postmastectomy radiation therapy in high-risk premenopausal breast cancer patients	USA	USD 2000	15,103 (25)								
Suh 2005	Cost-effectiveness of radiation therapy following conservative surgery for ductal carcinoma in situ of the breast	USA	USD 2002	9,424 (30)								
Suh 2005	A cost comparison analysis of partial versus whole-breast irradiation after breast-conserving surgery for early-stage breast cancer	USA	USD 2003	8,931 (25) 11,466 (30)	6,517 (16)		8,690 (10)	11,104 (10)		20,276 (10)		21,483 (10)
Prescott 2007	A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME-trial.	UK	£ 2004	3,894 (25)	3,248 (15)							
Sher 2009	Partial breast irradiation versus whole breast irradiation for early-stage breast cancer: a cost-effectiveness analysis	USA	USD 2004	13,303 (30)			9,392 (10)					22,351 (10)
Bai 2012	Economic evaluation of radiotherapy for early breast cancer after breast-conserving surgery in a health resource limited setting	China	USD 2012	5,198 (25) 5,804 (30)								
Gold 2012	Cost effectiveness of new breast cancer radiotherapy technologies in diverse populations	USA	USD 2008	11,989 (25)			11,253 (10)					24,141 (10)
Greenup 2012	Cost comparison of radiation treatment options after lumpectomy for breast cancer	USA	USD 2011	13,305 (30)	9,086 (20)		5,321 (9)					

Hamada 2013	Cross-national comparison of medical costs shared by payers and patients: a study of postmenopausal women with early-stage breast cancer based on assumption case scenarios and reimbursement fees	Japan	€ 2012	3,203 (25)										
		UK	€ 2011	11,698 (25)										
		Germany	€ 2012	11,441 (25)										
Alvarado 2013	Cost-effectiveness analysis of intraoperative radiation therapy for early stage breast cancer	USA	USD 2011	9,768 (25) 12,629 (30)		8,014 (15)				6,695 (1)				
Lanni 2013	A cost comparison analysis of adjuvant radiation therapy techniques after breast-conserving surgery	USA	USD 2011	11,679 (28) 13,774 (33)	20,555 (25) 22,042 (33)	7,795 (16)	13,602 (16)	6,552 (10)	10,505 (10)			12,552 (10)	13,453 (10)	
Shah 2013	Evaluating radiotherapy options in breast cancer: does intra-operative radiotherapy represent the most cost-efficacious option?	USA	USD 2011	11,680 (25)				6,552 (10)	10,505 (10)	3,082(1)	11,709 (10)	12,552 (10)	16,374 (10)	
Shah 2013	Cost-efficacy of acceleration partial-breast irradiation compared with whole breast irradiation	USA	USD 2011	11,680 (25)	20,555 (25)			6,552 (10)	10,505 (10)		11,709 (10)	12,552 (10)	16,374 (10)	
Min 2014	Hypofractionated radiation therapy for early stage breast cancer: Outcomes, toxicities, and cost analysis	USA	USD 2012	10,034 (25)		8,109 (13)		4,642 (4)						
Shah 2014	Cost-effectiveness of 3-Dimensional conformal radiotherapy and applicator-based brachytherapy in the delivery of accelerated partial breast irradiation	USA	USD 2011					6,575 (10)	10,543 (10)			12,597 (10)	16,431 (10)	
Wan 2015	Subgroup economic evaluation of radiotherapy for breast cancer after mastectomy.	China	USD 2014	5,803 (35)										
Dupin 2016	Evolution des pratiques médicales d'hypofractionnement en radiothérapie pour cancer du sein et impact économique	France	€ 2014	4,262 (25)		2,557 (15) 2,728 (16)		923 (5)*						

Mortimer 2016	Use of hypofractionated post-mastectomy radiotherapy reduces health costs by over $2000 per patient: an australian perspective	Australia	AUD 2014	5,670 (25)	3,848 (15)			
Vaidya 2016	An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving sugery for women with early-stage breast cancer (the TARGIT-A trial)	UK	£ 2013		3,582 (15) 4,333 (20)		2,536 (1)	
Real-cost based calculations								
Dunscombe 2000	A cost-outcome analysis of adjuvant postmastectomy locoregional radiotherapy in premenopausal node-positive breast cancer patients	Canada	CDN$ 1997	6,243 (25)				
Lievens 2010	Hypofractionated breast radiotherapy: financial and economic consequences	Belgium	€ 2007	7,047 (25) 8,906 (30)	4,705 (13) 4,862 (15) 5,179 (16)	2,816 (5)*		
Picot 2015	The intrabeam photon radiotherapy system of the adjuvant treatment of early breast cancer: a systematic review and economic evaluation	UK	£ 2013		3,190 (15)	3,000 (1)		
Schutzer 2016	Time-driven activity-based costing: a comparative cost analysis of whole-breast radiotherapy versus balloon-based brachytherapy in the management of early-stage breast cancer	USA	USD 2015?**	4,974 (30)	3,800 (20)		6,474 (10)	

Incremental costs are inflated to 2016 (Consumer price index of respective country) and converted to euro and grouped per publication and per category of fractionation and/or technique. * Costs of a 5-fraction EBRT-schedule for whole breast irradiation (Lievens et al. and Dupin et al.). Upper panel for reimbursement-based costs, costs in lower panel are real-cost based. ** No mentioning of reference year (Ref year) in publication – assumption based on publication date.

Abbreviations: EBRT = External beam radiotherapy with number indicating number of fractions; IMRT = Intensity-modulated radiotherapy; APBI = Accelerated partial breast irradiation; IORT = Intraoperative radiotherapy; APBI-IS = Interstitial brachytherapy; APBI-SL = Intraluminal brachytherapy with single-lumen balloon technique; APBI-ML = Intraluminal brachytherapy with multi-lumen balloon technique; APBI-IS = Interstitial brachytherapy.

Table 2: Overview of incremental cost (€, 2016), incremental outcome and ICER (€, 2016/QALY) per publication.

Publication		**Setting**		**Health Economic Evaluation**				
Author Year	**Title**	**Country**	**Original monetary unit, ref year**	**Comparators**	**Incremental cost**	**Incremental QALY**	**ICER (€/QALY)**	**Interpretation**
Radiotherapy vs no radiotherapy								
Dunscombe 2000	A cost-outcome analysis of adjuvant post-mastectomy loco-regional radiotherapy in premenopausal node-positive breast cancer patients	Canada	CDN$, 1997	EBRT-25 vs no PMRT	6,522 €	0.45	14,494 €	Increased effectiveness, increased cost
Lee 2002	Decision-Analytic model and cost-effectiveness evaluation of post-mastectomy radiation therapy in high-risk premenopausal breast cancer patients	USA	USD, 2000	EBRT-25 vs no PMRT	9,504 €	0.32	29,701 €	Increased effectiveness, increased cost
Suh 2005	Cost-effectiveness of radiation therapy following conservative surgery for ductal carcinoma in situ of the breast	USA	USD, 2002	DCIS, EBRT-30 vs no RT	4,092 €	0.09	45,468 €	Increased effectiveness, increased cost
Prescott 2007	A randomized controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME-trial.	UK	£, 2004	65y ESBC, EBRT-20 vs no RT	2,778 €	0.0075	370,445 €	Increased effectiveness, increased cost
Bai 2012	Economic evaluation of radiotherapy for early breast cancer after breast-conserving surgery in a health resource limited setting	China	USD, 2012	ESBC all, EBRT-30 vs no RT	621 €	1.5	410 €	Increased effectiveness, increased cost
			ESBC pN0, EBRT-30 vs no RT	914 €	1.6	570 €	Increased effectiveness, increased cost	
			ESBC pN+, EBRT-30 vs no RT	426 €	1.31	330 €	Increased effectiveness, increased cost	

Sen 2014	Examining the cost-effectiveness of radiation therapy among older women with favorable-risk breast cancer	USA	USD, 2012	70-74y, EBRT vs no RT	9,148 €	0.246	37,188 €	Increased effectiveness, increased cost
			75-79y, EBRT vs no RT	9,171 €	0.218	42,067 €	Increased effectiveness, increased cost	
			80-94y, EBRT vs no RT	9,234 €	0.17	54,316 €	Increased effectiveness, increased cost	
			70-74y, IMRT vs no RT	17,119 €	0.106	161,500 €	Increased effectiveness, increased cost	
			IMRT vs no RT	17,140 €	0.095	180,425 €	Increased effectiveness, increased cost	
			80-94y, IMRT vs no RT	17,203 €	0.074	232,479 €	Increased effectiveness, increased cost	
Wan 2015	Subgroup economic evaluation of radiotherapy for breast cancer after mastectomy.	China	USD, 2014	pN+, EBRT - 35 vs no PMRT	3,714 €	0.49	7,579 €	Increased effectiveness, increased cost
			pN1-3, EBRT - 35 vs no PMRT	2,732 €	0.71	3,847 €	Increased effectiveness, increased cost	
			pN1-3, chemo, EBRT-35 vs no PMRT	2,573 €	0.76	3,386 €	Increased effectiveness, increased cost	
			pN4+, EBRT-35 vs no PMRT	4,637 €	0.26	17,834 €	Increased effectiveness, increased cost	

Different fractionation schedules and techniques

Sher 2009	Partial breast irradiation versus whole breast irradiation for early-stage breast cancer: a cost-effectiveness analysis	USA	USD, 2004	APBI-EBRT vs EBRT-30	-3,911 €	-0.0052	752,181 €	*Decreased effectiveness, decreased cost*
			APBI-ML vs EBRT-30	9,047 €	-0.0052	-1,739,847	Dominated	
Gold 2012	Cost effectiveness of new breast cancer radiotherapy technologies in diverse populations	USA	USD, 2008	APBI-EBRT vs EBRT-25	-739 €	-0.001	738,529 €	*Decreased effectiveness, decreased cost*
			APBI-ML vs EBRT-25	12,196 €	-0.001	-12,196,115 €	Dominated	
Alvarado 2013	Cost-effectiveness analysis of intraoperative radiation therapy for early stage breast cancer	USA	USD, 2011	IORT vs EBRT-15	-910 €	0.014	-64,880 €	Dominant
			IORT vs EBRT-30	-5,189 €	0.00026	-19,957,157 €	Dominant	

