FACULTY OF MEDICINE AND HEALTH SCIENCES

Improving the risk-benefit ratio of breast cancer radiotherapy

Advancing deep inspiration breath-hold, positioning and accelerated hypofractionation

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Abbreviations

ABC	Active breathing control
ADC	Antibody-drug conjugate
AI	Aromatase inhibitor *or* Artificial intelligence
APBI	Accelerated partial breast irradiation
ALND	Axillary lymph node dissection
BCS	Breast conserving surgery
CALGB	Cancer and Leukaemia Group B
CO_2	Carbon dioxide
CPAP	Continuous positive airway pressure
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTV	Clinical target volume
DBP	Diastolic blood pressure
DIBH	Deep inspiration breath-hold
EBCTCG	The Early Breast Cancer Trialists' Collaborative Group
ECG	Electrocardiogramy
ESMO	European Society for Medical Oncology
ESTRO	European SocieTy for Radiotherapy and Oncology
$ETCO_2$	End tidal CO_2
FiO_2	Fraction of inspired oxygen
FNAC	Fine needle aspiration cytology
GEP	Gene expression profile
GTV	Gross tumour volume
HFNO	High flow nasal oxygen
HFPV	High frequency percussive ventilation
HI	Homogeneity index
HOBBIT	Hyperventilation oxygenation to prolong breath hold in breast cancer irradiation treatment

Abbreviations

HRQoL	Health related quality of life
ICI	Immune checkpoint inhibitor
ICRU	International Commission on Radiation Units & Measurements
IGRT	Image guided radiotherapy
IMN	Internal mammary nodes
IMRT	Intensity modulated radiation therapy
ITT	Intention-to-treat
LAD	Left anterior descending coronary artery
L-DIBH	Prolonged deep inspiration breath-hold
LINAC	Linear accelerator
LNI	Lymph node irradiation
LR	Local recurrence
MANIV	Mechanically-assisted non-invasive ventilation
MHD	Mean heart dose
MLC	Multileaf collimator
MLD	Mean lung dose
MRI	Magnetic resonance imaging
NACT	Neoadjuvant chemotherapy
NAPBI	Neoadjuvant partial breast irradiation
NART	Neoadjuvant radiotherapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OAR	Organ at risk
OTT	Overall treatment time
PBI	Partial breast irradiation
PCBC	Prone-crawl breast couch
pCR	Pathological complete response
PEEP	Positive end-expiratory pressure
PHAIR	Preoxygenated hyperventilated hypocapnic apnea-induced radiation
PMRT	Postmastectomy radiotherapy

PPA	Per-protocol-analysis
PTV	Planning target volume
RCT	Randomized controlled trial
RIHD	Radiation induced heart disease
RP	Radiation pneumonitis
RR	Respiration rate
RTN	Retrotrapezoid nucleus
RTT	Radiotherapy technologist or radiation therapist
SBP	Systolic blood pressure
SBRT	Stereotactic body radiotherapy
SEB	Sequential boost
SERM	Selective oestrogen receptor modulator
SGRT	Surface guided radiotherapy
SIB	Simultaneously integrated boost
SNB	Sentinel node biopsy
TNBC	Triple negative breast cancer
vDIBH	Voluntary deep inspiration breath-hold
VMAT	Volumetric modulated arc therapy
WBI	Whole breast irradiation

Chapter I: Benefits and risks of breast cancer radiotherapy

A. Breast cancer: a multimodality approach

Breast cancer is currently the most common form of cancer worldwide, since the incidence of female breast cancer recently surpassed the incidence of lung cancer.(1) Yearly, around 2.3 million women receive a diagnosis of breast cancer and around 685.000 women die due to the consequences of the disease. The lifetime probability to develop breast cancer has been estimated 1 in 11 in Europe by the European Cancer Information System.(2) Moreover, Belgium has the highest incidence rate of breast cancer worldwide. 10.962 women were diagnosed with breast cancer in Belgium in 2019, which resulted in a crude incidence rate of 189/100.000 person-years.(3) The average age at diagnosis was 63.4 years. This high incidence is undoubtedly related to the high prevalence of reproductive, hormonal and lifestyle risk factors compared to low- and middle-income countries, in combination with a high detection rate due to well-organized opportunistic mammographic screening. Why Belgium is the frontrunner of Western countries is not known. Reproductive and hormonal risk factors for breast cancer are a young age at menarche, an older age at menopause, advanced age at first birth, fewer children, less breastfeeding, menopausal hormone replacement therapy and oral contraceptives. Lifestyle risk factors include an excessive alcohol intake, overweight and low physical activity.(4) Another important risk factor for the development of breast cancer is a genetic predisposition. For instance, BRCA1 and BRCA2 are two genes that are associated with a higher risk of several cancers, including breast and ovarian cancer.(5)

Although breast cancer has the highest incidence, it is only the fifth leading cause of cancer mortality worldwide.(1) Accordingly, the current treatments of breast cancer are effective, especially compared to other types of cancer. However, the worldwide differences in the availability of these treatments and early detection efforts lead to a large difference in the mortality rate between transitioning countries and developed nations.(6)

Early-stage breast cancer is the focus of this thesis and can be defined as breast cancer that has not spread beyond the breast or regional lymph nodes (including the lymph nodes around the internal mammary chain).(7) Although the TNM staging, based on the anatomical extent of the disease is the most important determinant of survival, the molecular characteristics of the disease also have an important role. Lately, breast cancer has been subdivided into four different subtypes by the European Society for Medical Oncology (ESMO) based on routine histology, immunohistochemistry data and genomic profiling. The first subtype, Luminal A-like tumours are typically low grade, strongly ER positive/PgR positive and HER2 negative and have low proliferation. Secondly, the Luminal B-like tumours are HR positive but may have variable degrees

of ER/PgR expression, are higher grade and have higher proliferation (based on immunohistochemistry and genomic profiling) than Luminal A-like tumours. Thirdly, HER-positive breast cancer has HER2-receptors on its cell membrane. Finally, triple negative breast cancer (TNBC) lack both hormone receptors and the HER2-receptor. These different subtypes determine the need for additional treatment modalities, and can determine the sequence of treatments. The different treatment modalities for breast cancer include: surgery, radiotherapy, endocrine therapy, targeted therapies, immune therapy, and chemotherapy.(8)

B. Fundamentals of radiotherapy for breast cancer

Historically, mastectomy was the golden standard for treatment of breast cancer. Between 1920 and 1930 pioneers investigated a partial mastectomy, conserving part of the breast, followed by radiotherapy to reduce the risk of relapse. In the early 1970s research on breast conserving surgery (BCS) followed by radiotherapy showed a similar survival compared to mastectomy, with a local recurrence (LR) rate of around 5 to 10%.(4) Yet, BCS remained controversial, prompting the creation of several randomized prospective trials across Europe and the United States. These trials definitively showed the equivalence in 20-year survival of the two approaches. The first and largest trial was the NSABP B-06, in which women were randomized to BCS with radiotherapy, BCS without radiotherapy and mastectomy without radiotherapy. All three arms showed similar survival rates, but BCS without radiotherapy resulted in a nearly 40% for in-breast LR.(9) In 1990, the National Cancer Institute (NCI) of the United States developed a consensus statement that BCS followed by radiotherapy was the preferred treatment of choice.(10) The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) confirmed this choice in a meta-analysis, involving individual patient data on more than 25.000 patients, and found that the avoidance of a LR is important and affects the risk of breast cancer mortality.(11)

1. Targets for radiotherapy

Before delivering radiotherapy, the radiation oncologist needs to define the volume that requires treatment. The International Commission on Radiation Units & Measurements (ICRU) Report 50 has defined three different volumes required to deliver conformal radiotherapy.(12) The smallest volume is the gross tumour volume (GTV) that is defined as the palpable of visible extent of the malignant tumour. After the complete removal of the (primary) tumour during surgery, this volume cannot be defined. More important is the clinical target volume (CTV), a volume that includes direct and local subclinical spread of the tumour cells. Additional volumes not containing demonstrable tumour but at risk for microscopic spread are also included in the CTV. To ensure accurate radiation treatment, margins are added around the clinical target volume to account for

variations in CTV position and size caused by factors like patient movement, breathing, and setup inconsistencies. This adjusted area is known as the planning target volume (PTV). The PTV margin should be determined in each treatment centre based on the motion of the CTV, setup variability and delivery precision. Several formulas to calculate PTV margins are available, with the van Herk formula being the most famous.(13) Generally, a margin between 5 and 10mm is used for breast cancer treatments.

Whole breast irradiation (WBI) includes all glandular tissue in the treatment fields and is recommended after BCS in most cases. Several guidelines have been developed for breast and lumpectomy cavity delineation to reduce the large interobserver differences previously determined.(14–18) From the late 1980's two large randomized trials concluded that increasing the dose around the lumpectomy cavity decreased the risk of LR, at the risk of increased fibrosis.(19,20) Therefore, the current guidelines recommend a tumour bed boost in patients with risk factors for relapse.(21,22) An alternative for WBI is partial breast irradiation (PBI). It aims to reduce the target volume to a subsection of the breast. The main goal of PBI was a reduction in toxicity due to a reduction in the volume treated. However, the latest Cochrane review did not find an advantage with regards to acute or late toxicity.(23) Moreover, it concludes that local recurrence free survival is probably inferior with accelerated PBI. It must be noted that a large variation in PBI techniques have been studied, with mixed results. A study with a positive result was the UK IMPORT LOW trial, comparing three arms: 1) hypofractionated WBI with a total dose of 40Gy (2.67Gy/fraction); 2) a treatment with two dose levels, WBI to a dose of 36Gy (2.4Gy/fraction) and a dose of 40Gy (2.67Gy/fraction) around the tumour bed (PBI); and 3) 40Gy (2.67Gy/fraction) PBI only. This study did not find differences between the three arms.(24) However, PBI still included a large portion of the breast: a 15mm margin around the CTV of the tumour bed (and a 10mm PTV margin).

Postmastectomy radiotherapy (PMRT) is recommended in case of positive lymph nodes after mastectomy.(21,22,25) The National Comprehensive Cancer Network (NCCN) also suggests considering postmastectomy in case of positive (or small) margins or large tumour of 5 cm.(21) The European SocieTy for Radiotherapy and Oncology (ESTRO) developed guidelines for the delineation of the chest wall, and updated these results for the delineation after early breast reconstruction.(16,17,26) The target volume of the chest wall excludes the major pectoral muscle, ribs, intercostal muscle and the first 5mm underneath the skin. After early breast reconstruction, the autologous transplanted tissues and synthetic materials (implant, tissue expander), used for the breast reconstruction, are not part of the target volume, whilst the other criteria remain equal.

Lymph node irradiation (LNI) involves treating the lymph node areas around the breast, which can be affected by a breast cancer lymph node metastasis. Six different lymph-node volumes have been defined: the supraclavicular volume (level IV), the infraclavicular volume (level III), the axillary level 2 (level II), the interpectoral space (Rotter space), the axillary level I (level I) and the internal mammary nodes (IMN).(27) The use of LNI is recommended in most cases after a positive SNB, and can often replace an ALND based on the results of the AMAROS trial.(28) The choice of volumes is dependent on the characteristics of the individual patient, but involves level II, level III and level IV in most cases. When a good ALND was performed and only limited disease was found, level I can be omitted. The criteria to include the IMN in the treatment fields remains controversial.

2. The road to accelerated radiotherapy

Historically, normofractionation was the standard of care and the dose prescription for WBI was 50Gy in 25 daily fractions of 2Gy/fraction, resulting in a treatment duration of five week in total. However, this changed after the Canadian and British hypofractionation trials discovered hypofractionation in 13 to 16 daily fractions did not influence the risk of relapse or late toxicity.(29,30) The total dose in these trials was reduced to between 39 and 42,5Gy, and accordingly a dose per fraction between 2.66 and 3Gy/fraction. Hypofractionation results in a first two-week reduction in treatment duration. Based on these results and advances in radiobiology, a further reduction in the number of fractions was investigated. The first studies were held between the late 1987 and 1999, investigating radiotherapy in 5 fractions for mostly elderly patients. The results were reassuring. Afterwards, two randomized trials were started in the United Kingdom: the FAST trial and FAST-FORWARD trial. Recently, the 10-year results of the FAST trial, comparing normofractionation with hypofractionated radiotherapy in 5 weekly fractions of 6Gy/fraction (30Gy total dose) or 5.7Gy/fraction (28,5Gy total dose), demonstrated no difference in risk of relapse or toxicity.(31) These findings are confirmed by the recent publication of the 5-year results of the FAST-FORWARD trial, comparing hypofractionation in 15 fractions with 5 daily fractions of radiotherapy of 5.4Gy/fraction (27Gy total dose) or 5.2Gy/fraction (26Gy total dose).(32) Both trials again resulted in a two-week reduction in treatment duration for many patients.(31, 32) An overview of the pivotal hypofractionation trials can be found in Table 1.

Table 1: Common fractionation schedules for breast cancer radiotherapy

Name	Total dose	Dose per fraction	Toxicity
Normofractionation (NF)	50Gy	2Gy	
START-A (29)	41.6Gy	3.2Gy	Non-inferior to NF
START-A (29)	39Gy	3Gy	Lower compared to NF
START-B (29)	40Gy	2.67Gy	Lower compared to NF
Canadian Trial (30)	42.5Gy	2.66Gy	Non-inferior to NF
FAST-FORWARD (32)	26Gy	5.2Gy	Non-inferior to START-B*
FAST-FORWARD (32)	27Gy	5.4Gy	Higher compared to START-B

*NF normofractionation, * Higher clinician (OR 1.90, p=0.013) assessed and patient assessed (OR 1.22, p=0.048) breast induration and higher clinician assessed breast oedema (OR 1.47, p=0.032)*

Around one in four patients within the FAST-FORWARD trial received a tumour bed boost. There are two methods to deliver a tumour bed boost: a sequential boost (SEB) or a simultaneously integrated boost (SIB). A SEB is the most used method and involves adding treatment sessions, after the end of the WBI, to irradiate only the tumour bed. All patients within the FAST-FORWARD trial received a SEB, resulting in between 5 to 10 additional days of treatment. The boost with a SIB is given daily throughout the treatment of the whole breast by adding dose to the region of the tumour bed without adding extra treatment sessions. This allows shortening the treatment by another one to two weeks, without increasing toxicity as seen in two randomized trials.(33–35) Overall, WBI including a boost has been accelerated to a treatment of one to two weeks by using hypofractionation, compared to five to seven weeks during the era of normofractionation. At the Ghent University Hospital two randomized trials, one currently recruiting and one closed, are further investigating the safety of accelerated WBI with a SIB.

The publication of the FAST-FORWARD results during the COVID-19 pandemic have led to a rapid adoption, beginning in England and Wales.(36) In four months, the percentage of patients receiving five fractions rose from <1% in February 2020 to 70% in April 2020. Five fractions were more often delivered to node-negative patients after BCS, with few comorbidities. However, the rate of adoption has been asynchronous worldwide. The main reason is the follow-up of only five years since late side effects can take a very long time to develop. Also, the difference in overall treatment time between hypofractionation with a SIB and five fractions with a SEB is minimal. Therefore, some authors have expressed caution about the use in especially young patients with a favourable long-term prognosis.(37) Although the dissertation contains studies (POP-ART and PRO-SURF) that deliver radiotherapy in five fractions, the use of (ultra-)hypofractionation is not the main subject.

Normofractionation is the historic norm for PMRT as was the case for WBI. Overall, the data supporting hypofractionation for PMRT is more limited, compared to WBI. Wang et al. published

the 5-year results of a randomized trial comparing normofractionation and hypofractionation in 15 daily fractions of 2.9Gy/fraction (total dose of 43.5Gy).(38) The results mimic those found for WBI: hypofractionated radiotherapy was non-inferior to and had similar toxicities to conventional fractionated radiotherapy in patients with high-risk breast cancer.

3. Patient positioning and immobilization

During radiotherapy the patients are positioned on an immobilization device, often called a "breast board", that is used to ensure the stability and maintenance of the patient's position.(39) Most patients are treated in supine position, with one or a combination of multiple immobilization devices: an inclined or flat breast board, fixed or movable hand restraint systems, vacuum bags, thermoplastic masks and commercialized bras. Two main systems for supine positioning are utilized: an angled board system with an armrest or a vacuum bag system, and no clear winner has been found.(40) Elevating both arms, compared to only one, does increase the patient stability and treatment accuracy to a small degree.(41) The main advantages of the supine position are the ease of set-up, the wide adoption, and the lowest physique required to hold the position.(40) The main disadvantages of supine position are the difficulty in immobilizing large breast, the breast overhang inferiorly resulting in additional skin toxicity and the movement of the breast during respiration. To account for the disadvantages of supine position, two other treatment positions were proposed: lateral decubitus and prone positioning.