Shah 2013	Evaluating radiotherapy options in breast cancer: does intra-operative radiotherapy represent the most cost-efficacious option?	USA	USD, 2011	IORT(T) vs EBRT-25	-8,628 €	-0.04	215,711 €	*Decreased effectiveness, decreased cost*
			IORT (T, 15%) vs EBRT-25		-3,721 €	-0.04	93,037 €	*Decreased effectiveness, decreased cost*
			IORT (T, 21%) vs EBRT-25		-3,019 €	-0.04	75,469 €	*Decreased effectiveness, decreased cost*
			IORT(T) vs APBI-EBRT		-3,483 €	-0.04	87,064 €	*Decreased effectiveness, decreased cost*
			IORT(T) vs APBI-IMRT		-7,450 €	-0.04	186,248 €	*Decreased effectiveness, decreased cost*
			IORT(T) vs APBI-SL		-9,504 €	-0.04	237,602 €	*Decreased effectiveness, decreased cost*
			IORT(T) vs APBI-ML		-13,340 €	-0.04	333,488 €	*Decreased effectiveness, decreased cost*
			IORT(T) vs APBI-IS		-8,667 €	-0.04	216,686 €	*Decreased effectiveness, decreased cost*
			IORT(E) vs EBRT-25		-8,628 €	-0.06	143,807 €	*Decreased effectiveness, decreased cost*
			IORT(E) vs APBI-EBRT		-3,483 €	-0.06	58,042 €	*Decreased effectiveness, decreased cost*
			IORT(E) vs APBI-IMRT		-7,450 €	-0.06	124,165 €	*Decreased effectiveness, decreased cost*
			IORT(E) vs APBI-SL		-9,504 €	-0.06	158,401 €	*Decreased effectiveness, decreased cost*
			IORT(E) vs APBI-ML		-13,340 €	-0.06	222,325 €	*Decreased effectiveness, decreased cost*
			IORT(E) vs APBI-IS		-8,667 €	-0.06	144,457 €	*Decreased effectiveness, decreased cost*

Shah 2013	Cost-efficacy of acceleration partial-breast irradiation compared with whole breast irradiation	USA	USD, 2011	APBI-EBRT vs EBRT-25	-5,146 €	-0.07	73,512 €	*Decreased effectiveness, decreased cost*
				APBI-IMRT vs EBRT-25	-1,179 €	-0.07	16,836 €	*Decreased effectiveness, decreased cost*
				APBI-SL vs EBRT-25	876 €	-0.07	-12,509 €	Dominated
				APBI-ML vs EBRT-25	4,711 €	-0.07	-67,301 €	Dominated
				APBI-IS vs EBRT-25	31 €	-0.07	-443 €	Dominated
				APBI-EBRT vs IMRT-25	-14,053 €	-0.07	200,760 €	*Decreased effectiveness, decreased cost*
				APBI-IMRT vs IMRT-25	-10,086 €	-0.07	144,083 €	*Decreased effectiveness, decreased cost*
				APBI-SL vs IMRT-25	-8,032 €	-0.07	114,738 €	*Decreased effectiveness, decreased cost*
				APBI-ML vs IMRT-25	-4,196 €	-0.07	59,947 €	*Decreased effectiveness, decreased cost*
Picot 2015	The intrabeam photon radiotherapy system of the adjuvant treatment of early breast cancer: a systematic review and economic evaluation	UK	£, 2013	IORT vs EBRT-15	-190 €	-0.088	2,159 €	*Decreased effectiveness, decreased cost*
Vaidya 2016	An international randomized 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)	UK	£, 2013	IORT vs EBRT-15	-923 €	0.034	-27,143 €	Dominant

Incremental costs are inflated to 2016 (Consumer price index of respective country) and converted to euro. In italic, the situations where a lower cost comes with a loss in QALYs. Abbreviations: ICER = Incremental cost effectiveness ratio; QALY = Quality adjusted life years gained; RT = radiotherapy; PMRT = Post-mastectomy RT; WBI = Whole breast irradiation; EBRT = External beam radiotherapy with number indicating number of fractions; IMRT = Intensity-modulated radiotherapy; APBI = Accelerated partial breast irradiation; APBI-IS = Interstitial brachytherapy; APBI-SL = Intraluminal brachytherapy with single-lumen balloon technique; APBI-ML = Intraluminal brachytherapy with multi-lumen balloon technique; APBI-IS = Interstitial brachytherapy; IORT = Intraoperative radiotherapy with E indicating outcome data based on ELIOT-trial results, T on Targit-trial results and percentage indicating percentage of patients receiving additional WBI; ESBC = Early-stage breast cancer; y = years old; pN = pathological lymph node stage with pN0 for non-involved, pN+ for involved, pN1-3 for 1-3 lymph nodes involved and pN4+ for four or more lymph nodes involved; DCIS = Ductal carcinoma in situ.

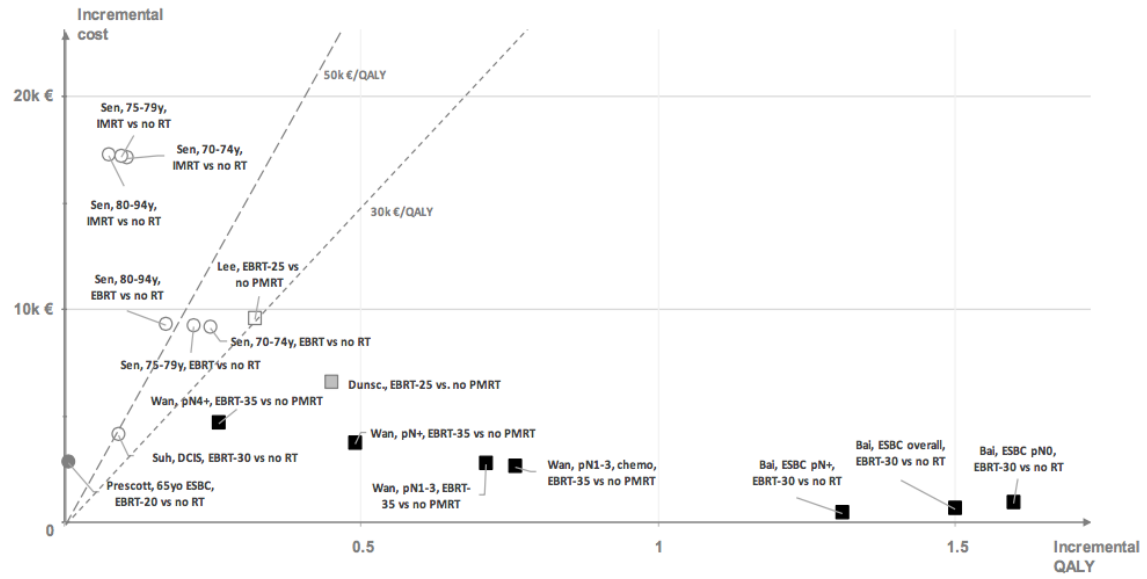
Figure 1: Cost results per category of fractionation and technique (€, 2016).

Technique - fractionation	Overall n	Overall Mean	Overall Range		Overall SD	Reimbursement-based n	Reimbursement-based Mean	Reimbursement-based Range		Reimbursement-based SD	Real-cost based n	Real-cost based Mean	Real-cost based Range		Real-cost based SD
EBRT (25-35)	27	9.219 €	3.203 €	15.103 €	3.423 €	23	9.641 €	3.203 €	15.103 €	3.493 €	4	6.792 €	4.974 €	8.906 €	1.427 €
IMRT (28-33)	3	21.051 €	20.555 €	22.042 €	701 €	3	21.051 €	20.555 €	22.042 €	701 €					
EBRT (13-20)	16	5.097 €	2.557 €	9.086 €	2.065 €	11	5.438 €	2.557 €	9.086 €	2.363 €	5	4.347 €	3.190 €	5.179 €	738 €
IMRT (16)	1	13.602 €	NA			1	13.602 €	NA							
APBI-EBRT (4-10)	10	6.834 €	2.816 €	11.253 €	2.303 €	10	7.222 €	4.642 €	11.253 €	1.882 €	1	2.816 €	NA		
APBI-IMRT (10)	5	10.632 €	10.505 €	11.104 €	236 €	5	10.632 €	10.505 €	11.104 €	236 €					
IORT (1)	4	3.828 €	2.536 €	6.695 €	1.668 €	2	2.809 €	2.536 €	3.082 €	273 €	1	3.000 €	NA		
APBI-IS (10)	3	14.565 €	11.709 €	20.276 €	4.038 €	3	14.565 €	11.709 €	20.276 €	4.038 €					
APBI-balloon (10)	12	15.611 €	6.474 €	24.141 €	4.829 €	11	16.442 €	12.552 €	24.141 €	4.142 €	1	6.474 €	NA		

Results are grouped per category of fractionation schedule and technique, inflated to 2016 (Consumer price index of respective country) and converted to euro. Grey shades evolve from low cost (light grey) to high cost (dark grey).

Abbreviations: NA = Not applicable; EBRT = External beam radiotherapy; IMRT = Intensity-modulated radiotherapy; APBI = Accelerated partial breast irradiation; IORT = Intraoperative radiotherapy; APBI-IS = Interstitial brachytherapy; APBI-balloon = Intraluminal brachytherapy with single- or multi-lumen balloon technique; n = number of cost data, SD = standard deviation of the means.

Figure 2: Cost-effectiveness plane representing incremental cost and health effect for radiotherapy versus no radiotherapy (€, 2016).



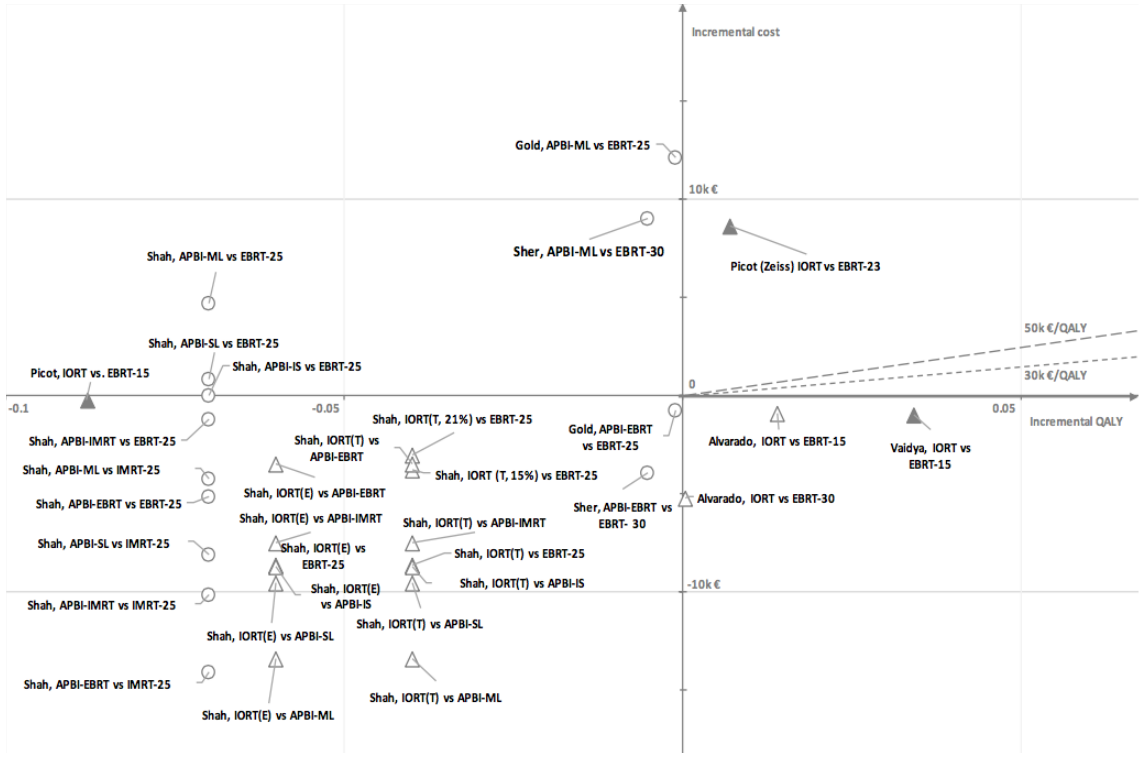
Location of the results on the X-axis indicates the incremental health effect and on the Y-axis, the incremental cost for the investigational strategy compared to the standard.

The dashed lines indicate willingness-to-pay thresholds of 30,000€/QALY and 50,000€/QALY.

Circles have WBI as comparator, squares indicate PMRT as comparator. Open markers are US-based, light-grey markers represent Canada, dark-grey Europe and black represents Asia.

Abbreviations: QALY = Quality adjusted life years gained; RT = radiotherapy; PMRT = Post-mastectomy RT; EBRT = External beam radiotherapy with number indicating number of fractions; IMRT = Intensity-modulated radiotherapy; ESBC = Early-stage breast cancer; y = years old; pN = pathological lymph node stage with pN0 for non-involved, pN+ for involved, pN1-3 for 1-3 lymph nodes involved and pN4+ for four or more lymph nodes involved.

Figure 3: Cost-effectiveness plane representing incremental cost and health effect for different fractionation schedules and techniques (€, 2016).



vLocation of the results on the X-axis indicates the incremental health effect and on the Y-axis, the incremental cost for the investigational strategy compared to the standard.

Results located in the lower right quadrant are dominant strategies, combining a lower cost with improved health effect. Results in the upper left quadrant are dominated situations, with the investigational strategy being more expensive for less health effect than the comparator. In the upper right quadrant, increased health effect comes at a higher cost. Strategies that are less costly but come with a loss in health effect, are found in the lower left quadrant. The dashed lines indicate willingness-to-pay thresholds of 30,000€/QALY and 50,000€/QALY.Triangles represent IORT, circles compare fractionated schedules. Open markers are US-based, dark-grey filled markers are European.

Abbreviations: QALY = Quality-adjusted life years gained; EBRT = External beam radiotherapy with number indicating number of fractions; IMRT = Intensity-modulated radiotherapy; APBI = Accelerated partial breast irradiation; APBI-IS = Interstitial brachytherapy; APBI-balloon = Intraluminal brachytherapy with single (SL)- or multi-lumen (ML) balloon technique; IORT = Intraoperative radiotherapy with E indicating outcome data based on ELIOT-trial results, T on Targit-trial results and percentage indicating percentage of patients receiving additional WBI.

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GENERAL DISCUSSION AND CRITICAL INTERPRETATION

Objective 1: Partial breast irradiation: is it feasible in prone position?

Evaluation of a practical approach to obtain precise and accurate target volume delineation for accelerated partial breast irradiation in prone position.

In search of a balance between small target volumes and accurate and precise tumourbed delineation for partial breast irradiation

Several trials have explored the safety and feasibility of APBI. Intra-operative techniques limit dose to the tissue adjacent to the excision cavity only. The 5-year results of randomized trials on these intra-operative techniques revealed increased local relapse rates[1, 2]. In contrast, local control remained equivalent to WBI in the GEC-ESTRO trial on interstitial brachytherapy[3]. The GEC-ESTRO did not provide information on the target volumes, but an expansion of at least 2cm from the tumourbed does suggest larger volumes. Five-year evidence on partial breast irradiation came with the IMPORT LOW trial. In this trial, a hypofractionated schedule in 15 fractions was delivered in all three arms, targeting either the whole breast or the tumourbed only (40Gy) and in the third arm delivering two doses, with the tumourbed receiving 40Gy and the remaining breast 36Gy. Local control was excellent. However, these good results may be partially related to the large fields receiving high-dose, also in the partial breast arm. To facilitate feasibility, supine position in combination with an easy tangential field set-up with field-in-field IMRT was applied. This led to large volumes receiving high doses, including one-third up to half of the breast and, for locations in the upper half, even part of the axilla.

It is an important merit of the IMPORT LOW trial to have compared volume as a single variable. Although impact on aesthetic outcome was altogether limited, they did

observe a significant increase in 'marked breast change', mainly due to breast shrinkage, in the WBI-arm. The relation between volume and breast appearance emphasizes the role that APBI could play in further improving aesthetic outcome for favourable ESBC, however at the condition of accurate delivery of the dose to the tumourbed to avoid relapses. This requires correct reconstruction of the preoperative tumour location in an operated, often deformed breast. The difficulty of reproducible tumourbed delineation can be deducted from the low inter-observer conformity rates in the literature, on boost as well as partial breast target volumes. Inter-observer delineation exercises report conformity rates between 0.35 and 0.54 despite optimal circumstances. To improve inter-observer conformity, delineation guidelines have been published, based on general information (preoperative imaging, surgical report, pathology, scar) complemented with planning-CT based landmarks (tissue distortion, seroma, clips). However, in our centre full thickness closure and prone position are applied. Full-thickness closure reduces the infection risk, thus improving aesthetic outcome[134]. The advantages of prone position have been explained in chapter 2.6.b. Prone positioning also helps in avoiding the axillary region.

What is needed to combine prone position and full-thickness closure with accurate and precise tumourbed delineation?

Prone positioning comes with some drawbacks, rendering existing guidelines insufficient and thus impacting accuracy and precision in tumourbed volume delineation:

– a larger anterior-posterior diameter amplifies the risk to miss the target along this axis. More than for supine position, the depth of the primary tumour location must be clearly defined.

– to distinguish tissue distortion from glandular tissue in prone position, one cannot rely on comparison with the contralateral breast as it lies compressed on the breast board

– relevant clips along the surgical trajectory are difficult to distinguish from irrelevant haemostatic clips, or from deep clips placed on the thoracic wall. Blind inclusion of all clips would lead to long, protracted target volumes unto the thoracic wall, thus foregoing the advantages of prone and partial breast irradiation, as demonstrated by Lakosi et al. [135].

We tested the added value on precision and accuracy of tumour bed delineation of an indicator-clip as indirect depth-marker and of a preoperative CT in treatment position. A target volume delineation exercise demonstrated an improved inter-observer conformity or precision for delineation based on the indicator-clip (0.75 vs 0.38). More importantly, even simple expansion based on this clip proved more accurate to cover the preoperative GTV with the CTV than standard delineation (overlap rate of 0.67 for clip-based CTV versus 0.48 for standard delineation). As could be expected, fusion with the preoperative CT in treatment position further improved the overlap rate to 0.88. Improved overlap resulted in higher mean dose to GTV and in less fails (underdosing of the GTV).

Conclusions from the inter-observer target volume exercise

Preoperative CT in treatment position may thus be regarded as the most accurate aid for target localization. Our results indicate that if postoperative APBI is aimed for, indirect tumourbed localization based on an indicator-clip improves inter-observer conformity but is not accurate enough if small volumes are aimed for. However, for boost delineation (with WBI compensating for the risk of missing the target) an indicator-clip may be sufficient to add information on depth of the tumour, especially if prone positioning is intended. The added value of such larger 'indicator-clip' over the 'ad random clips' in the cavity walls, is the additional information it brings on the anterior-posterior depth of the tumour in the preoperative breast. But although it takes only a short extra surgical handling to be inserted during the tumourectomy, agreement on the protocol, inclusion of the operation nurses in this strategy and regular feedback on the dosimetric impact of this clip, all may be required to ascertain understanding and collaboration of the surgical team in maximising the impact of such markers.

An indicator-clip clearly intended to mark the depth of the tumour increases the probability of covering the primary tumour location, but cannot entirely replace the additional value of a preoperative CT in treatment position. Avoiding the cost and effort

of such a preoperative CT, implies accepting a risk of missing the target, especially when small volumes are aimed for. Increasing target volumes may reduce this risk, but questions the concept of APBI. With shorter treatment schedules and lower costs of EB-APBI compared to WBI (publication 4), adding a preoperative CT may be considered as a marginal expenditure for improving accuracy.