The Institut Curie in Paris conceived the lateral decubitus technique, an alternative to supine positioning for large breasted women, to overcome nonhomogeneous dose distributions. Patients were positioned separately for the medial and lateral field. The lateral field is delivered with the patient lying on the contralateral side, the ipsilateral arm extended upward above the head and the breast supported on three centimetres of lead (designed to protect the contralateral breast). The medial field was delivered with the patient lying on the ipsilateral side, with the ipsilateral arm below the head, and the contralateral hand reclining the contralateral breast outside the beam.(42) The main disadvantages of the lateral decubitus technique are the requirement of meticulous positioning to exclude the contralateral breast from the treatment field, the lower reproducibility, and the lack of flexibility. Modifications to this lateral decubitus technique were proposed, but the positioning remained cumbersome.(43) Prone positioning was proposed as an alternative to the lateral decubitus technique. It combines the advantages of supine positioning (good reproducibility), with the advantages of the lateral decubitus technique (better dose homogeneity and normal tissue sparing).(44)

The first mention of prone position for WBI after BCS dates from 1994. Researchers from Memorial Sloan-Kettering used prone position, in large breasted women, as a method to improve dose homogeneity and normal tissue-sparing, compared to supine position.(44) The first prone positioning devices at Memorial Sloan-Kettering consisted of several different platforms, that evolved over time.(45) The experience acquired in the design of each generation of devices was shared in collaboration with the industry, leading to the development of several commercial positioning devices. These devices (mostly) position patients with both arms above the head, like in supine position. Certain prone positioning devices allow an antero-posterior supraclavicular field, allowing the delivery of WBI with LNI.(46) The main advantages of prone are the increase in dose homogeneity due to narrowing of the breast shape, better separation between breast and lung (and heart on the left side) and lower intrafractional motion.(40) The main disadvantage for the patient is the difficulty to climb onto the platform, the learning curve, and a reported lower setup accuracy.(47,48)

C. Benefits of breast cancer radiotherapy

Numerous randomized controlled trials compared the risk of LR and survival after surgery with or without radiotherapy, and these were combined in the meta-analysis by the EBCTCG. Figure 1 shows the results of the meta-analysis. WBI halves the risk of any breast cancer recurrence and yields a survival benefit.(49) Therefore, it is considered the standard of care after BCS for breast cancer and recommended by the guidelines.(21,22,25) The relative reduction in risk of LR is similar for all types of breast cancer, as seen in Figure 2. Accordingly, the absolute reduction in the risk of LR is dependent on the intrinsic likelihood of LR for each subgroup of breast cancer patients. The Cancer and Leukaemia Group B (CALGB) 9343 trial tried to omit radiotherapy in a group of patients over 70 years of age with a low risk of recurrence, stage I, hormone sensitive breast cancer after BCS.(50) The study still found a significant reduction in the risk of locoregional recurrence (from 10% to2% at 10-years). On the other hand, the reduced risk of locoregional recurrence did not result in an improvement in survival or freedom from mastectomy. Recently, the PRIME II trial reported analogous findings after BCS. The study included patients over 65 years with hormone receptor-positive, node-negative, T1 or T2 (but <3cm) primary breast cancer, after BCS with clear excision margins and adjuvant endocrine therapy. Patients were randomized between radiotherapy or no radiotherapy. With a median follow-up of 9 years the cumulative risk of LR within 10 years was reduced by a factor of 10.(51)

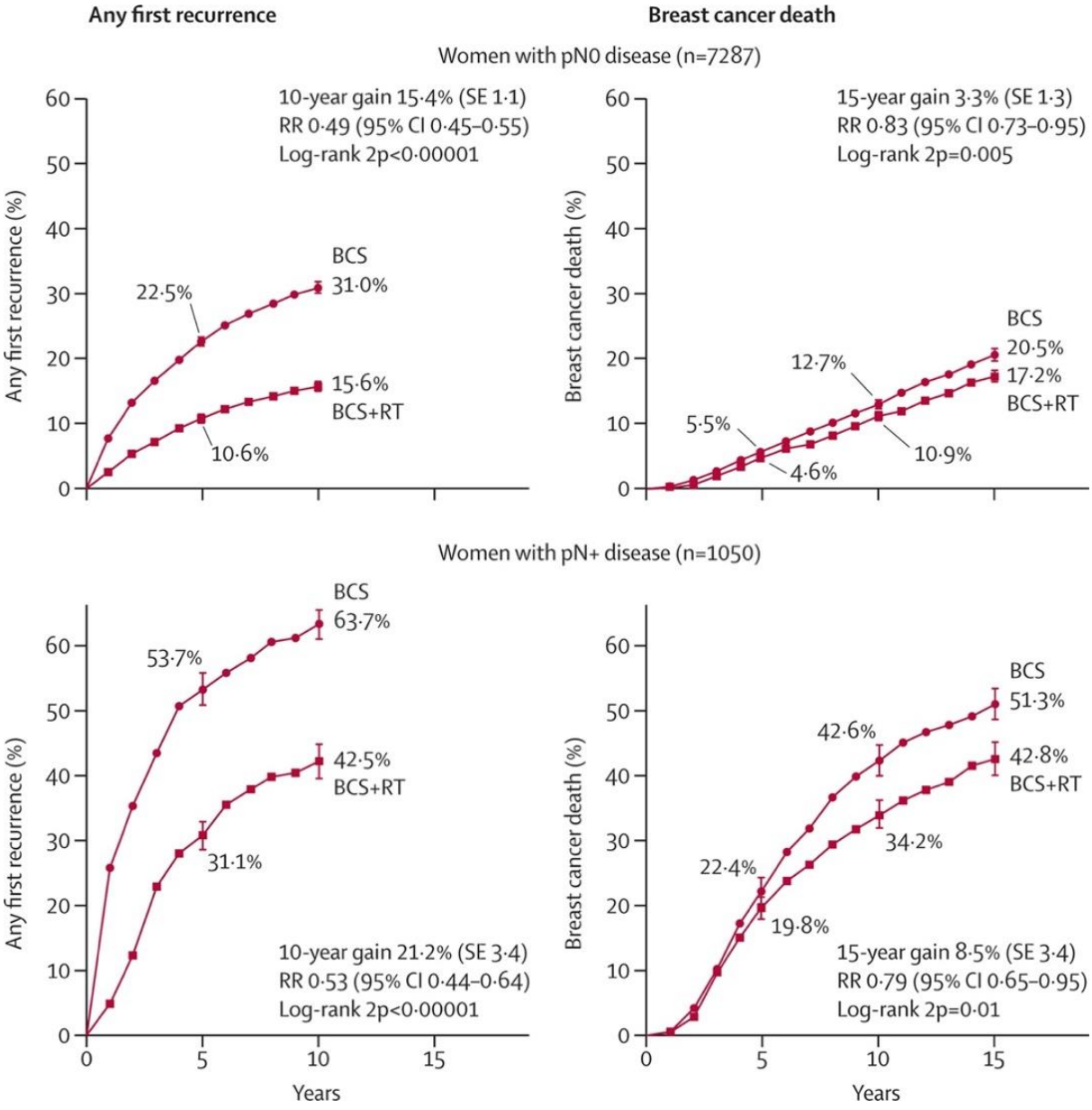

Figure 1: Effect of radiotherapy after breast-conserving surgery on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risk of breast cancer death in women with pathologically verified nodal status (From EBCTCG et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trails. Lancet. 2011;378[9804]:1707-1716.).

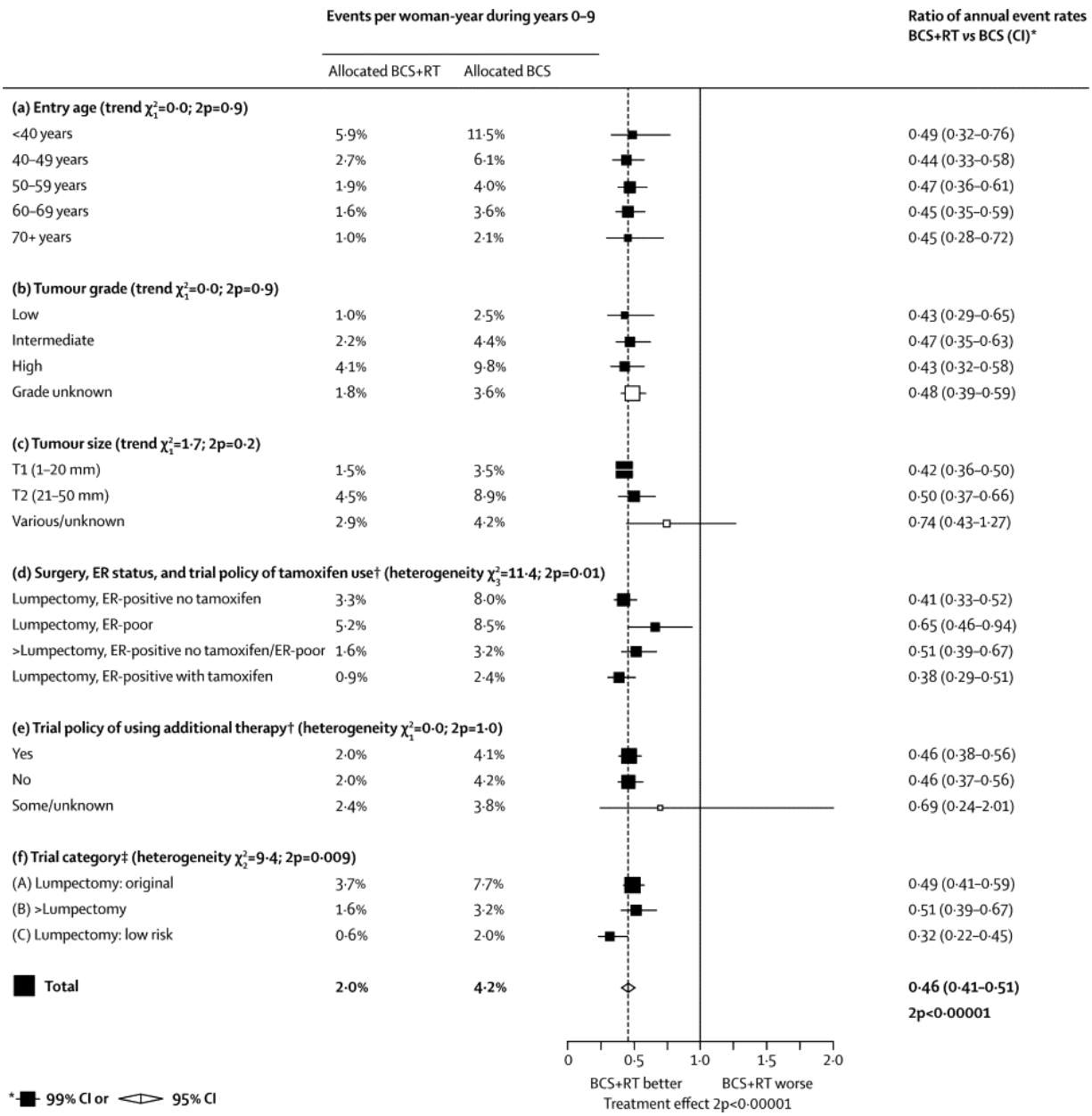

Figure 2: Event rates for any (locoregional or distant) first recurrence (% per year) and recurrence rate ratios for various factors, considered separately, during years 0–9 in women with pathologically node-negative disease (n=7287) (From EBCTCG et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trails. Lancet. 2011;378[9804]:1707-1716.).

The addition of LNI (including IMN radiotherapy) to WBI led to an improvement in the disease free survival in both the NCIC MA.20 and EORTC 22922 trials.(52,53) However, the addition of LNI only leads to better outcomes if the heart and lungs are spared. An EBCTCG analysis finds a reduction in breast cancer mortality and overall survival only for modern trials after 1989, with an estimated mean heart dose below 8Gy. In contrast, LNI lead to lower survival due to radiation exposure of the lungs and heart (estimated mean heart dose of >8Gy) in the era before.(54) As mentioned previously, the inclusion of the IMN remains controversial. The best evidence stems from the Danish DBCG-IMN trial that added IMN radiotherapy to patients with right sided breast cancer, and omitted the treatment in left sided patients. The trial showed an improvement in overall survival for right-sided patients.

D. Risks of breast cancer radiotherapy

1. Acute side effects

The side effects from radiotherapy of the breast usually start in the second week of treatment and are resolved around 8 weeks after the end of the treatment. Radiation related acute side effects include radiation dermatitis, skin desquamation, breast oedema, hyperpigmentation, breast pain, pruritus, and fatigue. The most common side effect is radiation dermatitis, occurring approximately 10 to 14 days after initiation of WBI. The radiation dermatitis will often progressively worsen throughout the course of the treatment and in the weeks following the end of treatment.(55,56) After the peak in toxicity, the side effects resolve after 4 weeks in most cases.

A side effect that can present during or shortly after treatment is a radiation pneumonitis (RP), often asymptomatic. The optimal treatment is a course of corticosteroids. The onset can occur during WBI or within months, and up to several years following WBI. The risk of RP is dependent on the dose delivered to the healthy lung tissue. A recent prospective trial of 396 patients found a risk of 38% for any grade RP, with 28% of cases being asymptomatic (grade 1) and no grade 3 or higher toxicity.(57) Finally, for patients requiring WBI with LNI a risk of radiation-induced oesophagitis is present. In a recent single-arm prospective observational study, around one in three patients (24/77) reported grade 2 oesophagitis.(58) Factors increasing the risk of oesophagitis were a mean oesophageal dose of ≥31Gy or ≥1cm of pharynx included in the supraclavicular fields.

2. Late side effects

2.1. COSMETIC IMPACT

Radiotherapy can induce reduce breast cosmesis gradually across several years. Late side effects from WBI include breast retraction, cosmetic changes, fibrosis, or breast induration within or outside the tumour bed, telangiectasia, breast oedema, breast pain and pigmentation changes.(32)

A recent systematic review showed risk factors for the development of late toxicity include the utilisation of a boost and the breast volume treated. However, patient related risk factors are not so clear. One publication mentions a high age as a risk factor, another publication found an association between late toxicity and young age, and eight other studies found no association. Similar inconsistent results were found between late toxicity and other patient or treatment related factors (e.g., diabetes, chemotherapy).(59) Genetic variations almost certainly play a role and several trials are investigating the critical locations in the genome.(60)

2.2. HEART TOXICITY

Radiation to the heart can lead to radiation induced heart disease (RIHD), including increased risk of coronary artery disease, cardiomyopathy, valvulopathy, arrhythmias and pericardial disease. The risk of RIHD differs based on the location of the tumour (left or right), the volume of heart irradiated, the location of the radiation damage (e.g., coronary arteries), the dose of radiotherapy, the concomitant use of cardiotoxic chemotherapy agents, and several patient related factors, like pre-existing cardiovascular disease, younger age at time of radiation and the presence of other cardiac risk factors (e.g. hypertension, diabetes, smoking, etc.). Women tend to have more cardiovascular events and are at increased risk of mortality compared with men with RIHD. A potential reason for this difference is the high percentage of post-menopausal women included in most studies, who lack the cardiovascular protective effect of oestrogen.(61)

Historic series, before 1970 and before the risks of RIHD were discovered, show a reduction in the risk of breast cancer mortality after radiotherapy, but an increase in the all-cause mortality 10 years after the treatment. In 1986, Host et al. reported a significant increase in the number of deaths caused by myocardial infaction in stage I patients after ^{60}Co radiation, treated between 1964 and 1972.(62) Two years later, Cuzick et al. reported an increase in the risk of death in a group of patients randomized to PMRT, surviving over 10-years after breast cancer.(63) Later analysis showed these excess deaths were mostly caused by RIHD and secondary lung cancer. Further research showed the rates of major coronary events increased linearly with the mean heart dose (MHD) by 7.4% per Gray, with no apparent safe threshold, as shown in Figure 3.(64)

Since the realisation of the risk of RIHD after breast cancer radiotherapy, around 1990, efforts have been made to reduce the dose to the heart. A recent large cohort study of 2 million women, confirmed a higher risk of cardiac mortality in women with left sided compared to right sided breast cancer (RR, left versus right, 1.04, 95% CI 1.02-1.06), due to the higher MHD in left-sided patients. However, this increase was confined to women whose cancer was diagnosed before 1990.(65) Further research is required to minimize the dose to the heart and reduce the risk of RIHD. However, this requires stringent follow-up over many decades since the effects of radiotherapy may present after a long lag time.

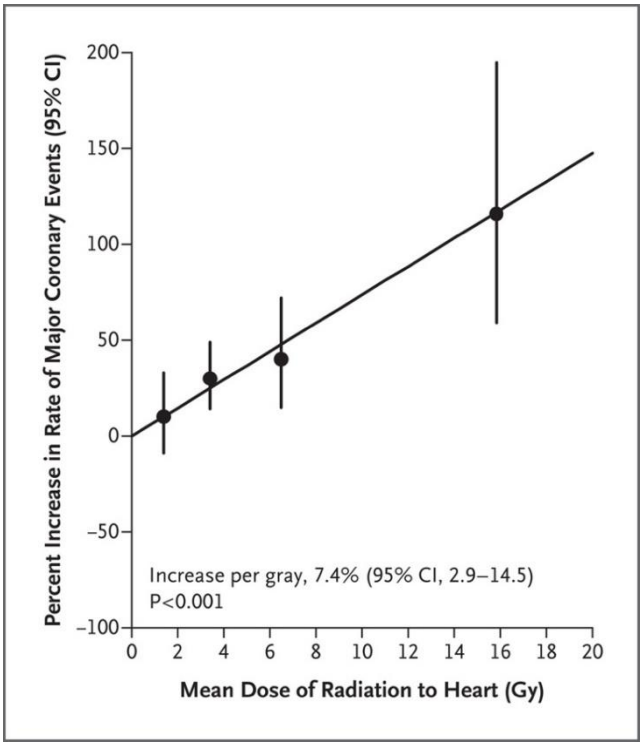

Figure 3: Rate of major coronary events according to mean radiation dose to the heart, as compared with the estimated rate with no radiation exposure to the heart. Major coronary events included myocardial infarction, coronary revascularization, and death from ischemic heart disease. The values for the solid line were calculated with the use of dose estimates for individual women. The circles show values for groups of women, classified according to dose categories; the associated vertical lines represent 95% confidence intervals. (From Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, Jensen MB, Nisbet A, Peto R, Rahimi K, Taylor C, Hall P. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med. 2013 Mar 14;368(11):987-98).