Preoperative APBI as an alternative for volume shrinkage

Although an indicator-clip in combination with a preoperative CT in treatment position leads to acceptable results in inter-observer conformity and overlap with the preoperative GTV, APBI still balances between the challenge to reduce volume and the risk of missing the target. A solution to this problem may be found in preoperative APBI: with the tumour present, delineation conformity further improves, as has been tested by Van der Leij et al.[136, 137]. However, preoperative radiotherapy holds several drawbacks:

– Treatment cannot be based on definite pathology, and if high radiation doses are delivered, this precludes subsequent WBI in case pathology reveals unfavourable prognostic features. In the ELIOT trial, pathology revealed upstaging of clinical evaluation in up to 25% of cases. This problem is partially resolved if a sentinel lymph node procedure is performed before radiotherapy, however at the cost of two separate surgical interventions for ESBC.

– Tumours are irregular in shape and medical imaging may underestimate the actual tumour size, a problem especially encountered with lobular carcinoma. Tackling this problem by substituting large margins for location uncertainty with large margins for unknown tumour diameter, would undo the advantage of smaller preoperative target volumes.

– If post-operative pathology warrants mastectomy, patients may have been needlessly exposed to potential radiation-induced toxicity.

- CT-based tumour location is not always clear-cut, especially for non-palpable small tumours, which are the primary indication for preoperative radiotherapy. This has already been confirmed in surgical studies, struggling with complete excision of non-palpable breast lesions, with over 20% of patients needing re-excision for involved excision margin despite wire-guided tumour-localization and wide resections[4]. The Milan group even developed a technique of Radio-guided Occult Lesion Localization (ROLL) with injection of technetium-labelled albumin particles in the centre of the tumour to improve the probability of complete excision[5, 6]. These surgical studies coincide with our experience in localizing the preoperative non-palpable tumour on CT, even in the presence of pre- and postoperative mammography, and are confirmed by the difficulties to identify the GTV for small tumours in the setting of preoperative radiotherapy[7]. Despite the radiologist accurately describing the tumour localization compared to the harpoon-tip on mammography, translating mammographic information to CT may remain difficult. During the interobserver exercise, uncertainty was larger for GTV-delineation in case of harpoon-localization compared to contrast-enhanced lesions.

MRI may solve this problem[7], but needs to be performed in treatment position and without deforming the pendant breast. In combination with breast coils and a strict contra-indication for metallic support as in breast boards, this is a difficult hurdle to take. From a more practical perspective, the unavailability of scanning slots and the long waiting-lists may not permit timely MRI in a preoperative setting.

Restrictive breast delineation as an alternative for volume shrinkage

A second alternative may be the combining of the advantages of WBI with lessons learned from APBI experiments. Why sacrificing OARs to cover each inch of the breast tissue if even half breast irradiation may be sufficient? In view of the good results for APBI, with dose mainly delivered in the region of the primary tumour location, one could argue that all other breast tissue is considered target, but not at the cost of nearby OARs. This seems in line with evidence from Holland et al. and Vicini et al., who demonstrated that the spread of microsatellites knows a geographic pattern, diluting when further away from the initial tumour[8, 9]. Knowledge on the primary tumour location is useful, even if no boost is intended, to cover the breast tissue most at risk. No compromises should be allowed in this region. However, at the medial and lateral side of the breast, no clear ‘demarcation’ line indicates where the breast stops and fatty tissue starts. With the breast being a large volume (+/-250cc to +/- 3000cc)

between indisputable anterior and posterior borders (skin and thoracic wall), inter-observer delineation differences in these directions are altogether limited. However, if we focus in on the medial and lateral borders, these appear the main source of delineation uncertainty[138, 139]. ESTRO guidelines suggest the mid-axillary line or the arteria thoracica lateralis as lateral border and the rami mammarii from the arteria thoracica interna as medial border[140]. But not only can these arteries be difficult to recognize, fatty tissue is interposed between the fascia surrounding the breast tissue and these vascular structures. The price of strictly respecting borders is paid in dose to lungs, heart and the contralateral breast, or, if large breast volumes are included, even in dose to the axilla. In prone, breast tissue falls forward, and so far, no evidence on the true borders of the pendant breast is available. Blind transposition of supine borders to the prone position leads to breast delineation high up along the thoracic wall and compromises the advantages of the breast hanging down. A more restrictive delineation, based on visible glandular tissue, judicious use of wires indicating the breast folds and for cranio-caudal borders, the second and sixth rib, may be more in line with the effect of gravity while prone is applied.

Patient- and tumour-tailored underdosage as an alternative for volume-shrinkage

Even if accurate delineation guidelines will become available, uncompromised dose coverage of the entire breast may still come at the cost of increased dose to OARs. In such situations, tailoring the dose to the risk profile of patient and tumour would consider the primary tumour location as a region of no compromise, whereas acceptance of under-dosage of regions, distant to the tumourbed, may well be justified as a less radical alternative for APBI to reduce dose to OAR, especially in case of ESBC. Factors to take into account in such trade-off between dose to PTV and OAR may be tumour-based, including tumour location, type and stage as well as lympho-vascular invasion or multi-focality. Relevant patient-related risk factors for radiation-induced morbidity are age, cardiac co-morbidity and smoking status, as discussed in chapter 1.2.

In this perspective, it is interesting to look once again into the results of the IMPORT LOW trial. Although statistical testing only compared experimental arms with WBI

(40.05Gy), differences in aesthetic outcome between WBI-SIB (36Gy with SIB 40.05Gy) and PBI (40.05Gy PBI) remained low and suggest equivalence. This coincides with the improvement in acute toxicity when SIB was compared to a sequential boost[141].

Conclusion

In conclusion, results of our inter-observer exercise demonstrated the need for a pre-operative CT in treatment position if small volume APBI is aimed for. The results also show that even if high inter-observer conformity is reached, this cannot substitute for accuracy, the main issue of target delineation. Increasing delineated volumes improves both, but comes at the cost of higher dose to OARs and disfavours the ratio between target and off-target breast tissue. In view of these findings and the small window of opportunity for APBI, we decided to abandon this strategy and to explore feasibility of accelerated radiotherapy beyond partial breast irradiation.

Research on the true borders of a breast in prone position is needed to further explore the impact of this position on avoiding toxicity. Depending on the risk profile, compromises between dose-coverage of the ipsilateral breast and dose to OARs seem acceptable. In our centre, the boost region is systematically delineated, even if no boost dose is given, to define the high-risk region where underdosage is not accepted. In this regard, a protocol on an indicator-clip in addition to the usual 'Solin' clips in the cavity wall[45] improves knowledge on the depth of the primary tumour location without additional imaging.

In selected cases, EB-APBI may remain interesting, but if true APBI with small volumes confined to the high-risk region are aimed for, preparation should include preoperative imaging in treatment position to permit maximal avoidance of off-target breast tissue without missing the target.

Objective 2: Accelerated radiotherapy: can it be extended beyond partial breast irradiation, without increasing acute toxicity?

Evaluation if accelerated breast irradiation may be safely be expanded to a broader population of elderly patients with early as well as locally-advanced stage breast cancer

Acceleration beyond partial breast irradiation

Based on the reassuring 3-year results of tumour control and toxicity of the FAST trial, as well as publications reporting longer follow-up from Ortholan, Kirova and Rovea[25, 142-144], acceleration of EBRT to 5 fractions was estimated a safe alternative for EB-APBI. However, these trials are limited to WBI with, only for Ortholan, TWI. No information was available thus far on acceleration in combination with a SIB or LNI.

As our centre has a long-standing experience with IMRT and simultaneous delivery of different dose levels, we decided to test the feasibility and efficacy of bringing the advantages of acceleration to a larger range of indications, including ESBC as well as LABC. All potential adjuvant target volumes were included: WBI, TWI, WBI with SIB if needed and LNI. Only TWI requiring a boost was excluded in this phase 1-2 trial. Because long-term data on the risk of acceleration in terms of aesthetic outcome or radiation-induced brachial plexopathy (RIBP) are not yet available, an age limit of at least 65 years was chosen for inclusion. In the higher age group, the highest rates of underutilization of radiotherapy are found, probably due to an underestimation of the impact on outcome, local control as well as survival, in combination with logistical obstacles. Finally, the long-term results of the boost-no boost trial confirmed age as an adverse factor for radiotherapy-related fibrosis. As such, this may be the most sensitive age group for detecting adverse effects of high-fraction doses on aesthetic outcome, together with less impact on body-image as compared to younger patients. The initial objective to implement EB-APBI was thus changed into a project on accelerated irradiation in 5 fractions, the HAI-5 trial, testing accelerated adjuvant breast radiotherapy in the elderly population, as described in publication 2.

Doses were 28.5Gy/5.7Gy for the breast or the thoracic wall after mastectomy, and 27Gy/5.4Gy for the lymph node regions. As discussed before, our SIB trial found less acute toxicity with SIB compared to a sequential boost[141]. In line with this finding and to respect treatment delivery within 5 fractions, SIB was applied in case a boost was needed, delivering 32.5Gy/6.5Gy for negative margins or 34.5Gy/6.9Gy if margins were involved. Fractions were delivered every other day to guarantee an inter-fraction repair-time of at least 24h.

Calculation of dose conversion was based on the linear quadratic model, with an α/β ranging between 2.8Gy and 4.6Gy for tumour control and for breast toxicity and an α/β of 1.5Gy for plexopathy. Conversion resulted in EQD2 ranging between 44.5-50.5Gy for WBI and 54.7-63Gy for the tumourbed or, in case of involved margins, 60.1-69.7Gy. For the brachial plexus, an EQD2 of 53.2Gy was calculated.

Multi-beam IMRT delivery was chosen to avoid all risk for overlap incidents, especially cumbersome in the region of the brachial plexus[22, 145, 146]. For complex fields, VMAT with concatenated arcs helped in accelerating delivery. Maximal tolerated doses were based on the AAPM-guidelines by Benedict et al. on SBRT[147].