2.3. SECONDARY CANCER RISK

An estimated 13% of patients develop a secondary malignancy after the diagnosis of breast cancer, based on a SEER analysis of around 375.000 patients. Approximately 3.4% of these were attributable to radiation therapy. Both breast cancer patients treated with radiotherapy and those treated without radiotherapy have an increased risk of secondary malignancies, although the risk after radiotherapy is higher compared to no radiotherapy. Also, patients treated with radiotherapy

have an increased risk in specific sites like lung cancer, contralateral breast cancer, oesophagus cancer, leukaemia, and soft tissue sarcomas. The risk for secondary malignancies is higher after PMRT compared to radiotherapy after BCS, in the form of an increased risk of ipsilateral lung cancer, due to the generally larger treatment fields with LNI after PMRT. Other risk factors for a secondary malignancy include a younger age at time of exposure to radiotherapy and the time from exposure.(66,67)

Besides RIHD, the second important lethal complication of breast cancer radiotherapy is the development of a secondary lung cancer. Based on the SEER data from 1983-1992, the evidence supporting radiation-related mortality from lung cancer is higher than RIHD.(68) In the same way the risk of major coronary events is dependent on the MHD, the risk of secondary lung cancer is dependent on the mean lung dose (MLD). The estimated excess relative risk for lung cancer more than 10 years after radiotherapy is 0.11 per Gray mean lung dose (to both lungs). The absolute risk to develop lung cancer after breast cancer radiotherapy is highly dependent on the individual lung cancer risk before radiotherapy. Therefore, this risk is highly dependent on smoking history. Quitting smoking greatly reduces lung cancer incidence. Taylor et al. predicted a 4% absolute increase in the risk of lung cancer death for a 50 year old patient who does not stop smoking (Figure 4). Hence, convincing a patient to stop smoking at time of radiotherapy is crucial to substantially reduce the risk of radiation induced lung cancer, but also RIHD.(67)

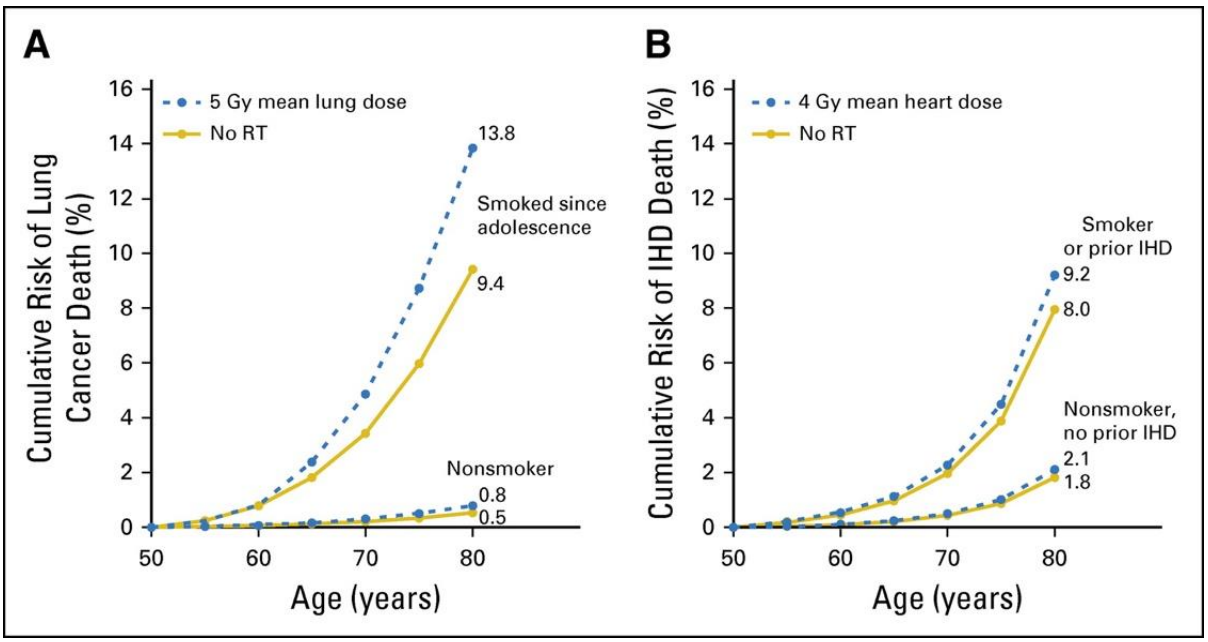

Figure 4: Estimated effects among 50-year-old smokers and nonsmokers of typical modern radiotherapy (RT) regimens on mortality from (A) lung cancer and (B) ischemic heart disease (IHD). Epidemiologic estimates of the risks without radiotherapy are multiplied by the rate ratios attributed to 5 Gy whole-lung dose and 4 Gy whole-heart dose. (From Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, Dodwell D, Ewertz M, Gray R, Jagsi R, Pierce L, Pritchard KI, Swain S, Wang Z, Wang Y, Whelan T, Peto R, McGale P; Early Breast Cancer Trialists' Collaborative Group. Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. J Clin Oncol. 2017 May 20;35(15):1641-1649.).

Chapter II: Prevention of side effects

Chapter one described the risks of radiotherapy of the breast. Fortunately, efforts have been made to reduce these risks. Innovations allowed for a reduction in acute and late toxicity and an improved cosmesis of the breast. As mentioned previously, the risk of RIHD can be reduced by lowering the MHD (see Figure 3) and minimizing the dose on the other healthy organs at risk, especially MLD (see Figure 4), reduces the risk of secondary malignancies.

A. Deep inspiration breath-hold

One of the first authors to report on the use of a deep inspiration breath-hold (DIBH), the patient holding their breath during the radiation treatment, was the Belgian radiation oncologist Vincent Remouchamps. In 2003 he published two articles in the red journal describing the advantages and use of a DIBH. The first publication in February 2003 described the reduction in heart and lung dose when performing a moderate DIBH using an active breathing control (ABC) device.(69) Five months later the initial clinical experience was described of moderate DIBHs (using the ABC device), with durations of 18 to 26 seconds and 4 to 6 DIBHs per fraction during a total of 25 to 28 fractions. The DIBH was well tolerated by patients, lead to lower dose to the heart and could be performed in a treatment slot of 15 minutes after gaining experience with the technique.(70) A systematic review of MHD published demonstrates a more than halving of the MHD using DIBH (Figure 5).(71) Since the description of DIBH 20 years ago, the technique has gained popularity worldwide.

Over the last 20 years, several techniques to achieve a DIBH during treatment have been developed. The two dominant methods are the spirometry-based ABC system developed by Elekta (a producer of linear accelerators for radiotherapy), and the voluntary deep inspiration breath-hold (vDIBH). The ABC system uses a mouthpiece attached to a spirometer that is connected to a computer. The patient also requires a nose clip to prevent breathing through the nose. The radiation therapist (RTT) can visualize the level of inspiration, and after reaching a predefined threshold a valve closes, inhibiting further inspiration. A vDIBH does not require a spirometer, but determines the adequate and reproducible inspiration through a measurement of the external anatomy of the patient. A popular system is the real time positioning management system, produced by Varian (a producer of linear accelerators), which utilizes an infrared camera and a marker box. The position and movement of the thorax is determined by tracking the reflective marker box. Once the marker box is moved within a certain threshold, through inspiration by the patient, the radiation treatment is started. A second method to follow the external anatomy of the patient is using surface guided radiotherapy (SGRT). Cameras detecting the 3-dimensional surface of the patient are used to determine the movement and position of the

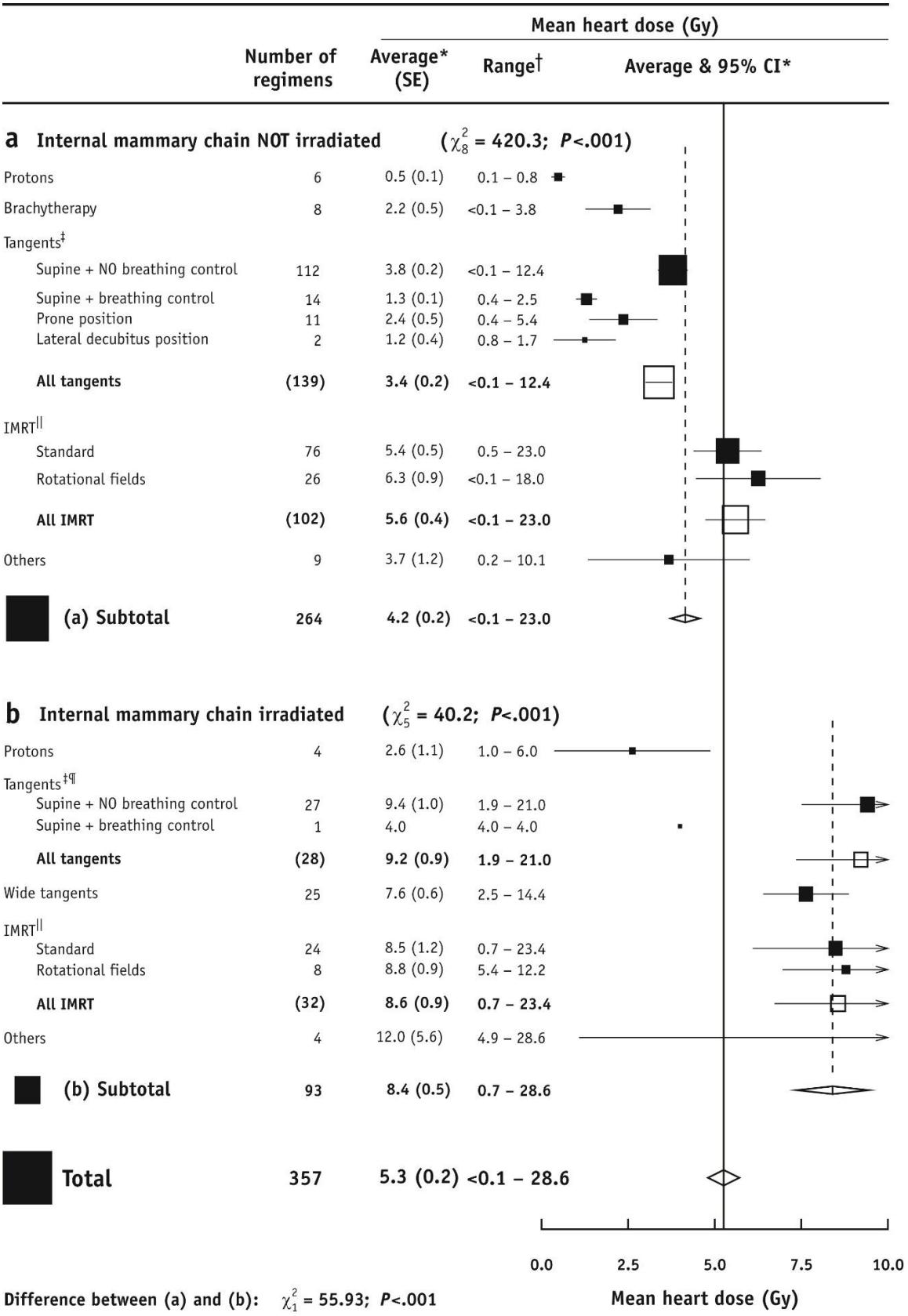

Figure 5: Mean heart doses from left-sided breast cancer radiation therapy regimens according to technique and whether or not internal mammary chain irradiation was given. Studies of women with unfavorable anatomy were excluded. (From Taylor CW, Wang Z, Macaulay E, Jagsi R, Duane F, Darby SC. Exposure of the Heart in Breast Cancer Radiation Therapy: A Systematic Review of Heart Doses Published During 2003 to 2013. Int J Radiat Oncol Biol Phys. 2015 Nov 15;93(4):845-53.).

thorax. Other vDIBH methods utilized in literature include: monitoring of the lateral tattoo position, the use of a real-time skin-surface-distance device to monitor the position of the patient's anterior surface, and magnetic sensors attached to the patient's thorax.(72)

An interesting string of three trials were the UK Heartspare studies that compared different DIBH techniques. The stage IA trial compared ABC and vDIBH and found that both techniques were comparable in terms of positional reproducibility and normal tissue sparing. However, vDIBH was preferred by patients and RTTs, took less time to deliver, and was cheaper than ABC.(73) The stage IB trial compared vDIBH and prone radiotherapy in larger-breasted women and found that vDIBH provided superior MHD reduction and reproducibility than prone radiotherapy.(74) The stage II trial evaluated vDIBH in a multicentre setting and confirmed its feasibility, safety, patient satisfaction, and cardiac sparing benefits.(75) Since the publication of these studies the vDIBH has become the most common technique to reduce cardiac dose during left-sided breast radiotherapy.

B. Prone radiotherapy

As mentioned in the previous paragraph, radiotherapy in prone position has been investigated as a method to reduce MHD. As shown in Figure 5, prone position leads to a reduction in MHD, compared with supine radiotherapy without DIBH.(71) The UK Heartspare stage IB, comparing supine DIBH and prone position in a cross-over design for patients with estimated breast volumes >750cm^3, showed a lower MHD for supine DIBH at 0.44Gy compared to a MHD of 0.66Gy in prone position($p<0.001$).(74) However, the reported MHD in both positions are a factor 9 or 6 times lower compared to the previously reported MHD in literature for supine radiotherapy without DIBH (see Figure 5).(71) Furthermore, the ipsilateral MLD in the UK Heartspare stage IB was clearly in favour of prone positioning, with a more than tenfold reduction of ipsilateral MLD in prone compared to supine position (0.34Gy vs 3.73Gy, $p<0.001$).(74) Wang et al. estimates that prone without DIBH is superior to supine DIBH in 62% (95% confidence interval 53% - 71%) of patients with left sided breast cancer, taking into consideration a combination of reductions in MHD and MLD.(76) A prospective trial for left-sided breast cancer patients confirmed these results showing no difference in MHD for prone shallow breathing compared to supine DIBH but a clear advantage for MLD.(77) A similar trial by Saini et al. came to similar conclusions: prone free breathing results in significantly lower lung doses compared to supine and DIBH for left-sided breast cancer patients.(78) The previous studies included only left-sided breast cancer patients, but similar results are found for patients with right sided breast cancer. A comparison of prone free breathing to supine free breathing on a total of 146 patients with right breast cancer found a

reduced MLD or MHD (or combination of both) in prone position for over 80% of patients.(79) Recently, a meta-analysis by Lai et al. that included data from 19 observational studies compared prone and supine free breathing.(80) Prone in free breathing, resulted in a significantly lower MHD and MLD, without a significant difference in target coverage between both positions.

Not only does prone position lead to a lower MLD and MHD in comparison to supine position (and free breathing) but less acute and late toxicity are also reported, as was shown in randomized controlled trials.(81–83)

C. Optimizing radiotherapy delivery techniques

Around the turn of the century, the introduction of the multileaf collimators (MLC) allowed a simple and effective way to modulate the dose to the breast and reduce the dose inhomogeneity found with employing wedged tangential fields. Before the introduction of the MLC, dose inhomogeneity as large as 20% in the superior and inferior regions of the breast was found. These regions of increased dose, also called hot-spots, lead to inferior cosmesis, especially in large breasted women.(84) Several different techniques have been developed to optimize dose delivery for WBI, including custom physical compensators (for each patient), external or internal wedges, intensity-modulated radiation therapy (IMRT) using a MLC, and non-coplanar beam arrangements. IMRT uses the ability of the MLC to form multiple small segments, each delivering part of the total dose, to greatly reduce the dose inhomogeneity.(85)

A little less than ten years after the introduction in clinical practice, a large multicentre randomized phase III trials confirmed the reduction in acute toxicity after WBI, in the form of a lower rate of moist desquamation.(86) Around the same time, researchers from the Royal Marsden Hospital demonstrated better 5-year cosmesis based on photographic assessment and a lower risk of palpable induration.(87) Furthermore, the dose modulation with IMRT allows besides a reduction in the volume of hot spots, an increase of the dose around the tumour bed to form a SIB. As mentioned previously, two prospective randomized trials have shown that integrating the boost using IMRT does not increase acute toxicity, or late toxicity at 2-years, although the duration of the treatment is considerably shortened.(33–35) Based on in silico studies, additional dose homogeneity is achievable by utilizing (multiple) non-coplanar beams.(88–90) (91)

Finally, IMRT can be used for cardiac shielding, further reducing the dose to the heart.(91) However, this advantage is controversial seeing that the systematic review of heart doses published between 2003 and 2013 shows an increase in MHD in publications using IMRT (see

Figure 5).(71) Therefore, careful planning is required for (all left-sided) patients and IMRT alone is probably not the optimal technique to reduce MHD or MLD. Better techniques have been previously mentioned.