Results from the HAI-5 trial

Feasibility and acute toxicity results of this first cohort of 95 patients are reported in publication 2. Despite older age and longer machine-time per fraction, delivery was feasible, including prone position where indicated. Doses were well tolerated, with low overall toxicity. Grade 2-3 toxicity was only observed in the SIB group.

We concluded that acceleration to 5 fractions is feasible. However, an equivalent EQD2, as for the boost, may underestimate the effect of higher doses per fraction and shortening of the overall treatment time on the repair mechanisms in between fractions. The same assumption has instigated the FAST trialists' group to compensate for shorter overall treatment time, by lowering the breast dose to even 26Gy/5.2Gy and 27Gy/5.4Gy in the FAST Forward schedule (5 consecutive days), resulting in EQD2 ranges of 38.6-43.3Gy and 40.9-46.9Gy[10].

As soon as 1- and 2-year follow-up data become available for our HAI-5 trial population, the results of tumour control and aesthetic outcome will be evaluated in a matched-pair analysis, comparing acceleration with hypofractionation.

The good results of the HAI-5 feasibility trial will be further explored in subsequent trials randomizing between hypofractionation or acceleration in WBI +/- SIB (YO-HAI-5 RCT), WBI and SIB with LNI adding randomization between prone versus supine position (PRO-SURF RCT) and in a patient preference trial comparing hypofractionation with acceleration for TWI+/- SIB with or without LNI (HAI-5-III patient preference trial, including only women of 65 years or over). We decided to maintain the convenience of dose-delivery every other day, partly because it guarantees a minimum of 24h repair time in between fractions but also because it is considered a convenient rhythm by patients and family. Because grade 2-3 dermatitis was only found in the group with boost, the SIB-dose is lowered to 31Gy/6.2Gy (EQD2 range 50.7-58.1Gy) and in case of involved margins, 32.5Gy/6.5Gy.

As explained in chapter 2.7.b, the LQ model is intended for doses up to 5Gy per fraction. With the LQmodel, EQD2s comparable to normofractionation were calculated and comparable toxicity was expected. However, acute toxicity seemed even lower than expected with standard hypofractionation, although this observation needs to be confirmed in an ongoing matched-case control study. This may signify that the LQ-model potentially overestimates toxicity or underestimates the effect of a lower total dose, whereas the effect of higher fraction doses on tumour control may be underestimated. This hypothesis has so far been confirmed in reports on 5-8-years follow-up after once weekly acceleration, displaying excellent tumour control and overall survival, even if WBI-only was applied for patients presenting with involved lymph nodes[25, 142-144].

The effects of high fraction doses on the brachial plexus remain closely monitored: effects of radiotherapy on this late reacting tissue may only become apparent many years after radiotherapy[22, 146]. Concern for cardiac injury should primarily lead to methods for shielding the heart, as no threshold dose for major cardiac events has been withheld[47]. With an α/β between 1.5 and 3Gy for cardiac toxicity, the EQD2 of an accelerated regimen is situated between 49.6 and 58.6Gy for a 28.5Gy/5fr regimen (to compare with 50Gy if normofractionation) and 57-68.2Gy for a 31Gy/5fr regimen if a SIB is added (compared with 66Gy if normofractionation)[106]. With acceleration permitting lower total doses, the LQ model may again overestimate the effect on the heart. Regarding the lungs, SBRT has shown a relation between pneumonitis and mean lung dose or irradiated volume. Lungs are a parallel organ, and therefor benefit from keeping the irradiated volumes as low as possible. With IMRT for accelerated breast radiotherapy including LNI, the ipsilateral lung V13 was in most patients below 20% (mean V13 was 15%), and mean ipsilateral lung dose was kept low (Dmean 5.3Gy). Doses became negligible with WBI in prone position.

The major advantage of the HAI-5 regimen is the inclusion of all curative indications for adjuvant breast radiotherapy, thus expanding the advantage of a short fractionation schedule from the limited indication of APBI to the entire breast cancer population. In our feasibility trial, age was limited to 65 years and over. In the subsequent RCTs, inclusion is accepted as of 18 years of age, as well for the cohort with WBI and LNI (PRO-SURF RCT) as for the WBI only group (YO-HAI-5 RCT).

Future perspectives of accelerated breast irradiation

A potential advantage of short schedules is the role that accelerated radiotherapy may play in a neo-adjuvant setting. With an overall treatment time of 10 days, radiotherapy becomes an interesting alternative for chemotherapy in LABC. The advantage of such approach is the possibility to explore the pathological effect of radiotherapy on tumour biology.

First attempts for neo-adjuvant radiotherapy go back to the seventies[148], but despite promising results, were abandoned with the uprising of chemotherapy. At this moment, large or inoperable LABC is treated with chemotherapy in a neo-adjuvant setting, resulting in variable tumour responses. However, since the past two decades, new studies on preoperative radiotherapy appeared and confirmed feasibility, either or not with concomitant chemotherapy. An interesting pathological analysis of 15 patients with large tumours, treated by radiotherapy alone in the neo-adjuvant setting,

showed good response in 60% of patients; a remarkable finding in this cohort is that although the invasive tumour decreased in size, tumour cells remained present in the peripheral zone of the initial primary tumour[149]. Riet et al. reported on 32 years of follow-up after preoperative hypofractionation (18-22x2,5Gy) to breast and lymph nodes, followed by ME and ALND. OS and DFS at 25 years were 30%, with 89% loco-regional control. Pathological revision of the specimen showed triple-negative (TN) phenotype in 22% of tumours. Complete response had been achieved in 10% of patients, but in 26% of TN tumours. On multivariate analysis, TN status was the only predictive factor for response, and together with pN status, for OS. Postoperative complication rate was high (>19% grade 3 or higher complications), but it should be kept in mind that this patient cohort had been treated between 1970 and 1984.

Within the group of patients requiring neo-adjuvant therapy, women under the age of 40 are particularly interesting. In these young women, age was found an independent adverse prognostic factor for loco-regional control (38% 10-year LRR in women younger then 40 years, diagnosed with ESBC), with a relative risk increase of 7% for every decreasing year of age[9]. Bringing radiotherapy to the neo-adjuvant setting may give insight into the question if this different tumour behaviour also translates in different radio-sensitivity.

To explore these questions, a study on the effect of accelerated radiotherapy in the neo-adjuvant setting is planned. Neo-adjuvant treatment cannot only evaluate the effect of radiotherapy on different tumour types, but also the effect of acceleration to even shorter schedules. Another issue would be the search for the ideal delay between radiotherapy and surgery, permitting maximal tumour shrinkage without compromising operability. Lastly, the combination of radiotherapy with chemotherapy in a neo-adjuvant setting has shown interesting results and deserves further research[150, 151].

From a global perspective, safe delivery of WBI or TWI in 5 fractions may be an attainable option for adjuvant breast cancer radiotherapy in low- and middle-income countries. Although awareness, diagnostic means and availability of treatment (surgery, systemic therapy as well as radiotherapy) are a first concern in these countries, easy access acceleration may help in reducing logistical obstacles such as waiting lists, costs of sessions, transport and lodging and socio-economic impact of absence during protracted treatment courses. The higher incidence of LABC with higher need for LNI requires technical experience that is seldom available in these countries. However, even if only the breast or thoracic wall are included, lowering the threshold for adjuvant radiotherapy may at least to some extent improve overall outcome[11, 12]. Lower acute toxicity because of decreased total dose adds to the list of advantages.

Objective 3: Health economic evidence of post-operative breast radiotherapy: is it valid?

Evaluation of the quality of the available health economic evidence on post-operative breast radiotherapy, and its validity to guide health care decision-making

Clinical trials mainly focus on efficacy (can it work?) and effectiveness (can we do it?) of new strategies[13, 14]. Whereas efficacy research is confined to strict recruitment and quality rules, effectiveness research will evaluate if these outcomes can be reproduced in a non-ideal but realistic every day clinical world. One step further is to analyse whether such effective strategies are worthwhile from an economic point of view, adding costs to the picture. This brings health research to the domain of HEE.

As extensively explained in publication 3, the results of a HEE strongly depend on the quality of the analysis performed. Before results can be interpreted or generalized to the own situation, the reader must have insight into what models were applied, which data sources where used and to what extent uncertainty and heterogeneity were explored. This can only be achieved with transparent reporting of each step taken. To homogenize reporting quality in HEE, guidelines have been published, listing the items needed to appreciate the validity of HEE[15-17]. The most recent publication comes from the ISPOR group, who published the CHEERS' guidelines with 24 items representing the most essential elements required for transparent reporting in cost-effectiveness analysis[18]. Although this checklist is not primarily conceived for quantification, its structure predisposes to a straightforward scoring system, as each of the items is limited to one single aspect. Such quantification facilitates benchmarking between publications and comparison with predefined thresholds. However, the scoring system accords equal weights to each item, regardless of its importance, varying from completeness of title over reporting of data sources unto presence of uncertainty analysis. For further nuancing, qualitative evaluation is also required. Moreover, transparency is not a substitute for validity: a transparently reported wrong method remains wrong. Nevertheless, as transparency of reporting is the first step in quality analysis of HEE, quantitative and qualitative evaluation of reporting quality, based on the CHEERS' checklist, allows to separate the chaff from the grain, for researcher, for journal editors and for policy makers.

We performed a systematic literature review on HEE of adjuvant breast radiotherapy and applied the CHEERS' criteria for qualitative evaluation of these publications. Results were also quantified, in line with similar examples in other healthcare domains[19]. As quantification of the CHEERS' checklist is not yet validated, scores were compared with two validated methods, the QHES and the Tufts' scores. The 24 items CHEERS' items were applied on the cost-effectiveness analyses (CEA) and a selection of 13 relevant items was applied on the cost comparison analyses (CC).