D. Image- and surface-guided radiotherapy

The correct positioning of a patient is crucial to deliver highly conformal radiotherapy, reducing the risk of radiation on healthy organs. Image guided radiotherapy (IGRT) utilizes verification imaging, obtained before, during or after treatment, to record a patient's position at the time of radiotherapy. This allows for repositioning of the patient in case of deviations from position at CT simulation, a shift of the treatment table to account for minimal daily changes in position, and replanning in case of changes in the anatomy of the patient.(92) The reduction in position uncertainty should help to reduce MHD and MLD, but also allows for safe hypofractionation through assuring correct dose delivery each fraction.

Several forms of IGRT exist, including two-dimensional imaging, three-dimensional imaging, and surface guided imaging (SGRT). A detailed description of all the different IGRT techniques available falls outside the scope of this thesis. However, a special mention of SGRT is still warranted. SGRT is the a form of IGRT, utilizing a specialized camera to detect the surface of the patient and determine the position of this surface in 3D-space. Therefore, allowing real-time feedback, patient monitoring throughout the treatment fraction and motion management (e.g. during DIBH treatments), without any additional exposure of the patient to ionizing radiation.(93) Another but more expensive solution for cross-sectional imaging of the patient during DIBH, is the use of an MRI and LINAC combination, although the literature for the treatment of breast cancer is limited.

E. Fractionation

The total dose and accompanying dose per fraction can also play a role in the risk of acute and late toxicity. Radiobiological modelling of breast cancer predicts that hypofractonation should lead to lower acute toxicity, due to the lower total dose, but equal or higher late toxicity, due to the high sensibility of late toxicity for the dose per fraction.(94) However, in practice the results of the FAST-FORWARD trial established that the late toxicity did not increase and acute toxicity was indeed lowered.(31,92)

F. Proton radiotherapy

The current standard of care for WBI uses a linear accelerator to create high energy electrons that are converted in gamma-rays (or photons) for treatment of the patient. In proton radiotherapy a cyclotron is used to accelerate protons that are deposited in the tumour. The chief advantage of proton (or particle therapy) over radiotherapy using photons, is that the dose is deposited over a narrow range of depth. Proton beams deliver a lower dose in before reaching the tumour, and deliver (almost) no dose after the Bragg peak, the depth of which is a function of the energy of the beam. By modulating the beam to deliver the Bragg peak inside the target volume, proton radiotherapy allows for higher dose conformity compared to photon beams, with less normal tissue irradiated.(95) Dosimetry studies have demonstrated that for WBI, with or without LNI, proton radiotherapy can achieve lower MHD, MLD and mean oesophagus dose compared to photon radiotherapy.(96) Our research group investigated the advantage of proton radiotherapy for prone WBI with LNI and found a reduction in MLD and MHD, although no clear reduction in the dose to the oesophagus.(97)

However, although proton radiotherapy is increasingly available, its place as a cost-effective, clinically beneficial alternative to photon radiotherapy has not yet been proven. At the moment of writing the thesis, no published RCTs comparing proton with photon radiotherapy are available. Fortunately, five RCTs are planning to recruit a total of 3210 patients for this comparison. Currently, data is available on acute toxicity, and the results seem to indicate no clear advantage for proton radiotherapy compared to photon radiotherapy.(96)

G. Combining multiple techniques

Finally, the optimal method to reduce MHD, MLD, acute and late toxicity is a combination of the techniques described previously. At Ghent University Hospital all patients receive a combination of techniques to maximize their risk-benefit ratio.

Firstly, the combination of DIBH and prone positioning synergizes to allow the lowest MHD and MLD currently achievable (besides the use of proton radiotherapy). As mentioned previously, DIBH lead to a higher reduction in MHD compared to prone positioning. On the other hand, prone positioning leads to large (10-fold) reductions in MLD due to the breast falling forward(74), pulling the heart away from the breast and internal mammary lymph node region, as shown in Figure 6.(98) It is a myth that a DIBH is hard to perform in prone position, and research on the prolongation of DIBH in prone positioning debunked this claim, showing no major differences in DIBH duration in prone position compared to supine position.(99) The meta-analysis by Lai et al

concluded that the combination of prone radiotherapy with DIBH resulted in superior results for the sparing of the heart and lungs compared to supine and DIBH (or prone position and shallow breathing). Another advantage of prone position is the fixation of the breast in space between shallow breathing and DIBH (see Figure 6). This means the target volume doesn't move when the patient fails to hold the full DIBH. Deseyne et al. demonstrated a failure to breath-hold resulted in adequate target coverage, but also the predictable increase MHD and MLD.(100)

Secondly, IMRT can be combined with DIBH or prone positioning. However, the use of highly conformal IMRT plans can lead to long delivery times. Xu et al. describes a treatment delivery time of around 7 minutes and 30 seconds for WBI with LNI (including IMN) using IMRT.(101) This can lead to fatigue for even the most fit patients. Remouchamps et al. used 4 to 6 DIBH of a median duration of 22 seconds to deliver a WBI treatment using IMRT.(70) Research is required to find support techniques to allow these long treatments to be delivered during DIBH. Several techniques have been developed and can be found in Chapter IV, Paragraph B. One potential solution could come from the combination of the PCBC and DIBH which allows simpler techniques like tangential field IMRT, having a shorter delivery time, to achieve equal results to multibeam IMRT.(90)

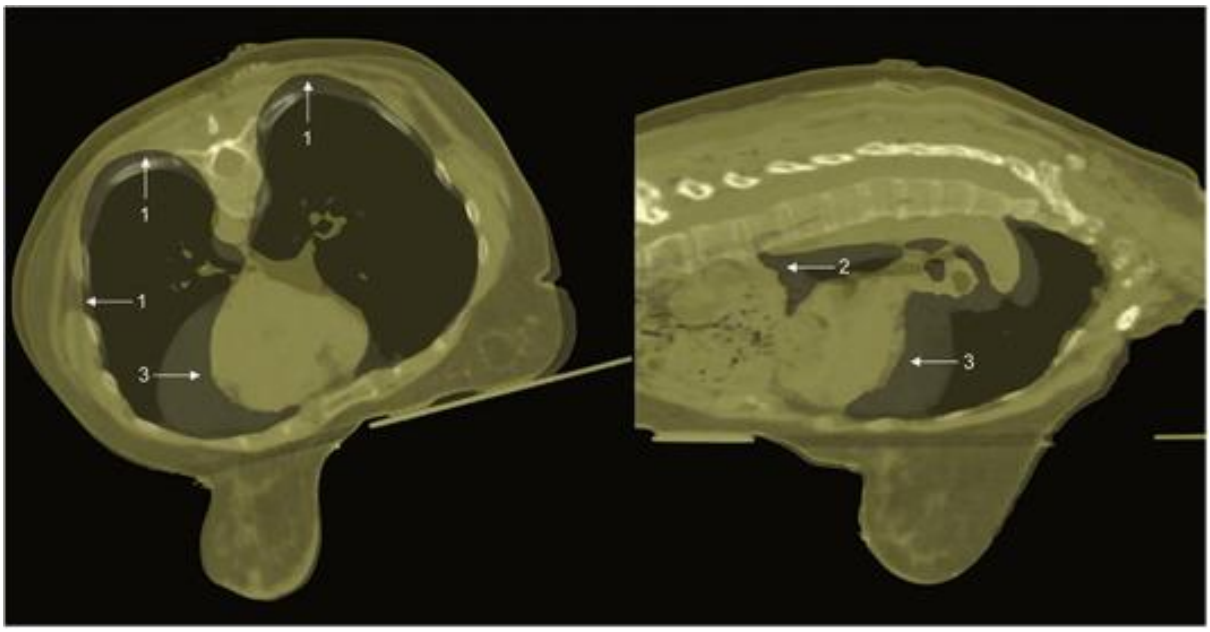

Figure 6: Rigid coregistration of CT-scans in a transverse and a sagittal plane during shallow breathing (dark gray) and deep inspiration breath-hold (light gray) in prone position. Note that the breast doesn't move between shallow breathing and deep inspiration breath-hold, instead the back of the patient moves cranially to allow for the lung volume expansion. (1) thoracic expansion (2) caudal shift of the diaphragm and (3) narrowing and caudal motion of the heart. (From 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. Radiother Oncol. 2015 Dec;117(3):473-6.).

Thirdly, the combination of IGRT, more specifically motion tracking during radiotherapy, can deliver feedback to the patient to increase the reproducibility of the voluntary DIBH. Several commercial systems are available, including systems utilizing SGRT.(102)

Fourthly, prone positioning and proton radiotherapy can be combined. A recent publication by Kim et al. compared six different radiotherapy techniques, including photon and proton radiotherapy techniques, in prone and supine position.(103) The advantage of prone is clear for photon radiotherapy, but these differences were less obvious for proton beam radiotherapy since the MLD and MLD were minimal in both positions. Going even further, prone position can be combined with DIBH and proton radiotherapy. For proton radiotherapy in prone position, the MLD actually increased during DIBH due to a larger dose spread of proton in the low density cavities (an intrinsic characteristic of protons), although the heart sparing effect of DIBH remained with proton radiotherapy in prone position.(97) Therefore, the combination of several techniques should always be carefully considered to avoid unanticipated interactions.

Finally, the use of hypofractionation can be combined with all previously mentioned techniques, and result in a reduction in acute toxicity as mentioned in paragraph E.(56,104)

To conclude, to achieve the highest risk-benefit ratio available, a combination of several techniques is required. These include, but are not limited to, motion management using DIBH, choosing the optimal position for the patient, optimizing treatment planning to increase dose homogeneity and reduce toxicity, whilst also accounting for the dose to the healthy organs and treatment delivery time. Finally, the choice of fractionation can also have an impact on the patient, through a reduction in the acute side effects and an improvement in quality of life after radiotherapy.(105)

Chapter III: Objectives

The overarching goal of this thesis, as mentioned in the title, is an improvement in the risk-benefit ratio of breast cancer radiotherapy. **Chapter I** describes the advantages and disadvantages of breast cancer radiotherapy, and **Chapter II** describes methods to reduce the side effects of radiotherapy. This thesis attempts to use a combination of new and existing techniques to optimise the benefit by reducing the side effects of breast cancer radiotherapy.

Objective 1: Allowing complex treatments during DIBH

For WBI with LNI, especially when the IMN are included, complex radiation techniques are required to achieve acceptable MHD and MLD. These techniques often lead to long beam-on times, up to 7 minutes and 30 seconds in some publications.(101) Hypofractionated schedules in 5 fractions further increase the beam-on time compared to 15 fractions. However, the most effective technique to reduce MHD is DIBH. Combining DIBH with complex techniques for WBI + LNI results in a large number of consecutive short DIBHs, leading to stress for the patient, a risk of position changes and the inability of treatment in DIBH for many patients.

To reduce the number of DIBHs required and allow for more patients to receive a full treatment session during DIBH, assistance techniques are required. Before starting this thesis, some techniques had already been proposed.(99,106) However, they required the use of mechanical ventilators. **Chapter IV** describes the development of a simple and effective technique to prolong DIBH durations to 2 minutes and 30 seconds in a comfortable way.

Objective 2: Strengthening the evidence behind prone positioning

Prone radiotherapy results in lower acute side effects, according to two RCT's.(81,83) However, data on late toxicity and cosmesis are rather limited. Health related quality of life (HRQoL) results are even more rare, with only one publication reporting the difference in HRQoL, at 6 to 8 weeks follow-up.(83) Finally, the advantage or disadvantage on dosimetry outcomes remains controversial. The UK HeartSpare stage IB found a lower MHD for DIBH, as a method of cardiac sparing, compared to prone positioning in shallow breathing, but a significantly lower MLD in prone compared to supine position.(74) However, the UK HeartSpare IB trial did not allow for the combination of DIBH and prone positioning, although the beneficial effect of DIBH on MHD remains in prone position.(107)

To confirm the advantageous effect of prone positioning seen in the RCT's, data from a large multicentre prospective observational trial, the REQUITE trial, was used. This data also allowed a first look into the HRQoL differences between prone and supine position two years after radiotherapy treatment (**Chapter V**). During the writing of this PhD, the 5-year data from the prone-supine RCT became mature, which created the opportunity to determine whether the

advantageous effects of prone positioning found after 2-years, remain after 5-years of follow-up (**Chapter V**).

The development of the PCBC before the start of the PhD led to the possibility to combine WBI with LNI, without sacrificing beam access. This resulted in the first RCT comparing prone and supine positions for WBI with LNI. The PRO-SURF trial goes even further and also investigated the advantages of acceleration in 5 fractions in patients receiving WBI with LNI (**Chapter V**).

Objective 3: Investigating the feasibility of pre-operative radiotherapy in five fractions

Historically, neo-adjuvant radiotherapy (NART) was used to reduce tumour volume, resulting in less extensive surgery.(108) Nowadays, neo-adjuvant chemotherapy (NACT), without NART, has largely replaced the use of NART. However, there are some other possible advantages of NART. The advent of shorter breast radiotherapy schedules sparked our interest in NART. In **Chapter VI** the results of the POP-ART trial are presented, a pilot trial , investigating the use of NART in five fractions for patients requiring NACT. In this study the 5 fraction schedule from the YO-HAI5 trial was used.(104) Finishing this schedule requires only 10-12 days of treatment. This should allow radiotherapy to be delivered before NACT and BCS, without causing an increase in the overall treatment time (OTT).

Chapter IV: Prolonging deep inspiration breath-hold

A. Introduction

Deep inspiration breath-hold (DIBH) is a commonly used technique to reduce the mean heart dose (MHD) for patients receiving breast cancer radiotherapy.(71) The combination of DIBH with modern radiotherapy can result in long beam-on times. Several factors increase beam-on time, including the use of IMRT, the inclusion of LNI (with or without the IMN), and hypofractionation. Firstly, IMRT reduces acute and late toxicity but results in longer beam-on times due to the use of several smaller beams to achieve beam modulation.(86,87) Secondly, the addition of LNI leads to more complex target volumes requiring additional radiotherapy fields, leading to a longer beam on time. The inclusion of the IMN further complicates the treatment. Thirdly, hypofractionation leads to longer beam on times, due to the higher dose delivered each fraction of treatment. The dose delivered within a certain timeframe is dependent on the type of beam and the type of machine used, but generally increases with more complex treatments. Several methods to decrease the beam on time, like the use of volumetric modulated arc therapy (VMAT) using a flattening filter free beam, have been proposed but fall outside the scope of this thesis.(69,109) To conclude, beam on times can vary greatly based on the planning technique, beam characteristics and the volumes included in the treatment.

The longest plans, with the highest beam on times, are given to patients requiring WBI with LNI including the IMN. Hence, IMRT combined with LNI including the IMN can require beam-on times of around 7 minutes and 30 seconds, requiring a large number of DIBHs.(101) Since these patients also have a higher MHD (see Figure 5), the use of DIBH is particularly useful. Most patients can achieve DIBH durations of around 30 seconds resulting in a high number of DIBHs, possibly resulting in larger set-up errors in the superior-inferior direction compared to patients only requiring WBI.(69,110) There are three main reasons to develop DIBH support techniques: 1) to reduce the risk of position changes, 2) to increase the comfort of the patient and 3) to allow more patients to perform DIBHs the treatment. To address these issues the Hyperventilation Oxygenation to prolong Breath-hold in Breast cancer Irradiation Treatment (HOBBIT) study was started. The goal was to find a technique for prolonged deep inspiration breath-holds (L-DIBHs) of 2 minutes and 30 seconds to allow long treatment to be given in two to three L-DIBHs.

B. Methods of prolonging a DIBH

Voluntary breath-holding leads to physiological changes in the human body, eventually resulting in an irresistible impulse to restart breathing at the breaking-point. Before the breaking-point a discomfort is felt which is not equally tolerated by all subjects. Hence the duration is variable, between studies, between subjects and within subjects. The precise mechanisms explaining breath-holding and causing the breath at breakpoint are unknown. Yet, through experimentation the main mechanisms have been determined. This knowledge on breath-holding physiology, combined with mental tenacity, can help to prolong a DIBH performed during radiotherapy.

1. Hypocapnia

Breath-holding leads to an increase in the level of carbon dioxide (CO_2) released at the end of expiration, a proxy for the level of CO_2 in the blood. This increased level of CO_2 leads to the activation of chemoreceptors that lead to an involuntary breath. A long-standing hypothesis was the involvement of the arterial chemoreceptors located at the bifurcation of the carotid artery, in the carotid body. Notably, this chemosensory organ was discovered by one (of the two) Nobel prize winners of our university, Corneel Heymans, and remains the only known means of detecting arterial hypercapnia (and hypoxia).(111) The hypothesis was that the sensing of the increase in CO_2 (and decrease in O_2) during breath-holding by the carotid body led to the breakpoint. However, others have found conflicting evidence: 1) the arterial gas pressures are inconsistent at the breaking-point, 2) denervation does not influence breath-hold duration, 3) breath-holding is achievable after inspiring an asphyxiating gas mixture.(112) Therefore other locations of chemosensing have been proposed like the diaphragm muscle chemoreceptors, or central chemoreceptors.