As explained in publication 3, qualitative analysis revealed that several items, including data sources, population heterogeneity and sensitivity analysis, essential for reliable cost-effectiveness results, could benefit from more transparent reporting and justification of choices made. Selective data input may bias results, potentially resulting in misleading information and jeopardizing valid decision-making on the allocation of limited health-care resources. Hence, in the absence of a systematic review, choices made should at least be clearly motivated. Where most publications contained a sensitivity analysis, the topic of heterogeneity, analysing the impact of the population chosen on the final results, was rarely discussed. This seems connected to the recurrent neglect of generalizability in the discussion. Without heterogeneity analysis, evidence of cost-effectiveness risks to be transferred erronously to different indications or modified base cases.

Quantification of scores resulted in an acceptable high to intermediate level for most publications, with an overall score of 75.6% for CCs and 74% for CEAs. These results did not significantly differ from QHES' or Tufts' scores. If a threshold of 75% would have been applied, only 6 out of 13 CCs and 13 out of 20 CEAs would have been considered valid, whereas a medium quality threshold (50% score) was reached by all CCs and almost all CEAs. Although practicable, it must be kept in mind that such thresholds remain altogether arbitrary. Firstly, quantitative benchmarking may forego important items like reporting of data sources, population heterogeneity and sensitivity analysis, especially when all items are attributed an equal weight. Secondly,

transparent reporting may be a prerequisite, but not a substitute for model validity. A wrong model remains wrong, even if transparently reported[20].

Overall, quantitative CHEERS' evaluation was found feasible and reliable compared to validated instruments. HEE evaluation for adjuvant breast radiotherapy is of an acceptable quality, but further efforts are needed to improve comprehensive reporting of all data, indispensable for assessing relevance, reliability and generalizability of results.

Objective 4: Post-operative breast radiotherapy: what are its cost and cost-effectiveness?

Evaluation of the available health economic evidence on post-operative breast radiotherapy regarding the balance between costs and effectiveness of different techniques and fractionation schedules

A next step was taken in publication 4, where costs and cost-effectiveness were compared for a subset of the HEEs on adjuvant breast radiotherapy, more specifically HEEs that compared different fractionation schedules and/or techniques or evaluated the cost of adding radiotherapy for specific risk populations. Costs were converted to euro, 2016, and were brought together in cost-effectiveness planes to permit comparison of outcomes and cost-effectiveness results.

Although many caveats must be taken into account, as extensively explained in the discussion of this publication, some conclusions can be drawn: substituting normo- by hypofractionation reduces healthcare costs for an at least equivalent health-effect and should be considered the new gold standard for comparison. In very favourable subgroups, omission of radiotherapy is a valuable option as comparator for APBI.

Results of HEEs on APBI are controversial: interstitial and balloon-based techniques prove too expensive to compete with less costly WBI EBRT techniques, especially when normofractionation is replaced by hypofractionation or acceleration. However, caution is needed as data mainly come from the US, are reimbursement-based and potentially overestimate the costs. Results on IORT are diverging, mainly due to discrepancy in estimated QALYs. Two authors righteously compared IORT with hypofractionation. Whereas the ICER, calculated by Vaidya et al., led to a dominant situation, combining a gain in QALY with a lower cost, Picot found a comparable lower cost to come with a loss in QALY, thus situating the result in the "lower-benefit-for-lower-cost" trade-off quadrant. Publications on IORT are all based on the premature data of the TARGIT trial, with a median follow-up of less than 3 years for a very favourable subset of ESBC. It seems advisable to await long-term data, preferentially beyond 5 years, and to add omission of radiotherapy as comparator, before settling the place of IORT in the spectrum of adjuvant treatments.

With several ICERS located in the "lower-benefit-for-lower-cost" trade-off quadrant, combining a financial benefit with a loss in QALY, the question rises how much loss in QALY is acceptable in return for budgetary savings. *If an alternative treatment is less expensive but comes with a loss in effectiveness, would this be acceptable for society? And if so, what is the willingness-to-accept threshold of society? The authors of the PRIME trial, which includes a piggyback analysis on omission of radiotherapy for low risk breast cancer in the elderly, state that omission of radiotherapy comes at a saving of over 200.000£ for one QALY lost, which is well above the UK threshold of 30.000£ acceptable as extra expenditure per QALY gained. Such reasoning foregoes the difference between a willingness-to-accept versus a willingness-to-pay threshold. In fact, the acceptable selling-price has been found systematically larger than the buying price, resulting in a 'kink' in the accept-reject threshold of a cost-effectiveness plane, with a larger rejection area in the lower-benefit-for-lower-cost quadrant compared to the 'higher-benefit-for-higher-cost' quadrant[21]. One of possible explanations may be the 'endowment effect', which implies the psychological reflex of considering the utility of a loss greater than the utility of an equivalent gain.*

In view of the results of the Canadian and the START trials, proving equivalence in terms of tumour control and overall survival, HEEs comparing hypo- with normofractionation are expected to approach cost minimization strategies, with shorter schedules winning the game. However, for partial breast strategies, stating budgetary savings together with other advantages, several publications reported not only a loss in QALY, but also a higher societal cost. Such findings seem to contradict the wide-spread implementation of intraluminal balloon-techniques, especially in the US. At least part of the explanation for such paradox may be found in an exercise by Schutzer et al., who calculated the real cost for balloon-based brachytherapy within the US and reported a cost less than half the reimbursement advocated in other publications[22]. From an institutional perspective, such profitable balance may become an attractive source of income, justifying a slight loss in QALY, especially because the patient shares in the benefits from a shorter treatment course.

Economic issues may also explain to some extent the implementation pattern of hypofractionation. A review on publications exploring the uptake of hypofractionation revealed this to be slow, despite robust evidence on the clinical safety and the evidently lower societal cost (figure 13). This may become more comprehensible, when changing again the perspective from payer to institutional: in fraction-based reimbursement systems, loss in reimbursement may not be compensated for by lower treatment costs. Radiotherapy costs indeed do not

scale linearly with fraction number: the cost of treatment preparation (simulation, planning, dosimetry check…) is independent from the number of fractions, implying a higher relative preparation cost per fraction for accelerated schedules. Moreover, the cost of quality assurance may rise, as the relative contribution of each fraction to the entire treatment increases, leaving little room for error. Hence, in case of a negative cost balance, robust clinical evidence may not be sufficient to overcome the financial hurdle of radiotherapy departments who need to function within an economic reality.

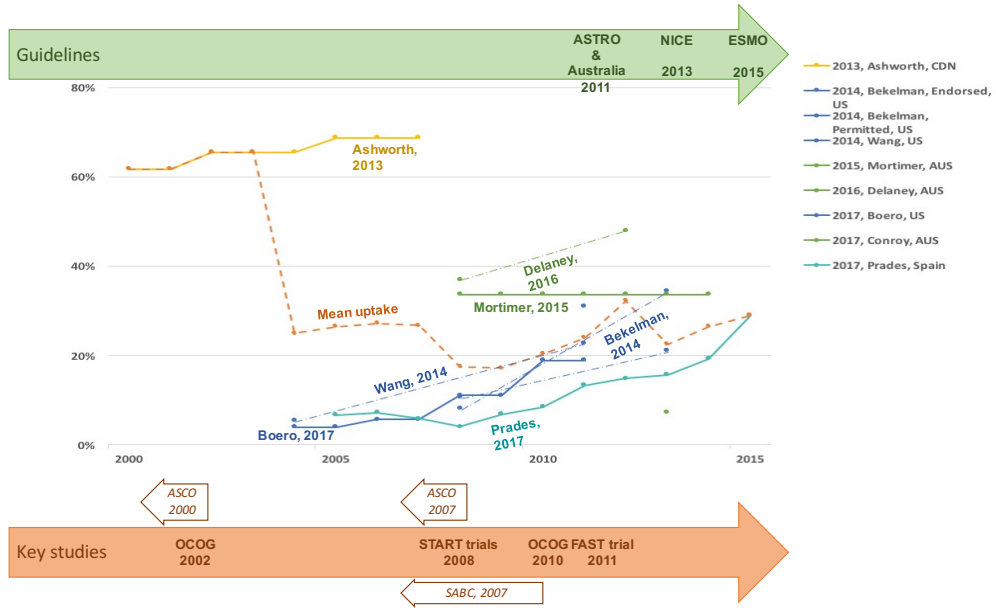

Fig 13 - Timeline indicating the milestones on hypofractonation in relation to the progressive uptake of hypofractionation in different countries[23-29]

Consequently, it seems overhasty to conclude that the ultimate societal saving will be found in acceleration to 5 fractions or even less, since higher doses imply more complex planning and intensified quality assessment. Delivery of multiple high dose levels over large fields requires multibeam-IMRT or VMAT to avoid the risk of accidental or systematic overlap with adjacent field set-up. Shorter high-dose treatment schedules are less tolerant in terms of random errors, hence require more intense quality assessment, including IGRT: each fraction of a HAI-5 regimen contributes 20% of the radiotherapeutic treatment. Judicious policy making should therefore not blindly focus on potential budgetary savings and reallocate budgets, but use liberated means to improve quality and reduce long-term toxicity in this large cohort of cancer patients.

General considerations

Objective 1

An indicator-clip improves inter-observer delineation conformity for tumourbed delineation in prone position and after full thickness closure, with results comparable to more favourable delineation circumstances as supine positioning and visible seroma. This is an easy solution to improve precision for boost indications.

However, in APBI, delineation errors are not compensated for by the WBI component. Even if conformity is acceptable, accuracy without preoperative CT in treatment position was in our opinion too low to proceed to EB-APBI. Therefore, also in view of our experience with complex planning techniques, it was decided not to proceed with the development of prone IMRT-APBI, but to extend the advantages of accelerated fractionation beyond partial breast indications.

Objective 2

Accelerated radiotherapy of the whole breast or thoracic wall, including a simultaneously integrated boost and/or lymph node irradiation is feasible and well tolerated in terms of acute toxicity. Longer follow-up data are needed before implementing such high doses outside of clinical trials.

Acceleration to five fractions expands the small window of opportunity for APBI to the wide range of adjuvant indications in ESBC as well as LABC. Bringing accelerated radiotherapy to the neo-adjuvant setting will help in understanding the tumour-biologic impact of high-dose fractions.

Objective 3

Quantification of CHEERS' evaluation on reporting transparency in HEE is feasible and results in comparable results compared to validated instruments.

Quality of reporting in HEE on adjuvant breast radiotherapy is of an acceptable intermediate to high level. However, there is still room for improvement, especially regarding the use of valid and reliable data sources and more elaborate handling of uncertainty, through sensitivity analysis including population heterogeneity, to provide data for sound health-care decision-making.

In general, the systematic use of quality checklists, both for reporting and methodologic evaluation, would help policy-makers in assessing the validity of HEE when reimbursement for new technologies is discussed. In line with the ACCP guidelines on quality of clinical evidence, categorizing HEE according to methodologic quality and robustness of input data would provide a simple and transparent means for comparing decisions regarding acceptance and level of reimbursement policy across nations[30].

Objective 4

Based on the available evidence, HEE indicate hypofractionation and acceleration are less costly and appear cost-effective strategies compared to normofractionated WBI. Accelerated partial breast techniques, as intraluminal balloon-based and interstitial APBI, have not yet established cost-effectiveness when compared to WBI. Stronger evidence, with longer effectiveness data and the use of relevant comparators is needed before the role of IORT within the spectrum of breast radiotherapy can be defined, with personalised approaches for the individual patient going from accelerated WBI schedules over APBI up to omission of radiotherapy.

For favourable ESBC, choosing hypofractionated WBI as gold standard and comparing this with the omission of radiotherapy, intra-operative and external-beam APBI, would clarify which strategies are the most efficient in a population where the benefit of adjuvant breast radiotherapy is limited. A heterogeneity analysis based on different age groups would help further refine outcomes. Health-effect should be based on long-term follow-up of at least 5 to 10 years to avoid underestimation of the loco-regional relapse risk. Real-costing exercises are less likely to overestimate the budgetary weight of the different strategies. With avoidance of toxicity as the main driver in the search for alternative strategies, a scenario-analysis could explore the impact on cost-effectiveness of adding techni-

cal solutions to further reduce toxicity, such as IMRT, prone positioning and breath-hold techniques.

Whereas accelerated schedules may liberate both financial means and machine time, it also requires more complex planning and increases the need for quality assessment. This comes with a redistribution of personnel and infrastructural resources and costs. Judicious policy making should therefore not simply translate shorter fractionation schedules to budgetary savings, but reallocate at least part of such savings to investments required for safe delivery of high fractional doses and for further reducing long-term toxicity in this large cohort of patients.

Summary

My thesis was initially intended for introducing accelerated partial breast irradiation in very early stage breast cancer. The first hurdle to take in this process, was getting the target right, so we started with exploring how precise the tumourbed could be delineated, without giving up assets as full-thickness closure and prone positioning. An inter-observer exercise demonstrated the need for additional preoperative preparation to permit a reproducible as well as accurate delineation of the tumourbed. Preoperative contrast-enhanced imaging in treatment position was deemed necessary, besides the usual cavity wall clips, to clearly indicate the depth of the tumour in the breast. A purposely inserted indicator-clip, marking the depth of the primary tumour in the breast, was found an acceptable compromise for boost delineation, but not accurate enough for partial breast irradiation.

The two main advantages of partial breast irradiation are reduction of overall treatment time together with reduced toxicity of the surrounding tissue. However, without abandoning whole breast irradiation, improved radiation techniques, including prone positioning, intensity-modulated radiotherapy and deep inspirational breath-hold, significantly reduce doses to heart, lungs, contralateral breast and axilla. The original protracted treatment schedules of 25 to 33 fractions were already addressed by the introduction of hypofractionation to 15 fractions[31, 32] and by the promising results of our simultaneously integrated boost trial that led to further shortening of the overall treatment time[33].

With the promising results of accelerated whole breast irradiation in mind[10-12, 34, 35], we decided to take acceleration one step further and implement it for all indications, including whole breast, thoracic wall and lymph node irradiation as well as simultaneous boost delivery if needed. We hypothesized that by integrating our technical abilities to simultaneously deliver different dose levels without overlap risk, acceleration could safely offer the advantages of a shorter treatment schedule to the entire group of patients needing adjuvant breast radiotherapy. Because long-term data on such a schedule are not yet available and because undertreatment – partly due to the burden of protracted radiotherapy schedules – is mainly a problem in elderly women, inclusion was in this first phase limited to women over 65 years[36, 37].

Delivery of high doses was found feasible, even in prone position, and results on acute toxicity were more than reassuring, with occurrence of grade 2 dermatitis limited to the group including a boost. Only one patient developed a grade 3 dermatitis. These first experiences are now further explored in a patient-preference trial for mastectomized patients over 65 years and two randomized trials for whole breast and whole breast with lymph node irradiation, applying the same strategy, yet with a lower boost dose and extending inclusion to younger patients as well.

To answer the question if accelerated and partial breast techniques are worthwhile from an economic perspective, we performed a systematic literature review on health economic evaluations in this domain. In a first phase, the validity of HEE in adjuvant breast radiotherapy was evaluated through a qualitative analysis, based on the Consolidated Health Economic Evaluation Reporting Standards' guideline, and publications were benchmarked by translating the results to percentages. Because quantification is not yet a validated method, scores were compared with the Quality in Health Economic Studies' and the Tufts' scores, two validated scoring instruments. Results did not differ significantly and indicated an acceptable quality for most publications, although some caveats must be kept in mind, most importantly concerning validity of source data and handling of uncertainty, which may obviate applying the results in a broader context than the one described in the actual analyses.

Then, costs or cost-effectiveness for different fractionation schedules and/or techniques or for adding radiotherapy were analysed. To allow comparison, costs were converted to euro, 2016 and brought together in cost-effectiveness planes. Hypofractionation and accelerated external beam radiotherapy were found less costly and more cost-effective strategies. Accelerated partial breast techniques, as intraluminal balloon-based and interstitial APBI, have not yet established cost-effectiveness when compared to WBI. Stronger evidence, with longer effectiveness data and the use of relevant comparators is needed before the role of IORT for early stage breast cancer can be defined. In this subgroup of patients, a personalised choice will have to be made, ranging from hypofractionated or accelerated whole breast irradiation over partial breast irradiation up to omission of radiotherapy.

In conclusion, robust long-term evidence on the effectiveness and cost-effectiveness for accelerated radiotherapy, is not yet available. So far, it appears both feasible and safe to reduce the number of fractions from 15 to 5 within the confines of a trial. Although accelerated schedules may lower machine time and thus reduce resource needs and treatment cost, it should be kept in mind that higher fraction doses require more complex planning and increased quality assessment.

All in all, the one-disease-one-treatment paradigm no longer prevails: whereas different strategies have proven benefit, an evolution to tailor-made allocation of the most efficient radiotherapy option, including the equilibrium between patient- and tumour-related risk factors, could be facilitated if besides sufficiently long-term clinical evidence also evidence from cost-effectiveness research were more systematically implemented.

Samenvatting

Initieel beoogde mijn thesis de implementatie van versnelde partiële borstbestraling bij vroegtijdige borstkanker. De eerste stap in dit proces was het accuraat definiëren van het doelvolume, zonder de voordelen van diepe wondsluiting en buikligging op te geven. Een oefening die de intekening van meerdere radiotherapeuten vergeleek, toonde aan dat bijkomende preoperatieve voorbereiding noodzakelijk was, zowel om reproduceerbaarheid als accuraatheid van de intekening van het tumorbed te verbeteren. De oefening toonde de noodzaak van preoperatieve beeldvorming met contrast in bestralingshouding om de locatie van de tumor in de borst zo nauwkeurig mogelijk te reproduceren. Een indicator-clip, tijdens de operatie ingebracht en bedoeld om de diepte van de tumor in de borst aan te geven, bleek een aanvaardbaar compromis, bruikbaar voor intekening van het boost-volume, maar onvoldoende accuraat voor partiële borstbestraling.

De twee belangrijkste voordelen van partiële borstbestraling zijn het inkorten van de totale behandelingsduur en het verminderen van de dosis op de omliggende organen. Maar met verbeterde bestralingstechnieken, waaronder buikligging, intensiteits-gemoduleerde radiotherapie en diepe ademhalingsstop kunnen dosis op hart, longen, contralaterale borst en okselregio ook bij volledige borstbestraling laag gehouden worden. De vroegere langdurige schema's van 25-33 fracties werden inmiddels reeds vervangen door hypofractionatie in 15 fracties, en sedert de gunstige resultaten van de SIB-trial werd de sequentiële

boost vervangen door een simultaan geïntegreerde boost, met verder verkorten van de totale behandelingsduur als resultaat.

In navolging van de geruststellende resultaten met versnelde borstbestraling in meerdere publicaties, beslisten we om versnelde borstbestraling ter beschikking te stellen voor een bredere waaier aan indicaties, inclusief bestraling van borst, thoraxwand, lymfeklierregio's en/of geïntegreerde boost. Onze hypothese was dat we op basis van onze technische ervaring om simultaan meerdere dosisniveaus te bereiken binnen één bestralingsveld en –sessie, alle overlaprisico konden vermijden en zo de voordelen van versnelde bestraling veilig konden aanbieden aan de hele groep van patiënten verwezen voor adjuvante borstbestraling. Vermits er nog geen lange-termijn data beschikbaar zijn over de neveneffecten van dit schema en ook omdat onderbehandeling vooral een probleem is in de oudere populatie, werd de inclusie in deze eerste fase beperkt tot vrouwen vanaf 65 jaar.

De studie toonde dat bestraling met hoge dosis per fractie niet alleen haalbaar was, zelfs met toepassing van buikligging, maar dat de eerste gegevens over acute toxiciteit geruststellend bleken, met het optreden van graad 2 roodheid en irritatie van de borst enkel in de groep mét geïntegreerde boost. Graad 3 huidschade (vochtige desquamatie) trad slechts op in één patiënte. Deze eerste ervaringen worden inmiddels verder geëvalueerd in een studie met versnelde bestraling na mastectomie, waarbij de patiënte zelf mag kiezen tussen het 15- of 5-fractie schema (HAI-5-III studie), en in twee gerandomiseerde studies die beide schema's vergelijken voor borst-bestraling (YO-HAI5 studie) en voor borst mét lymfeklierbestraling (PRO-SURF studie). In deze vervolgstudies werd de boost-dosis wel lichtjes gereduceerd en werd de intrede-leeftijd verlaagd tot 18 jaar.