Recent advances in neurophysiology have found strong evidence for the existence of central chemoreceptors. A defect in PHOX2B, a transcription factor essential in the development of respiratory control neurons and the autonomic nervous system, causes the congenital central hypoventilation syndrome in patients who lack a ventilatory response to CO_2 and are prone to life-threatening hypoventilation during sleep.(113,114) PHOX2B is essential in the development of the retrotrapezoid nucleus (RTN), located in the medulla oblongata (brainstem), a key anatomical location for breathing control.(115) The RTN is very responsive to CO_2 in vivo and drives breathing through increasing breathing frequency and contraction of the inspiratory and expiratory muscles. Lesions in the RTN virtually eliminate the breathing stimulation caused by brain acidification. However, the RTN is not the only region involved in breathing control, other regions like the nucleus tractus solitarius, the locus ceruleus and the hypothalamus are also

involved.(114,116) Overall, the rising level of CO_2 in the blood is one of the most important determinants of the breakpoint.

2. Hypoxia

The delivery of oxygen to the brain is required for consciousness, and the oxygen levels in the blood are carefully monitored. The carotid bodies, together with the aortic bodies, are the sensitive to changes in O_2 levels in the blood and to a lesser degree changes in CO_2 levels (central chemoreceptors are more important for measurement of CO_2).(114) The signals are given through the glossopharyngeal nerve and the nucleus of the solitary tract to the brainstem. From the brainstem, a ventilatory response, expressed as increases in tidal volume and breathing frequency, along with coordinated changes in the sympathetic and parasympathetic outflows, with increased cardiac output, are generated.(117) The response to hypoxia is strong enough to evoke the breaking-point, even during hypocapnia.(112,118)

3. Deep inspiration

It has long been established that breath-holding after inspiration can be maintained longer compared to breath-holding after expiration.(119) This effect has been shown during radiotherapy for lung cancer patients.(120) Tibdewal et al. found that DIBH were longer than midventilation breath-holds, which are longer than deep expiration breath-holds.

4. Low metabolic rate

To prolong a DIBH to the maximum value, it is required to reduce the metabolic rate as much as possible. Therefore, patients should be in rest during DIBH. An increased metabolic rate intensifies the production of CO_2 and the exhaustion of O_2 from the blood, both leading to a reduction in the DIBH duration.(121)

5. Distractions

The perception of breathlessness is a multidimensional process, which is not only influenced by sensory input but also by nonsensory factors like attention.(112,122,123) Von Leupoldt et al. showed that the distraction of reading texts, during exercises causing dyspnoea, resulted in a reduction of the perceived unpleasantness of dyspnoea. Either performing a basic task, like a rubber-bulb squeeze, or mental calculations can improve breath-hold duration.(124) Another experiment by Vigran et al. found that manipulating the perception of time affects breath-hold duration.(125) During breath-holding, volunteers saw a timer showing the real time, or a timer running 40% faster or slower. Contrary to their hypothesis, the duration of the struggle phase

remained equal, but the duration of the easy-going phase was influenced by changing the speed of the timer. Hence, it is clear that unconscious pshycological factors and cognitive processes can significantly influence the response to apnea.

6. Training

Breath-holding related activities have been performed throughout history, but in the last 30 years it has also emerged as a competitive sport.(126) Training clearly plays a very important role with certain elite apneists being able to supress the respiratory urges to the point where consciousness fundamentally limits the breath-hold duration. The International Association for the Development of Apnea attributes the longest apnea, without the use of oxygen, to Mufsud Stéphane at a duration of 11 minutes and 35 seconds.(127) Therefore, preperatory DIBH training and home self-practice during the 1 to 2 week period before the radiation treatment planning procedure improves breath-hold durations.(128)

C. DIBH and breathing support techniques in breast cancer radiotherapy

Before the start of the HOBBIT trial around 2018, limited literature on how to prolong a DIBH or regulate the breathing pattern (for radiotherapy purposes) was already available. In most cases a mechanical ventilator was used to achieve a longer DIBH, although some publications also mentioned the use of oxygen therapy. Already, four major different methods were described: oxygen delivery, hyperventilation using mechanically-assisted non-invasive ventilation (MANIV), MANIV to reduce breathing irregularities and high frequency non-invasive percussive ventilation. An overview of the literature can be found in Table 2.

1. Oxygen delivery to prolong DIBH

Before 1950, even before the first World War, the relation between breath-hold duration and oxygen delivery was described in the medical literature. Engels et al. found an almost doubling of the average breath-hold duration from 1 minute 43 seconds with 21% oxygen (atmospheric oxygen pressure) to three minutes with 100% oxygen.(129) To deliver the oxygen, several solutions are available and three methods were investigated during this thesis: a Hudson non-rebreather oxygen mask, a leak-free mask connected to a mechanical ventilator (for MANIV) and high flow nasal oxygen (HFNO). Photographs of each type of oxygen delivery system can be found in the final publication (Article 1). The main disadvantage of the Hudson (non-rebreather) mask is the reduction in effective oxygen delivery at higher respiratory rates.(130) On the contrary, the oxygen concentrations remain stable with an increased respiratory rate with a MANIV or HFNO. The use of HFNO has gained popularity in recent years, it combines a nasal cannula with a humidified air/oxygen mixture at high flow rates, allowing high levels of oxygen to be delivered comfortably.(131) Contrary to the leak-free face mask required for MANIV, the set-up of HFNO is quick and does not require the adjustment of several (ventilation) parameters.

At the time of the HOBBIT investigations, the use of HFNO to prolong DIBH was not described yet. However, two publications recently used HFNO (without hyperventilation) to prolong DIBH in locally advanced lung cancer and mediastinal lymphoma.(132,133)

2. Non-invasive mechanical hyperventilation

Hyperventilation, or excessive breathing, leads to hypocapnia which prolongs the breath-hold duration.(134) A short duration of hyperventilation and hypocapnia are well tolerated with only few transient effects like paraesthesia, palpitations, and muscle cramps. To achieve the longest

competitive breath-hold (without oxygen), athletes will start with a voluntary hyperventilation. The advantage of hyperventilation in the context of longer breath-holds for radiotherapy was first described by Roth et al. The preoxygenated hyperventilated hypocapnic apnea-induced radiation (PHAIR) protocol utilized the combination of oxygenation and hyperventilation to achieve prolonged breath-holds.(135) Hyperventilation increased the DIBH times from around 40 seconds to one minute and 40 seconds for breast cancer patients. The addition of oxygen further increased these durations to two minutes and 45 seconds. Later, Parkes et al. demonstrated L-DIBHs of over 5 minutes to be safely achieved.(136) Both authors utilized MANIV during hyperventilation. These require long set-up times and a leak-free seal around a face mask. One of the goals of the HOBBIT trial was to establish a simpler hyperventilation protocol and compare these methods with MANIV.

3. Non-invasive mechanical ventilation to reduce the irregularity in the patients breathing

Besides the use of a mechanical ventilator to assist with hyperventilation, MANIV can also reduce the breathing variability. Parkes et al. found a reduction of 85% in the variability of the breathing frequency, and a reduction of 29% for the variability in inflation volumes. Therefore, breathing becomes very predictable, potentially allowing better adaptation of radiotherapy to the breathing of the patient.(137) Van Ooteghem et al. utilized several modes on a mechanical ventilator to increase the robustness of the current motion mitigation strategies.(106) Three modes during MANIV were chosen to regulate amplitude and respiratory rate: the volume-controlled mode, the shallow-controlled mode, and the slow-controlled mode. Volume-controlled mode and shallow-controlled mode were tested in ten lung or liver cancer patients, the slow-controlled mode was investigated in 12 left sided breast cancer patients. The slow-controlled mode induces repeated breath-holds with constrained ventilation pressure and results in several 17 seconds breath-holds with similar end-inspiratory plateaus compared to spontaneous breathing.

4. High frequency non-invasive percussive ventilation, increasing lung volume and DIBH duration

A particular form of MANIV is high frequency percussive ventilation (HFPV), a form of ventilation that administers small volumes of air (also called “percussions”) with adjustable pressure and frequency.(138) These percussions can be superimposed and replace spontaneous ventilation. A modified HFPV technique was tested on 10 volunteers and 3 patients by Péguret et al. and published in 2016. A full treatment could be given during HPFV resulting in an apnea-like

suppression of the respiratory motion. More recently, Audag et al. developed a protocol using HFPV to allow breath-holds of 20 minutes.(139) However, the protocol requires at least 3 training sessions (or 4 training sessions in 6 out of 10 volunteers) to reach a 10 minute DIBH. Furthermore, the setting needs to be changed for each individual patient. During HFPV, the motion deviations were small with reaching only one millimeter around the mean position. Currently, the first patients with Hodgkin lymphoma have been treated for the full 15 radiotherapy fractions during a prolonged apnea-like state using HFPV in Lausanne, Switzerland.(140) The technique resulted in an average reduction of 3Gy MHD in these patients, without notable side effects.

Table 2: Descriptive literature overview of the different methods to manage motion in breast cancer radiotherapy

First author	Year	Title	Description	Ref
1) Oxygen delivery				
Parkes et al.	2006	Breath-holding and its breakpoint	Review of methods to prolong breath-holding.	(112)
Parkes et al.	2014	Assessing and ensuring patient safety during breath-holding for radiotherapy	Discussion on the lack of published guidelines for monitoring patient safety during DIBH.	(141)
Peeters et al.	2021	Visually guided inspiration breath-hold facilitated with nasal high flow therapy in locally advanced lung cancer	Use of HFNO to treat 9 patients with locally advanced lung cancer, flow of 40 L/min with 80% oxygen.	(133)
Canters et al.	2023	Radiotherapy for mediastinal lymphoma in breath hold using surface monitoring and nasal high flow oxygen: Clinical experiences and breath hold stability	11 mediastinal lymphoma patients, 6 received HFNO during DIBH. DIBH stability, internal movement were investigated.	(132)
Zhao et al.	2023	A Convenient and Effective Preoxygenation Technique for Prolonging Deep Inspiration Breath-Hold Duration With a Venturi Mask With a 50% Oxygen Concentration	Preoxygenation with a Venturi mask for 15 minutes effectively prolongs the duration of a DIBH, with convenience, good tolerability, and effectiveness.	(142)

2) Non-invasive mechanical hyperventilation				
Cooper et al.	2003	CO2-dependent components of sinus arrhythmia from the start of breath-holding in Man	Investigates the CO2-dependent central respiratory rhythm in healthy volunteers.	(143)
Roth et al.	2011	Preoxygenated hyperventilated hypocapnic apnea-induced radiation (PHAIR) in breast cancer patients	Experiments with pre-oxygenated hyperventilation apnea to improve DIBH durations, 10 breast cancer patients included	(135)
Parkes et al.	2016	Safely achieving single breath-holds of >5 minutes in cancer patients: feasibility and applications for radiotherapy	Protocol combining the use of oxygenation and hyperventilation to prolong DIBH to over 5 minutes.	(136)
Parkes et al.	2019	The feasibility, safety and optimization of multiple prolonged breath-holds for radiotherapy	Investigates the feasibility and safety of multiple prolonged breath-holds in a single session on 30 healthy volunteers.	(144)
Parkes et al.	2021	Shortening the preparation time of the single prolonged breath-hold for radiotherapy sessions	Study on 44 healthy volunteers to decrease preparation time with limited reduction in DIBH duration.	(145)
Parkes et al.	2021	Safely achieving single prolonged breath-holds of > 5 minutes for radiotherapy in the prone, front crawl position	Prolonging DIBH to over 5 minutes is also achievable in prone crawl position.	(99)
Van Kesteren et al.	2022	Quantifying the reduction of respiratory motion by mechanical ventilation with MRI for radiotherapy	MRI investigation testing different methods of respiratory motion management, including hyperventilation and oxygenation to prolong DIBH	(146)

3) Non-invasive mechanical ventilation to reduce the irregularity in the patients breathing				
Parkes et al.	2016	Reducing the within-patient variability of breathing for radiotherapy delivery in conscious, unsedated cancer patients using a mechanical ventilator	Use of a mechanical ventilator for regularizing breathing, tested in breast cancer patients.	(137)
West et al.	2018	Mitigating respiratory motion in radiotherapy: rapid, shallow, non-invasive mechanical ventilation for internal thoracic targets	Measurement of the internal anatomic motion during mechanical ventilation to regularize and minimize respiration	(147)
Van Ooteghem et al.	2019	Mechanically-assisted non-invasive ventilation: A step forward to modulate and to improve the reproducibility of breathing-related motion in radiation therapy	Improvements in intra- and inter-session reproducibility, in 12 healthy volunteers, using mechanically-assisted non-invasive ventilation.	(148)
Van Ooteghem et al.	2019	Mechanically-assisted and non-invasive ventilation for radiation therapy: A safe technique to regularize and modulate internal tumour motion	The use of mechanically-assisted non-invasive ventilation on 10 patients with lung or liver cancer. Safety and feasibility.	(106)

4) High frequency non-invasive percussive ventilation, increasing lung volume and DIBH duration				
Péguret et al.	2016	Apnea-like suppression of respiratory motion: First evaluation in radiotherapy	Testing of high frequency percussive ventilation in 10 volunteers, inducing long breath-holds of over 10 minutes. Evaluation on 4 patients performed.	(138)
Ogna et al.	2017	Prolonged Apnea Supported by High-Frequency Noninvasive Ventilation: A Pilot Study	Development of a protocol to induce apnea with high frequency non-invasive ventilation, in 10 healthy volunteers	(149)
Audag et al.	2019	Intrapulmonary percussive ventilation leading to 20-minutes breath-hold potentially useful for radiation treatments	20 minutes of breath-holding using intrapulmonary percussive ventilation, severely reducing the motion.	(139)
Durham et al.	2020	Percussion assisted radiation therapy in Hodgkin lymphoma allows a marked reduction in heart dose	Use of high frequency percussive ventilation in 8 patients with Hodgkin lymphoma.	(140)

DIBH, Deep Inspiration Breath-hold; HFNO, high flow nasal oxygen; MRI, magnetic resonance imaging.

D. Development of a L-DBIH protocol

Article 1: Prolonging deep inspiration breath-hold time to 3 minutes during radiotherapy, a simple solution

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Reference:

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Abstract

BACKGROUND AND PURPOSE

Deep inspiration breath-hold is an established technique to reduce heart dose during breast cancer radiotherapy. However, modern breast cancer radiotherapy techniques with lymph node irradiation often require long beam-on times of up to 5 minutes. Therefore, the combination with deep inspiration breath-hold (DIBH) becomes challenging. A simple support technique for long duration deep inspiration breath-hold (L-DIBH), feasible for daily use at the radiotherapy department, is required to maximize heart sparing.

MATERIALS AND METHODS

At our department, a new protocol for multiple L-DIBH of around 2 minutes and 30 seconds was developed on 32 healthy volunteers and validated on 8 breast cancer patients during radiotherapy treatment, using a pragmatic process of iterative development, including all major stakeholders. Each participant performed 12 L-DIBHs, on 4 different days. Different methods of pre-oxygenation and voluntary hyperventilation were tested, and scored on L-DIBH duration, ease of use, and comfort.

RESULTS

Based on 384 L-DIBHs from 32 healthy volunteers, voluntary hyperventilation for 3 minutes whilst receiving high-flow nasal oxygen at 40L/min was the most promising technique. During validation, the median L-DIBH duration of 8 breast cancer patients improved from 59 seconds without support to 3 minutes and 9 seconds using the technique ($p<0.001$).

CONCLUSION

A new and simple L-DIBH protocol was developed feasible for daily use at the radiotherapy centre.

Introduction

Radiation treatment has an established role in breast cancer, complementing surgery and systemic therapies to prevent recurrences and improve survival, both in women with node negative and node positive disease.[1] Long term follow-up, however, shows that the beneficial effect on survival is weakened by radiation-induced cardiac and lung cancer mortality.[2,3] The risk is highest for left-sided breast radiation therapy and irradiation of the internal mammary nodes, due to the proximity of the heart and subsequent higher heart doses.[4] Deep inspiration breath-hold (DIBH) is an established technique to reduce cardiopulmonary doses in breast cancer irradiation treatment.[5-8] For most radiation treatments of the breast, the duration of beam-on time is around 1 to 2 minutes.[9] However, when more complex techniques are used, e.g. multi-beam intensity modulated radiotherapy (IMRT) for whole breast with lymph node irradiation, beam-on time can be extended to up to 5 minutes, especially in combination with hypofractionated schedules.[9,10] Therefore, a high number of consecutive short DIBHs are required, leading to stress for the patient, a risk of position changes and the inability of treatment in DIBH for many patients.

Three mechanisms to prolong breath-holding are well established. Firstly, hyperventilation as a method to prolong DIBH times is extensively used by breath-hold divers, due to inducing hypocapnia and decreasing the CO_2-drive to breath.[11,12] Secondly, pre-oxygenation increases oxygen reserve and delays the onset of hypoxia up to 8 minutes.[13] Thirdly, an increase in lung inflation increases breath-hold duration.[14] A combination of these three methods has already been tested in breast cancer patients as a technique to prolong breath-holding during radiotherapy.[15,16]

The protocol from Parkes et al. uses a mechanical ventilator for 15 minutes of forced hyperventilation, whereas Roth et al. uses it for oxygenation followed by a short period of voluntary hyperventilation. To our knowledge, these protocols have not been implemented at radiotherapy departments, possibly due to the complexity of the mechanical ventilator, the required capital expenditure, and the high set-up time. Simpler methods of oxygenation like high-flow nasal oxygen or an oxygen mask have not been investigated in this context. Our goal was to develop a simpler protocol to deliver the treatment in multiple consecutive L-DIBHs of 2 minutes and 30 seconds. We developed the protocol on healthy volunteers; followed by a validation on breast cancer patients after a radiotherapy session.

Methodology

VOLUNTEERS AND PATIENTS

The protocol was developed on 32 healthy female volunteers and validated on 8 patients receiving curative radiotherapy for breast cancer. All volunteers and patients gave a written informed consent, and the study was approved by the ethics committee of Ghent University Hospital and registered on ClinicalTrials.gov, number NCT04091542. Eligibility criteria included women above the age of 18 without any history of cardiac or pulmonary disease. Exclusion criteria were currently smoking, not able to perform a single unassisted DIBH of over 20 seconds, previous breath-holding experience, and WHO obesity class II (BMI > 35kg/m^2).

PROTOCOL DEVELOPMENT AND VALIDATION PHASE

In 4 successive development cycles of 8 volunteers, the protocol was optimized to reach our L-DIBH target of 2 minutes and 30 seconds based on 3 additional goals: comfort for the patient, ease of use and the time required for set-up and patient preparation. For these criteria, no strict cut-off values were chosen but each criterion was evaluated in a joint meeting by a group of stakeholders including radiation oncologists, anesthesiologists, and radiotherapy technologists. The number of cycles was not predefined but, if according to the group of stakeholders, the last research cycle did not show a marked improvement over the previous cycle, the development phase was ended.

The 8 volunteers in each cycle were randomized to different nests of volunteers. Each nest performed the baseline protocol as well as a specific range of predefined variations on this protocol. The volunteers performed 4 different examinations on 4 separate days during a working week, each time performing 3 consecutive L-DIBHs and ending when they chose to breath-out (e.g. due to discomfort). Every L-DIBH was preceded by a preparatory phase of voluntary hyperventilation, using audio-assistance, and oxygenation. The volunteers were blinded to their L-DIBH durations until completion of all their examinations. Prior to the first examination the volunteers did not receive any preparatory instructions, except for information on the types of oxygenation devices used during their examinations. All participants performed 3 unassisted DIBHs to establish their baseline DIBH duration.

The first baseline protocol was an adaptation of Roth et al. using a mechanical ventilator for oxygenation.[16] In the subsequent development cycles, the baseline protocol was based on the results from the previous cycle and feedback from the stakeholders. During each examination, the vital parameters of the volunteer were monitored using a Carescape B650 anesthesia monitor (GE Healthcare, Finland). The full details of an examination and the safety criteria can be found in

appendix A. After each examination of 3 consecutive L-DIBHs the side effects and comfort of the technique were evaluated using patient questionnaires (appendix B).

At the end of the cycle mean L-DIBH length, comfort and side-effects were analyzed and presented to the group of stakeholders. Throughout the cycles, the following parameters were optimized: oxygenation device, duration of hyperventilation, hyperventilation frequency (RR), fraction of inspired oxygen (FiO2); L-DIBH position and flow rate (L/min) both during hyperventilation and breath-holding. The following three oxygenation devices, ordered by higher ease of use and lower set-up time, were investigated (Figure 1): 1) mechanical ventilator (Leon Plus, Löwenstein, Germany) and a face mask (Series 6700, Hans Rudolph, USA) in pressure support ventilation at 25mbar peak pressure, 2) High-flow nasal oxygen or HFNO (Optiflow Thrive, Fisher & Paykel, New Zealand), 3) non-rebreathing mask with oxygen reservoir (Ecolite, Intersurgical, UK), also called a Hudson mask. For the mechanical ventilator or HFNO, a maximum FiO2 of 80% was allowed to reduce the risk of absorption atelectasis.[17] After 4 development cycles, the stakeholders decided that the protocol met all preset requirements and was ready to be validated on a group of 8 patients. They were examined on 4 days after a radiotherapy session for breast cancer, and they performed 3 consecutive L-DIBHs on each day. These examinations were not part of their curative radiotherapy treatment.

STATISTICAL ANALYSIS

Study data were collected and managed using REDCap electronic data capture tools hosted at Ghent University Hospital. All analyses and data visualizations were done with R-studio (version 3.6.2). During protocol development median and corresponding interquartile range (IQR) for L-DIBH durations, and, the comfort and pain assessments were compared pairwise using the Wilcoxon rank sum test within the same subject. The non-parametric Friedman test was used to compare median breath-hold durations and corresponding IQR for each consecutive day and L-DIBH attempt, during the validation phase. The improvement from the baseline were tested using the Wilcoxon rank sum test between all baseline DIBH durations and all L-DIBH attempts. A two-sided significance level of 0.05 was chosen.

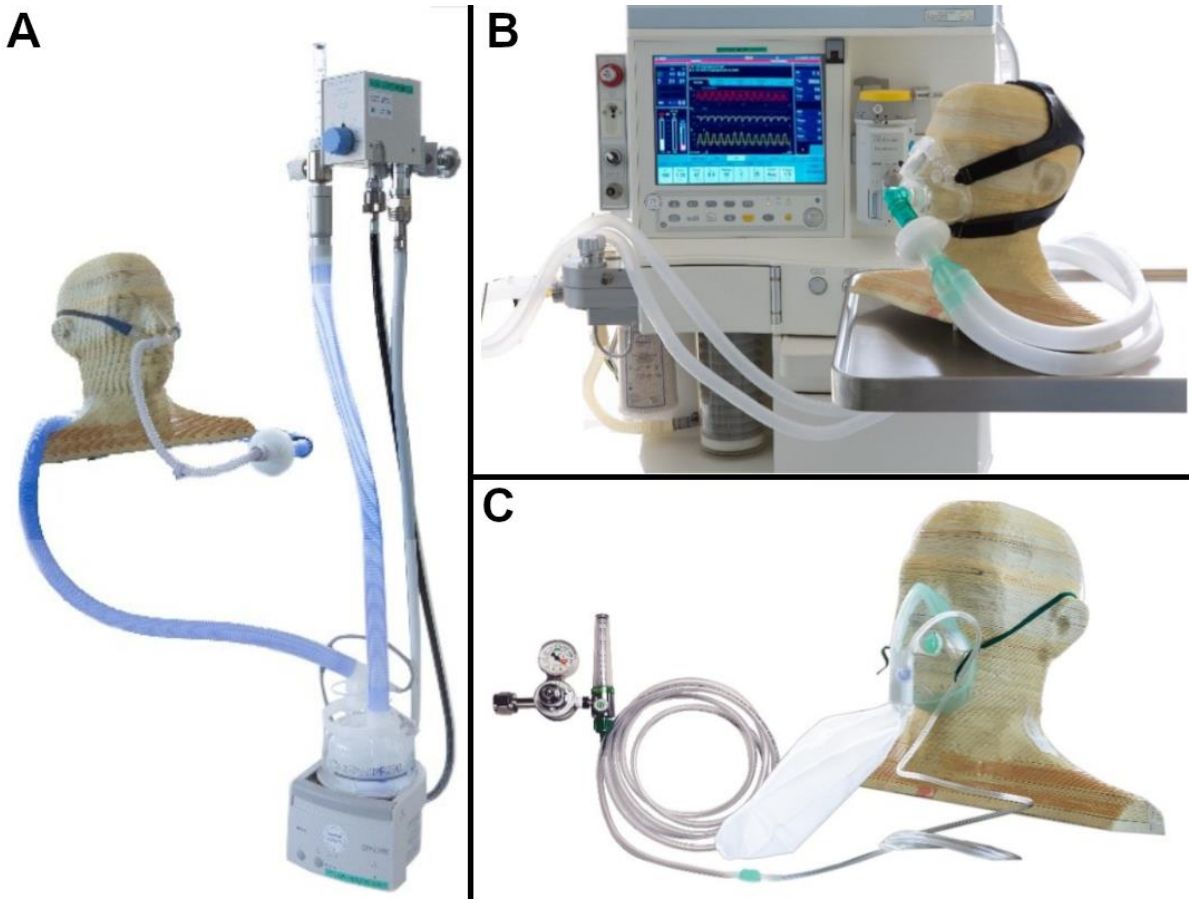

Figure 1: Oxygenation methods tested during protocol development. A. High-flow nasal oxygen (Optiflow Thrive device), delivery of a heated and humidified oxygen mixture through a nasal cannula. B. Mechanical ventilator with face mask. C. Non-rebreather mask with oxygen reservoir or Hudson mask.

Results

From March 2019 until December 2019 a total of 32 healthy volunteers were included in the development phase, and 8 patients in the validation phase. Baseline characteristics of the volunteers and patients can be found in Table 1. Unassisted DIBH times were 1 minutes and 2 seconds for the volunteers and 59 seconds for the patients.

PROTOCOL DEVELOPMENT

Figure 2 shows an overview of the L-DIBH protocol development in the 4 consecutive research cycles. A summary of median L-DIBH durations can be found in Table 2. In total 390 L-DIBHs were performed and 21 L-DIBHs were missing: 12 L-DIBHs due to involuntary breathing of a single volunteer, 3 due to claustrophobia when putting on the ventilator mask, 2 because of mask leakage, 2 due to incorrectly following the instructions on the first try, and 2 because of a technical issue. A total of 369 L-DIBHs were used for the optimization of the protocol.

Table 1: Baseline characteristics and results of baseline examination for healthy volunteers and patients.

	Healthy volunteer	Patient during RT	Total
n=	32	8	40
Baseline characteristics			
Age, years	43 (34–51)	56 (41–60)	44 (36–54)
Length, cm	168 (163–172)	162 (158–171)	167 (162–172)
Weight, kg	63 (57–63)	62 (59–69)	62 (58–70)
BMI	22 (21–24)	24 (22–27)	23 (21–25)
Current alcohol use	23 (72%)	7 (88%)	30 (75%)
Former smoker	8 (25%)	3 (38%)	11 (28%)
Medication use	19 (59%)	7 (88%)	26 (65%)
Comorbidities			
Thyroid disease	0 (0%)	3 (38%)	3 (8%)
Diabetes	0 (0%)	0 (0%)	0 (0%)
Back pain	12 (38%)	5 (63%)	17 (43%)
Shoulder pain	4 (13%)	3 (38%)	7 (18%)
Cancer treatment			
Previous chemotherapy		6 (75%)	
Hormonal therapy		3 (38%)	
Baseline examination			
Unassisted DIBH time – m:ss	1:02 (0:52 – 1:17)	0:59 (0:40 – 1:08)	1:02 (0:46 – 1:15)
Systolic blood pressure – mmHg	125 (109–134)	136 (115–140)	126 (112–136)
Diastolic blood pressure – mmHg	68 (61–78)	72 (63–89)	68 (62–78)
Heart rate - BPM	67 (60–77)	68 (62–74)	67 (61–77)
Respiratory rate - /min	12 (10–16)	17 (12–25)	12 (10–16)

Data are median (IQR) or number (%). Some percentages do not total 100 because of rounding. BMI: body mass index, BPM: beats per minute, RT: radiotherapy.

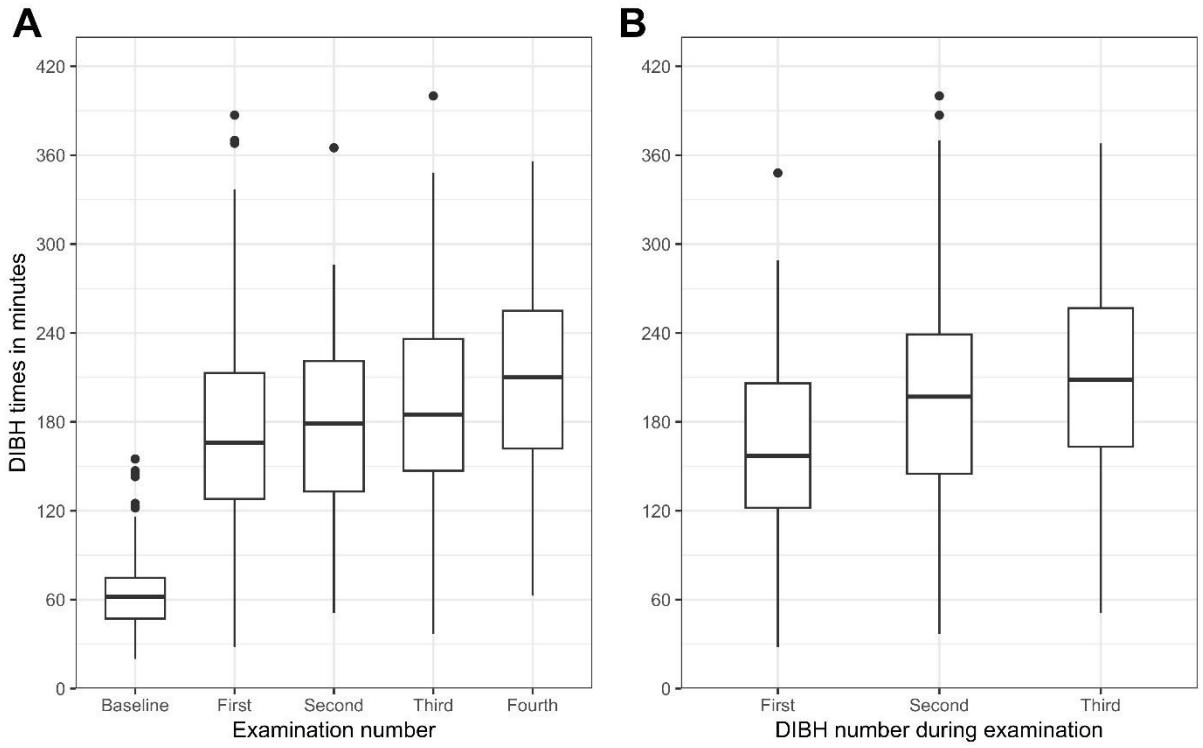

Figure 2: Boxplots of the L-DIBH durations during validation with 8 breast cancer patients a) according to the day of the examination or b) according to the order of L-DIBHs during each examination day.

Table 2: Median L-DIBH durations of the volunteers in m:ss (Interquartile range m:ss – m:ss) in all the comparisons made during the iterative development.

N*	Standard protocol	mm:ss (IQR)	P-value†	mm:ss (IQR)	Alternative protocol
	Cycle 1				
8	Mechanical ventilator	3:25 (2:47 – 3:53)	0.2	3:39 (2:39 – 4:10)	High Flow Nasal Oxygen
2	2 minutes of hyperventilation	3:12 (2:36 – 4:31)	N/A‡	4:52 (4:10 – 5:44)	6 minutes of hyperventilation
2	Supine position	3:40 (2:51 – 4:09)	N/A‡	3:08 (2:32 – 3:38)	Prone position
2	16 breaths/minute during hyperventilation	3:36 (3:11 – 3:55)	N/A‡	3:13 (2:44 – 4:00)	20 breaths/minute during hyperventilation
2	60% fraction of inspired oxygen	2:55 (2:26 – 3:43)	N/A‡	2:48 (1:54 – 3:07)	80% fraction of inspired oxygen
	Cycle 2				
8	High Flow Nasal Oxygen	2:58 (2:00 – 3:40)	0.001	2:37 (1:44 – 3:13)	Hudson mask
4	3 minutes of hyperventilation	2:52 (2:14 – 3:28)	0.2	3:02 (2:23 – 3:47)	5 minutes of hyperventilation
4	Supine position	2:57 (1:31 – 3:46)	0.3	2:36 (1:37 – 3:21)	Prone position
	Cycle 3				
8	3 minutes of hyperventilation	3:28 (2:40 – 4:28)	0.002	3:09 (2:34 – 3:51)	2 minutes of hyperventilation
8	16 breaths/minute during hyperventilation	3:28 (2:40 – 4:28)	0.2	3:24 (2:40 – 4:20)	12 breaths/minute during hyperventilation
8	40L/minute flow during hyperventilation	3:28 (2:40 – 4:28)	0.001	2:59 (2:19 – 4:03)	20L/minute flow during hyperventilation
	Cycle 4				
8	16 breaths/minute during hyperventilation	2:53 (2:00 – 4:00)	0.2	3:42 (1:49 – 4:18)	Volunteer choice during hyperventilation
8	60% fraction of inspired oxygen	2:53 (2:00 – 4:00)	<0.001	2:13 (1:23 – 2:43)	21% fraction of inspired oxygen
8	20L/minute flow during L-DIBH	2:53 (2:00 – 4:00)	0.3	3:36 (2:30 – 4:04)	0L/minute flow during L-DIBH

* Number of volunteers in the comparison † Wilcoxon signed rank test within a volunteer performing the baseline and alternative protocol ‡ P-values not shown due to the small number of subjects investigated (N=2)

First cycle

The first cycle focused on the difference between a mechanical ventilator and HFNO (Figure 1A&B). No significant difference was found in median L-DIBH duration (p= 0.2) between both oxygenation devices. At the end of the week, median comfort score on a scale from 1 to 10 was 6.5 for the ventilator and 7.8 for HFNO (p= 0.5). Since there were no differences in median L-DIBH

duration or comfort, but HFNO has a shorter set-up time and is easier in use, the stakeholders decided to continue using HFNO. Four other parameters were investigated in smaller nests of 2 volunteers: 1) duration of hyperventilation of 2 versus 6 minutes, 2) prone and supine positioning, 3) RR during hyperventilation (16/min versus 20/min) and 4) FiO2 of 60% versus 80%. Increasing the duration of hyperventilation from 2 minutes to 6 minutes resulted in a 1 minute and 40 seconds longer median L-DIBH duration. Supine position prolonged L-DIBH duration by 32 seconds. Increasing RR during hyperventilation shortened L-DIBH duration by 23 seconds. However, a change in FiO2 had a minimal impact. Based on these results, the stakeholders decided to investigate 3 and 5 minutes of hyperventilation and prone and supine positioning in the second cycle.