Alvorens een antwoord te kunnen geven op de vraag of versnelde en partiële borstbestralingstechnieken ook interessant kunnen zijn vanuit een economisch oogpunt, startten we met een systematische literatuurstudie van gezondheids-economische evaluaties in dit domein. In een eerste stap evalueerden we de betrouwbaarheid van gezondheids-economische evaluaties in adjuvante borstbestraling middels een gevalideerde kwalitatieve checklist, de CHEERS' checklist, en zetten we deze kwalitatieve evaluatie om in scores om vergelijking oftewel benchmarking van de kwaliteit van de publicaties mogelijk te maken. Gezien deze omzetting tot nog toe nog niet gevalideerd werd, vergeleken we onze

resultaten met de scores van twee gevalideerde checklists. Deze bleken gelijklopend en bevestigden een aanvaardbare kwaliteit voor de meeste studies, al moet opgemerkt worden dat bepaalde items zoals rapportering en motivatie van de gekozen brondata evenals probabiliteits-analyse zeker meer aandacht verdienen.

In een volgende stap werden de kost en kosteneffectiviteit van de verschillende bestralingsschema's en –technieken vergeleken, evenals de impact van het weglaten van bestraling. Om de gegevens van de publicaties te kunnen vergelijken, werden kosten geconverteerd naar euro (2016) en samengebracht in kosteneffectiviteitsdiagrammen. De oefening toonde dat hypofractionatie en versnelde externe bestraling de laagste kost genereren en het meest kosteneffectief zijn. Technisch geavanceerde technieken zoals interstitiële en ballon-brachytherapie konden dusver geen kosteneffectiviteit aantonen. De resultaten voor de intraoperatieve Intrabeam toepassing (IORT) zijn eerder controversieel: sterkere evidentie, met langere-termijn data over de effectiviteit van deze techniek en vergelijking van de resultaten met relevante bestralingsschemata (hypofractionatie en/of weglaten van radiotherapie) zijn nodig alvorens de rol van IORT voor vroegtijdige borstkanker finaal bezegeld kan worden. In deze doelgroep van laag-risico patiënten zal op basis van patient- en tumorkarakteristieken een gepersonaliseerde aanpak mogelijk zijn, met keuzemogelijkheden gaande van gehypofractioneerde of versnelde borstbestraling over partiële borstbestraling tot weglaten van radiotherapie.

Tot besluit moet gesteld dat robuuste, lange termijn evidentie over effectiviteit en kosteneffectiviteit van versnelde borstbestraling voorlopig nog niet beschikbaar is. Tot nog toe lijken de resultaten erop te wijzen dat het haalbaar zowel als veilig is om het aantal fracties verder te reduceren van 15 naar 5 fracties, maar bij voorkeur binnen een klinische studie. Alhoewel versnelde borstbestraling minder 'machinetijd' vereist en dus de behandelingskost kan verlagen, vereist deze techniek complexere bestralingsplannen en intensievere kwaliteitsbewaking.

Als finale conclusie willen we stellen dat het 'één-ziekte-één-behandeling' paradigma ook voor borstbestraling niet langer kan weerhouden worden: verschillende strategieën hebben inmiddels voordeel aangetoond. De ideale strategie neemt zowel patiënt- als tumorgerelateerde factoren mee in rekening, en is gebaseerd op zowel klinische lange-termijn-data als de resultaten van kosteneffectiviteitsonderzoek.

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DANKWOORD

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Na maanden broeden op welke richting uit te gaan, uiteindelijk toch een telefoon aan **Wilfried De Neve**.

Zou ik als 40-jarige alsnog het roer omgooien en vanuit mijn comfortabele positie binnen de ziekenfondswereld durven terugkeren naar het assistentschap, om zo mijn droom om radiotherapeut-oncoloog te worden alsnog te realiseren?

Eén telefoon heeft het gekost.
Met één cruciale vraag terug: ben je wetenschappelijk nieuwsgierig?
Een dag later al zijn antwoord: 'Wanneer kan je beginnen?'.

Die ene telefoon heeft veel veranderd. Heel veel. Op zowat alle vlakken. Met vandaag de grande finale van dat keerpunt – een doctoraat afleveren.

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***

In retrospect zie ik één rode lijn doorheen mijn traject: alles durven in vraag stellen: 'Zijn we wel zo goed bezig als we denken?' Verandering als enige constante van het leven. Met vallen en opstaan. Telkens weer opstaan, want daarin schuilt ware kracht.

Ik meen dus het juiste antwoord gegeven te hebben op die simpele vraag van **Wilfried De Neve** in 2011: Ben je wetenschappelijk nieuwsgierig?

Ja, ik ben nieuwsgierig, op wetenschappelijk vlak, en ver daarbuiten. En hoop dat mijn nieuwsgierigheid een heel klein beetje mag bijdragen aan een betere wereld.

CURRICULUM VITAE

Chris Monten (° Jan 28TH, 1971)

Positions

1996-1997: Trainee in Radiation Oncology, Leuven University, Belgium
1997-1999: Free assistant in Orthopaedics, Sint-Lucas Hospital, Bruges
1999-2011: Medical advisor Mutualité Libre – Onafhankelijke Ziekenfondsen

Member of the College of Medical Directors
Member of the Technical Medical Board and related working groups
Member of the Technical Board for Implants

2011-2016: Trainee in Radiation Oncology, Ghent University, Belgium
2016 till now: Research fellow at the department of Radiation Oncology, Ghent University, Belgium
February 2018: President of the Commission for reimbursement of implants and invasive devices, NIHDA

Education

1989-96: Medical sciences, Leuven University, Belgium
1998-99: Advanced master of Insurance Medicine and Medico-legal Expertise, Inter-university Course (Leuven – Antwerp – Ghent)
2011-16: Master of specialist Medicine – Radiation Oncology, Ghent University, Belgium

Additional courses

Manama-related courses:

Good clinical practice, EBM, Hospital management and practice, Communication skills (teach the teacher), Ghent University

Statistical analysis using SPSS, Ghent University

Doctoral School:

Writing abstracts
Graphical design
R-statistics
Process Management

Publications

Mulliez, T., Van de Velde, J., Veldeman, L., De Gersem, W., Vercauteren, T., Speleers, B., Degen, H., Wouters, J., Van Hoof, T., Van Greveling, A., **Monten, C**., Berwouts, D., De Neve, W. Deep inspiration breath hold in the prone position retracts the heart from the breast and internal mammary lymph node region. Radioth Oncol 2015, 117: 473-6

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Monten, C., Lievens, Y., Olteanu, L. A., Paelinck, L., Speleers, B., Deseyne, P., Van Den Broecke, R., De Neve, W., Veldeman, L. Highly Accelerated Irradiation in 5 Fractions (HAI-5): Feasibility in Elderly Women With Early or Locally Advanced Breast Cancer. Int J Radiat Oncol Biol Phys 2017, 98: 922-30

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Deseyne, P., Speleers, B., De Neve, W., Boute, B., Paelinck, L., Van Hoof, T., Van de Velde, J., Van Greveling, A., **Monten, C**., Post, G., Depypere, H., Veldeman, L. Whole breast and regional nodal irradiation in prone versus supine position in left sided breast cancer. Rad Oncol 2017, 12: 89

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Boute, B., De Neve, W., Speleers, B., Van Greveling, A., **Monten, C**., Van Hoof, T., Van de Velde, J., Paelinck, L., De Gersem, W., Vercauteren, T., Detand, J., Veldeman, L. Potential benefits of crawl position for prone radiation therapy in breast cancer. J Appl Clin Med Phys 2017, 18: e-link

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Monten, C., Veldeman, L., Verhaeghe, N., Lievens, Y. A systematic review of health economic evaluation in adjuvant breast radiotherapy: Quality counted by numbers Radioth Oncol 2017, 125: 186-92

DOI 10.1016/j.radonc.2017.08.034

Monten, C., Lievens Y. Adjuvant breast radiotherapy: How to trade-off cost and effectiveness? 2017, Radioth Oncol 2018, 126: 132-38

DOI 10.1016/j.radonc.2017.11.005

Mbah, C., De Ruyck, K., De Schrijver, S., De Sutter, C., Schiettecatte, K., **Monten, C.**, Paelinck, L., De Neve, W., Thierens, H., West, C., Amorim, G., Thas, O., Veldeman, L.

A new approach for modeling patient overall radiosensitivity and predicting multiple toxicity endpoints for breast cancer patients. Acta Oncol 2018, 57

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Monten, C., Veldeman, L., Vandecasteele, K., Oltéanu, L., De Gersem, W., Vercauteren, T., Mulliez, T., Van Den Broucke, R., Depypere, H., De Neve, W., Lievens, Y. External partial breast irradiation in prone position: how to improve accuracy Acta Oncol – submitted

Posters on international meetings

Monten C., Veldeman L., Olteanu L., Vercauteren T., Van Greveling A., Van den Broecke R., De Neve W., Lievens Y. Prone breast irradiation: can we improve precision and accuracy of tumour bed delineation. Poster at Bigart, Aarhus, June 2017.

Monten C., Veldeman L., Lievens Y. Treatment time in breast irradiation: a trade-off between positioning and complexity. Radioth & Oncol, 2016, abstract PO-0789

Monten C., Veldeman L., Olteanu L., Vercauteren T., van Greveling A., Van den Broecke R., De Neve W., Lievens Y. Prone partial breast irradiation: from indirect to direct tumour bed localization. Poster at the 3rd ESTRO Forum in Barcelona, April 2015.

De Neve W., Veldeman L., Ost P., Duprez F., Vandecasteele K., De Wolf K., **Monten C**., Berwouts D., Olteanu AML., Vercauteren T., De Gersem W. The promises of dose painting. Radioth & Oncol, 2016, abstract SP-0520