Second cycle

The second research cycle investigated whether oxygenation using a simple Hudson mask (Ecolite, Intersurgical, UK) is equal to HFNO (Figure 1A&C). Median L-DIBH duration was 22 seconds longer using HFNO (p= 0.002), and both methods showed similar comfort scores (7.5 for HFNO and 8.0 for Hudson mask, p= 0.5). The success rate to reach our goal of 2 minutes and 30 seconds was slightly higher with HFNO compared to the Hudson mask (69% vs 62%). Therefore, the stakeholders decided on further using HFNO. The difference between 3 minutes and 5 minutes of hyperventilation was only 10 seconds, so consensus was to remain at 3 minutes in view of the limited treatment time slots at a radiotherapy department. Supine positioning was again superior, and starting from the third cycle, the protocol was optimized in prone position for two reasons: 1) to be more conservative and, 2) since this is the standard position at our department.

Third and fourth cycle

In the third and fourth cycle, the duration of hyperventilation and RR during hyperventilation were further investigated. Also, 3 changes to decrease the oxygen consumption were tested: 1) decreasing FiO2 to 21%, 2) decreasing HFNO flow during hyperventilation and, 3) decreasing HFNO flow during breath-hold. Decreasing hyperventilation time from 3 minutes back to 2 minutes, significantly decreased median L-DIBH duration by 19 seconds (p=0.002). Normal air decreased the L-DIBH duration by 40 seconds (p<0.001). Reducing the flow rate to 20L/min. during hyperventilation, significantly decreased L-DIBH durations with 29 seconds (p=0.001). Switching off the flow during breath-hold compared to 20L/min flow rate, did not significantly influence L-DIBH duration (p=0.3), nor comfort (p=0.2). Slowing RR during hyperventilation did not influence the median L-DIBH duration (p=0.2), nor increase the comfort for the volunteer. Neither did a RR based on volunteer preference. After the third and fourth cycle no major changes

to the protocol were made compared with the second cycle and the protocol was accepted by the stakeholders for validation in breast cancer patients.

VALIDATION PHASE

The final protocol that was validated on 8 breast cancer patients after a radiotherapy session uses 3 minutes of hyperventilation at 16 breaths/min with pre-oxygenation using HFNO (FiO2 of 60%; 40L/min. during hyperventilation and 20L/min. during breath-hold), in prone position. In total 97 L-DIBHs were performed using the final protocol during the validation phase with 1 L-DIBH missing due to coughing during hyperventilation. Median L-DIBH duration improved from 59 seconds (IQR 41 seconds:1 minute 8 seconds) without support to 3 minutes and 9 seconds (interquartile range (IQR) 2 minutes 6 seconds: 3 minutes 45 seconds) using the protocol ($p<0.001$). In total 64% of L-DIBHs were above 2 minutes and 30 seconds. Figure 2 shows the improvement in L-DIBH duration with (a) each consecutive day, and (b) during a single examination. For each consecutive L-DIBH attempt during a single examination, median L-DIBH times were significantly better: 2:25 (IQR 1:49 – 3:03), 3:18 (IQR 2:04 – 3:55) and 3:35 (IQR 2:44 – 4:30) ($p<0,001$), at the first, second and third attempt respectively. This is also reflected in the success rate to reach 2 minutes and 30 seconds, with only 44% success on the first attempt, increasing to 69% and 78% for the second and third attempt respectively. The median L-DIBH duration on each consecutive day, also increased significantly ($p<0,001$): 2:46 (IQR 2:08 – 3:33) on day 1, 2:59 (IQR 2:13 – 3:41) on day 2, 3:05 (IQR 2:28 – 3:59) on day 3, and 3:30 (IQR 2:42 – 4:15) on day 4.

SIDE EFFECTS

Table 3 contains a summary of volunteer and patient reported side effects after the examination. During development and validation, the side-effects were similar with the different protocols. One breast cancer patient with hypogamma-globulinemia (IgG3-deficiency) developed an upper airway infection after the examinations, needing a treatment with antibiotics and antimycotics.

Table 3: Overview of side effects both during the examination and after ending the examination.

Side effects during examination		**Side effects after examination**	
Number of examinations	n=160	Number of examinations	n=160
Did you feel any?		Do you now feel any?	
Tingling feeling in fingers/feet or limbs	40 (25%)	Dizziness	20 (13%)
		Fatigue	16 (10%)
Pain	25 (16%)	Do you now have?	
Need to cough	21 (13%)	Dry mouth	41 (26%)
Dizziness	16 (10%)		

Discussion

We developed a protocol, feasible to use at a radiotherapy department, using the combination of voluntary hyperventilation and oxygenation. Validation on 8 breast cancer patients showed that this technique can prolong the DIBH duration to or beyond 2 minutes and 30 seconds (Figure 2). This should permit most treatment plans to be delivered in a single L-DIBH, unlike the current delivery using multiple short DIBHs.[9,18] Furthermore, up to 3 consecutive L-DIBHs of 2 minutes and 30 seconds are achievable, thus permitting more extensive treatments or cone-beam CT (CBCT) using L-DIBH. This protocol could be especially important for plans that include the internal mammary nodes, which have average delivery times of 7 minutes and 30 seconds if IMRT is used.[10]

Prolonging breath-hold using a combination of deep inspiration, hyperventilation and pre-oxygenation has previously been investigated in breast cancer patients using a mechanical ventilator (Figure 1B).[15,16] We compared pressure support mechanical ventilation with HFNO using an Optiflow Thrive device (Figure 1A&B). No differences in L-DIBH durations were observed, but HFNO has several advantages. Firstly, ease of use is higher compared to the mechanical ventilator. As described by Parkes et al., the ventilator parameters need to be adapted to the volunteer,[19] and this requires training for appropriate operation. Secondly, set-up of the mechanical ventilator takes significantly longer and is prone to failure since an air-tight fit of the face mask is essential.[20] Thirdly, the HFNO system with nasal cannula is perceived as less claustrophobic and preferred by most of the volunteers. Notably, one volunteer developed a panic attack due to claustrophobia, during the application of the air-tight face mask, despite achieving proficient L-DIBHs using HFNO. Schwabbauer et al. also showed HFNO is more comfortable and preferred by patients with acute hypoxic respiratory failure.[21]

We also compared HFNO to a Hudson mask (Figure 1A&C) for pre-oxygenation. HFNO enables around 20 seconds longer median L-DIBH durations. This could be due to the higher levels of end expiratory pressure generated by HFNO, reducing lung collapse, and increasing the oxygen delivery. Also, flushing of the upper-airway dead space increases the alveolar oxygen concentration.[22-24] Consequently, this results in higher apneic oxygenation and sustained high alveolar and blood oxygen levels, although probably without a decrease in blood carbon dioxide levels, which is the strongest trigger to breathe.[14,25,26] This is probably the reason why switching off the oxygen flow during the breath-hold did not influence L-DIBH duration.

We propose a 3-minute period of voluntary hyperventilation before L-DIBH. This is similar to the preoxygenated hyperventilated hypocapnic apnea-induced radiation (PHAIR) protocol, but

considerably shorter than the protocol of Parkes et al.[15,16] It seems that most of the effect of hyperventilation is reached after 3 minutes. Further prolonging hyperventilation probably leads to longer L-DIBH duration, but is time-consuming and therefore difficult to implement in the daily routine of a radiotherapy department. In the PHAIR protocol, volunteers were asked to perform 1 minute of hyperventilation after 4 minutes of oxygenation, resulting in similar L-DIBH durations compared with our protocol. However, our protocol has a shorter preparation time, allows consecutive L-DIBHs and does not require a mechanical ventilator. During the research cycles an optimal breathing frequency was not found. This endorses the hypothesis that hypocapnia caused by hyperventilation can be similarly achieved with slow and deep or rapid and shallow ventilation combinations.[19] Empirically we choose a value of 16 breaths per minute since this was well tolerated.

Other techniques have been developed to prolong DIBH duration in breast cancer, not using hyperventilation and oxygen. High Frequency Percussive Ventilation (HFPV) was developed for unanesthetized patients with lung or breast cancer. Very long breath-holds are achievable using HFPV, with 3 patients reaching breath-hold durations of over 7 minutes.[27,28] However, adaptation to the individual patient is necessary and a leak-free seal, crucial to prevent motion drift due to air leakage. Finally, a mechanical ventilator can be used to change breathing patterns and reduce motion variability of the tumour.[19,29,30] This approach requires both an airtight face mask and expertise in mechanical ventilation at the radiotherapy department. In contrast to all previous techniques, our protocol is simple, requires minimal set-up time and equipment and limited training.

The volunteers and patients could easily perform 3 consecutive L-DIBHs with only a minimal resting-time in-between 2 L-DIBHs and this during 4 successive sessions. Hyperventilation has long been known to cause symptoms of dizziness, tingling and light headedness, and these side effects were also common in our volunteers. [31,32] No serious adverse events were observed, besides a grade 2 laryngitis in an immunocompromised patient. Further investigation is needed to determine whether this was caused by the study procedures. However, previous studies also established similar techniques to be safe to perform.[15,16,33] L-DIBH duration increases with each successive breath-hold during a single examination, and progressively throughout the 4 sessions, which highlights the possible benefit of a training phase before using the technique during radiotherapy treatment. Our L-DIBH durations could potentially be further increased by using visual feedback in addition to audio guidance[34,35] and by instructing patients to perform home practice.[36,37] The proposed protocol was developed and validated in 32 volunteers and 8 patients, who were all highly motivated and presenting with low comorbidity. Further research

needs to validate the effectiveness in a broader population of breast cancer patients with a history of cardiac or pulmonary disease, who smoke during treatment or with obesity. For instance, obesity is a risk factor for ischemic heart disease and has a major impact on lung function, mainly due to the decreased functional residual capacity.[38] In these patients heart dose reduction is especially important.[4,3] Furthermore, imaging studies are necessary to determine the intra- and interfraction motion variability during L-DIBH.

In conclusion, HFNO combined with a short period of voluntary hyperventilation significantly prolongs DIBH durations, allowing for treatments with multiple consecutive L-DIBHs of 2 minutes and 30 seconds.

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Supplementary materials

APPENDIX A EXAMINATION PROCEDURE

Each examination is separated in four different steps. The first step is preparation of the volunteer with positioning of the volunteer in treatment position according to the volunteers protocol, attachment of the monitoring equipment, preparation for the oxygenation and placement of the earphones inside both ears. Secondly, the patient performed three consecutive L-DIBHs procedures. Each L-DIBH procedures is separated in two phases, the oxygenation and hyperventilation phase and the breath-hold phase. During the first phase the volunteer receives beeps with two tones with a different pitch, one for inhalation and one for expiration, at a predefined RR. During this hyperventilation the patient receives additional oxygen using one of the three oxygenation devices (Figure 1). For the mechanical ventilator or HFNO, a maximum FiO2 of 80% was allowed to reduce absorption atelectasis, most examinations were performed with an FiO2 of 60%. The duration of the oxygenation and hyperventilation phase is predetermined. After the first phase, the spoken command is given to “breath-in deeply” and “breath-out deeply” twice, followed by “breath-in deeply and block” after which the L-DIBH is started.

Safety criteria
The volunteer ends the examination
The investigator ends the examination
Symptoms
Loss of consciousness
Vomiting
Severe nausea
Vertigo
Palpitations between examinations
Chest pain
Vital parameters
< 92% SpO_2
>210mmHg SBP or 30% increase from baseline SBD
>120mmHg DBP or 30% increase from baseline DBP
Increase of HR >40 BPM from baseline
Broad QRS complex arrhythmias
Irregular heart rate

SpO_2: Oxygen saturation
SBP: Systolic blood pressure
DBP: Diastolic blood pressure

During the apnea phase the volunteer heard music and was continuously monitored using a Carescape B650 anesthesia monitor (GE Healthcare, Finland) and captured with Collect S5 (Datex-Ohmeda Division, Instrumentarium Corporation, Finland) for oxygen saturation, heart rate, 3-lead electrocardiogram (ECG), expired CO2 (EtCO2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) are measured in 1 minute intervals on the Carescape B650 anesthesia monitor and continuously on the Nexfin monitor (BMEYE, Netherlands). If the safety criteria were met, the examination was ended. Expiration is monitored using an EtCO2 measurement near the mouth of the volunteer. Finally the side-effects from the technique was assessed with a questionnaire.

The healthy volunteers were blinded for changes in the baseline protocol for the following parameters: duration of hyperventilation, hyperventilation frequency, fraction of inspired oxygen (FiO2); and flow rate (L/min) both during hyperventilation and apnea. The healthy volunteers could not be blinded for changes in L-DIBH position and oxygenation device. After each L-DIBH healthy volunteers were not given the duration of the L-DIBH until every volunteer of the cycle had finished all the examinations. No feedback was given on their performance. The breast cancer patients were given the same protocol every single examination. After each L-DIBH, the duration was told. The breast cancer patients were also asked to hold their breath for as long as they supported or until they felt uncomfortable.

APPENDIX B

B 1 Side effect questionnaires

B 1.1 Side effects questionnaire for volunteer after each examination

Did you feel any of these senations after performing a breath-hold?			
Dizziness	Yes	No	
Headeache	Yes	No	
Tingling feeling in fingers/feet or limbs	Yes	No	
Risk of losing consciousness	I did not feel like losing consciousness	I have felt like I could lose consciousness	I think I have been unconscious
Need to cough	Yes	No	
Nausea	Yes	No	
Itching	Yes	No	
Pain	Yes	No	
If yes, how much pain on a scale from one to ten?			
If yes, where did you feel pain?			
If yes, can you describe the kind of pain?			
Palpitations	Yes	No	
Muscle cramps	Yes	No	
Claustrophobia	Yes	No	
Fear			
Other sensations			

Do you currently feel any of the following symptoms (around 5 minutes after last L-DIBH)?		
Fatigue	Yes	No
Dizziness	Yes	No
Headache	Yes	No
Need to cough	Yes	No
Nausea	Yes	No
Itching	Yes	No
Pain	Yes	No
If yes, how much pain on a scale from one to ten?		
If yes, where did you feel pain?		
If yes, can you describe the kind of pain?		
Palpitations	Yes	No
Hoarseness of your voice	Yes	No
Muscle cramps	Yes	No
Do you currently have (around 5 minutes after last L-DIBH)?		
Headache	Yes	No
Shortness of breath	Yes	No
Dry mouth	Yes	No
Blurred vision	Yes	No

B 2 Comfort assessment

B 2.1Comfort questionnaire after each examination

Was the hyperventilation difficult to sustain?	Yes	No
Any discomfort during this examination?	Yes	No
If yes, on a scale from one to ten, how comfortable did you feel during the examination?		
If yes, why did you feel uncomfortable		
Could you support 60 minutes in this position	Yes	No
If no, how long could you support this position		
Do you feel discomfort right now?	Yes	No
If yes, on a scale from one to ten, how comfortable do you currently feel		
If yes, why do you feel uncomfortable		
Did you have any fear during the examination	Yes	No
Did you feel out of breath after ending a breath-hold	Yes	No
Was resting time between breath-holds sufficient	Yes	No
Were distracted during the examination?	Yes	No
If yes, why were you distracted?		
On a scale from one to ten, how comfortable was the examination today?		
Only for non-breast cancer volunteers		
How long do you think the first breath-hold was?		
How long do you think the second breath-hold was?		
How long do you think the third breath-hold was?		

B 2.2 Comfort questionnaire after all four examinations

Do you think you could perform the L-DIBH daily for an additional 10 days	Yes	No		
On which day do you think you performed the longest breath-hold?	Day 1	Day 2	Day 3	Day 4
Did you feel it become easier or harder to perform the technique during the week?	Easier	Neutral	Harder	
Do you think you breath-hold times improved or declined during the week?	Improved	Neutral	Declined	
If declined, why do you think that?				
From one to ten, how comfortable did you feel during the examinations				
At the last examination, where you more comfortable compared with the first?	Yes	No		
Did side effects change during the examination period?	Decreased	Neutral	Worsened	
How do you think your times were affected by the music	Improved	Neutral	Declined	
How did you feel during the first part of the breath-hold				
How did you feel during the middle part of the breath-hold?				
How did you feel during the last part of the breath-hold?				
Only for non-breast cancer volunteers				
Do you think breast cancer patients will be able to perform this technique?	Yes	No		
If no, why not?				
Which day did you feel the most supported by the technique	Day 1	Day 2	Day 3	Day 4
Depending on the research cycle				
On a scale from one to ten, how comfortable did you feel with the …				
ventilator				
optiflow				
oxygen mask				

E. Impact of hyperventilation duration and the possibility of repeat L-DIBHs

Article 2: Minimizing preparation time for repeated prolonged deep-inspiration breath holds during breast cancer irradiation using pre-oxygenation with high flow nasal oxygen and voluntary hyperventilation

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Abstract

INTRODUCTION

Deep inspiration breath-holds (DIBHs) reduce heart and lung toxicity during breast cancer radiotherapy. Consecutive DIBHs are stressful, time-consuming and leads to position changes. Pre-oxygenation using high flow nasal oxygen (HFNO) and hyperventilation prolongs DIBHs (L-DIBHs). We examined the effect of hyperventilation time on the duration of L-DIBHs. Additionally, to minimize total treatment time the feasibility of several successive L-DIBHs was examined.

MATERIALS AND METHODS

The method imposed 3 minutes of hyperventilation at 16 breaths per minute with preoxygenation using HFNO, in prone position. In the first phase, the effect of preparation time on the length of the breath-hold was investigated. The aim of the second phase was to investigate the feasibility of shorter preparation times before the second and third L-DIBH in the case of three consecutive L-DIBHs of 2 minutes.

RESULTS

There is a positive but weak correlation between preparation time and L-DIBH duration. With either 3 min 30 second or 6 minutes 20 seconds (depending on fitness) of voluntary hyperventilation duration, 93% of subjects could hold three consecutive L-DIBHs for over 2 minutes. The median duration of the third and last L-DIBH was 3min 17s (SD 1min 4s).

CONCLUSION

A weak relationship exists between the hyperventilation time and L-DIBH duration. Repeating L-DIBHs with shorter preparations is achievable, resulting in a shorter total time required.

Introduction

Adjuvant radiotherapy after breast conserving surgery (BCS) for breast cancer reduces the locoregional recurrence rate and improves overall survival.(1) However, acute and late radiotherapy-related toxicity may occur. Heart and lung toxicity can result in increases in morbidity and mortality.(2,3) Darby et al. showed that mean heart dose is a predictor for excess risk of major coronary events after radiotherapy for breast cancer.(2) Furthermore, estimates show an 8.5% increase in the rate of lung cancer for each additional one gray (Gy) of mean lung dose, further increasing to 17.3% for smokers.(3) Voluntary deep inspiration breath-hold (DIBH) is a popular technique to reduce the mean heart and lung dose, due to an increase in distance between the heart and the breast and increasing lung volume.(4) Another method to move the breast away from the heart and lung, by gravity, is prone positioning.(5) Lung dose is substantially reduced in prone position and for most left-sided breast cancer patients, a reduction in heart dose can be achieved. Combining prone position and DIBH results in a maximal heart and lung sparing effect.(6)

However, the need for several DIBHs in succession is stressful for the patient, time-consuming and increases the risk of position changes during radiation. A combination of three support methods can lead to prolonged breath holds: pre-oxygenation, voluntary hyperventilation, and deep inspiration before breath hold. Parkes et al. achieved longer DIBHs (L-DIBHs) of >5 minutes using a mechanical ventilator for 15 minutes of forced hyperventilation.(7) However, the Parkes technique is time-consuming and requires specific skills to handle the mechanical ventilator. Additionally, it is difficult to implement into the daily routine of a radiotherapy department. Recently, Parkes et al. demonstrated a shortened preparation of 3 minutes 30 seconds, not accounting for the training period to define the optimum ventilation parameters for each patient, could also reach 5 minutes of breath-hold duration.(8)

The Ghent University Hospital developed a simpler method.(9) Effectiveness, patient comfort and economic impact (time) were the most important criteria to be met. A duration of 3 minutes of voluntary hyperventilation and pre-oxygenation, using High Flow Nasal Oxygen (HFNO) therapy, was found to be optimal for L-DIBHs of 3 minutes. The volunteers and patients could easily perform three consecutive L-DIBHs with only a minimal resting-time in-between on multiple occasions. The advantage of this technique over the technique of Parkes is that there is no need for mechanical ventilation or fine-tuning. The HFNO cannula is more comfortable for patients compared to a strap-on full face mask during mechanical ventilation, and it does not require a leak free seal. Nevertheless, the HFNO technique developed at Ghent University Hospital still

requires a fairly long preparation time of at least 3 minutes. In the daily flow at the radiotherapy department, time is precious and not all techniques require a L-DIBH of 3 minutes.

The duration of voluntary hyperventilation and pre-oxygenation prior to L-DIBH, further called the preparation time, seems to be correlated with the maximum duration of the L-DIBH that can be achieved. Reducing the preparation time for L-DIBH is important to increase patient comfort, increase patient turnover and reduce costs. In the present article, we examined the effect of preparation time on the duration of a L-DIBH and the feasibility of shortening the preparation time when several successive L-DIBHs are needed.

Methodology

The L-DIBH method, used for the present study, was based on the technique previously developed in the Ghent University Hospital.(9) This protocol imposed 3 minutes of voluntary hyperventilation at 16 breaths per minute, using audio-assistance, with pre-oxygenation using HFNO (FiO2 of 60%; 40 litre per minute during hyperventilation and 20 litre per minute during breath-hold), in prone position. Prone and supine position were both examined in the previous study, but since L-DIBH was found to be more challenging in prone position, it was decided to proceed with this position. Because the participants received HFNO during hyperventilation, the measurement of the EtCO2 was considered not reliable as the high flow of oxygen/air mixture dilutes the exhaled air.

Only healthy women above the age of 18 were included in the present study. Exclusion criteria were: cardiac or pulmonary disease, currently smoking, not able to perform a single unassisted DIBH of over 20 seconds, and WHO obesity class II (BMI > 35 kg/m2). All volunteers gave a written informed consent, and the study was approved by the Ghent University Hospital ethics committee and registered on ClinicalTrials.gov, number NCT04091542.

The study consisted of two phases. Before the start of the examinations, the volunteers had the choice to participate in only the first phase or in both phases, depending on their availabilities and willingness to participate.

During phase one, the effect of the duration of hyperventilation with HFNO, further referred to as the preparation time, on the length of the L-DIBH was investigated. 24 volunteers (Table 1) performed three successive L-DIBHs with a long resting period in between, and before every L-DIBH, they were asked to hyperventilate at 16 breaths per minute while receiving HFNO. For each L-DIBH, the preparation times were randomized between one and six (whole) minutes. The order of the preparation times was randomized to avoid bias related to a training effect. After

hyperventilation, the volunteers were asked to hold their breath as long as possible, whereafter they chose the duration of the period between the previous L-DIBH and the following hyperventilation, further referred to as the resting period. This experiment was repeated on two separate days. The endpoint was the length of the L-DIBHs.

In the second phase, 11 of the 24 volunteers performed again three successive L-DIBHs on two additional days (six L-DIBHs in total). During this phase, the duration of the first two L-DIBHs was set at 2 minutes, and the preparation times before the second and the third L-DIBH were shorter than in phase one (only five seconds). For the last L-DIBH, the participants were asked to hold their breath as long as possible. Two schedules were created: a short and an ultrashort schedule (Figure 1). Based on the experience, sense of safety and capability in the first phase, the volunteers were allowed to choose between the two schedules. The short schedule starts with a preparation time of 3 minutes, and allows 1 minute and 40 seconds of hyperventilation before the second and third L-DIBH. The resting period is only 5 seconds after each L-DIBH. In comparison, the ultrashort schedule involves a first preparation time of 2 minutes, and only allows 45 seconds of hyperventilation before the other L-DIBHs. The resting period stays the same. The aim of this phase was to investigate the feasibility of shorter preparation times, and the endpoints were the success to reach three consecutive two-minute L-DIBHs, and the duration of the last L-DIBH.

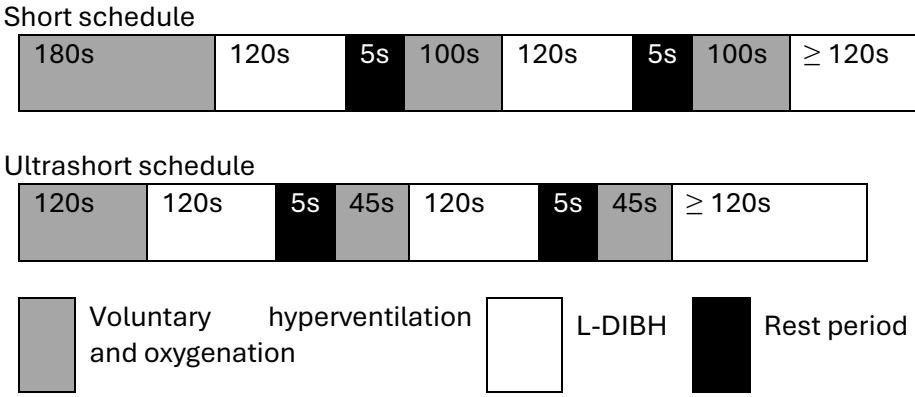

Figure 1: Study design for the second phase with predetermined preparation, resting period, and L-DIBH time in seconds (s). Colour codes for the schedule categories are shown in the figure; L-DIBH prolonged deep inspiration breath-hold.

Table 1: Baseline characteristics.

	Phase 1	Phase 2
N	24	11
Age		
mean	46 years	50 years
range	25 – 69	37 – 69 years
BMI		
mean	22	22
range	18 – 30	18 – 30
Behaviour		
former smoker N(%)	3 (13)	1 (9)
current alcohol use N(%)	18 (75)	10 (91)
Unassisted breath-hold		
mean (s)	46	46
range (s)	20 – 91	28 – 83

Results

From 28 April 2021 until 7 May 2021, a total of 24 healthy volunteers were included. Baseline characteristics of the volunteers can be found in Table 1.

Figure 2 shows the L-DIBH duration in function of preparation time (phase I). There is a positive but weak correlation between preparation time and L-DIBH (Spearman's rank correlation coefficient 0.35), showing a 17 seconds increase in L-DIBH duration for each additional minute of preparation time. Notably, median L-DIBH duration with 6 minutes preparation time was lower than with 4 or 5 minutes preparation time. The resting time in between two L-DIBHs was chosen by the volunteers, but did not correlate with the preparation time nor the length of L-DIBH. All volunteers wanted to start almost immediately after a L-DIBH with the preparation of the next L-DIBH.

Table 2 represents repeated L-DIBH results of phase II. 7 of the 11 volunteers chose the ultrashort schedule and four volunteers chose the short schedule based on the experience, sense of safety and capability in phase I. All but one volunteer in the 'ultrashort preparation group' achieved the goal of three successive L-DIBHs of at least 2 minutes duration. One volunteer failed to reach 2 minutes for the second L-DIBH. In the 'short preparation group', one volunteer failed twice in the same schedule to reach at least 2 minutes, but she did succeed every other L-DIBHs (4 out of 6 were successful in total). Due to a sneeze at the beginning of the third L-DIBH, another volunteer in the 'short preparation group' could not reach 2 minutes.

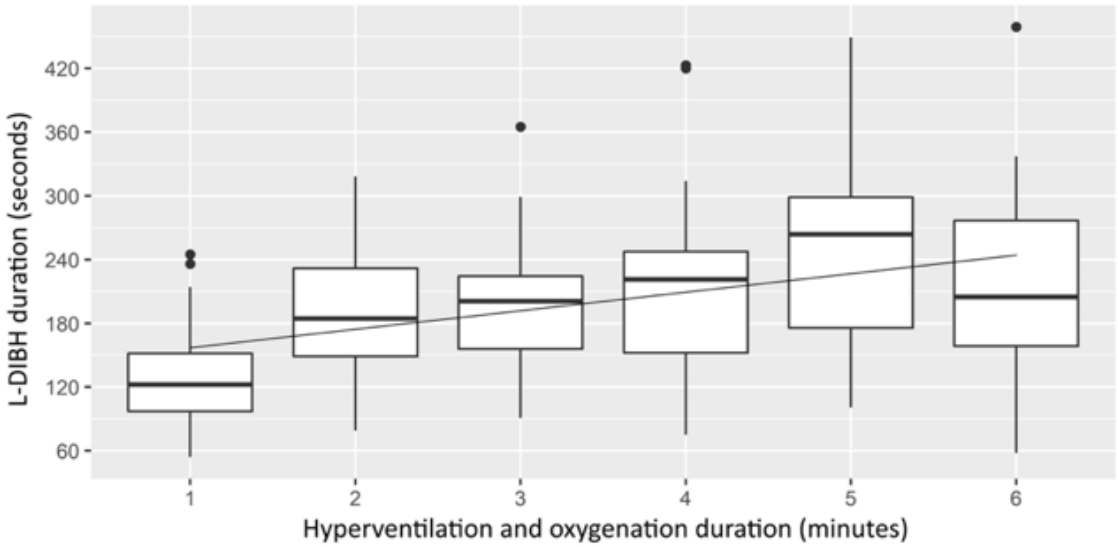

Figure 2: Boxplots with L-DIBH duration in function of preparation time for all 24 volunteers in the first phase (results of all L-DIBHs of both days combined), trendline shows linear regression line. There is a weak correlation between preparation time and L-DIBH duration (Spearman's rank correlation coefficient 0.35). For each additional minute of preparation time, there is a 17 seconds increase in L-DIBH duration.

Table 2: Repeated L-DIBH results of phase II. Two L-DIBH preparation schedules were created to achieve three successive L-DIBHs of at least two minutes or 120 seconds (schedules shown in Figure 1). Each volunteer chose a schedule based on the experience and sense of safety and capability in the first phase. The ultrashort preparation involves 3 minutes and 30 seconds of voluntary hyperventilation, with 10 seconds of resting time. The short preparation asks 6 minutes and 20 seconds of voluntary hyperventilation with 10 seconds of resting time. During this exercise the volunteers were asked to breath out after 2 minutes for the first and second L-DIBH. For the third and last L-DIBH the volunteers held their breath for as long as possible. Each volunteer performed the L-DIBH preparation schedule twice a day on 2 different days within the span of a week (a total of 4 sequences).

	ultrashort preparation	short preparation	Total
N	7	4	11
First L-DIBH			
success to reach 120s	28/28 (100)	15/16 (94)	43/44 (98)
Second L-DIBH			
success to reach 120s	27/28 (96)	16/16 (100)	43/44 (98)
Third L-DIBH			
success to reach 120s	28/28 (100)	14/16 (88)	42/44 (95)
median (m:ss)	3:22	3:11	3:17
range (m:ss)	2:31 – 4:00	1:51 – 6:08*	1:51 – 6:08*
sd (m:ss)	0:51	1:22	1:04
All three L-DIBHs			
Success to reach 120s	27/28 (96)	14/16 (88)	41/44 (93)

L-DIBH: long deep inspiration breath-hold
* Failed L-DIBH of 0:02 (2 seconds) due to sneezing at start of the third L-DIBH was not included

Discussion

DIBH is an established technique to reduce heart and lung toxicity in breast cancer patients, especially in case of left-sided breast cancer.(4) However, also in right-sided breast cancer, lung dose can be reduced by prone positioning and/or L-DIBH. When a breath-hold of more than 30 seconds is required, it is difficult for the average breast cancer patient to achieve this goal without any support. Moreover, even for a breath-hold of 30 seconds, most patients need some training. Pedersen et al. found an average time of 24 seconds for voluntary expiration breath hold and voluntary DIBH.(4) Unassisted breath hold times of our volunteers ranged between 20 and 91 seconds (Table 1). Earlier research showed the possibility of a L-DIBH for a duration of 3 minutes with pre-oxygenation using HFNO (9) and even >5 minutes using mechanical ventilation.(7,8) Parkes et al. have shown that the length of L-DIBH using mechanical ventilation depends on the preparation time. After shortening the total preparation time from 26 to 9 minutes, mean breath-hold duration significantly reduced from 6.5 minutes to 5.2 minutes. However, a final total preparation time of 3.5 minutes with a shorter and more vigorous hyperventilation and shorter hypocapnia still led to a mean breath-hold duration of >5 minutes.(8) The technique of pre-oxygenation using HFNO and hyperventilation is easier to implement, less expensive and requires less qualified personnel. However, with our technique using HFNO, very long L-DIBHs of >5 minutes are only exceptionally feasible. Consecutive shorter L-DIBHs of 2-3 minutes might also be very useful in daily practice. During a radiotherapy treatment, interruptions often occur during which DIBH is not strictly necessary, although sustaining one very long DIBH might have advantages in terms of positioning stability. Examples are the time needed to evaluate images from portal imaging or cone-beam CT, or to perform manual couch shifts. In the present study we investigated the effect of further reducing the preparation time on the length of L-DIBH, using HFNO. In daily practice, this information might be useful to tailor the number and the length of DIBHs to the complexity of the treatment and the capacities of the patient.

In the first phase of this study, we investigated the relationship between preparation time and L-DIBH duration. If a breath-hold of less than 1 minute and 10 seconds is required, the recommended preparation time for voluntary hyperventilation and pre-oxygenation using HFNO is only 1 minute and in case of breath-hold times between 1 and 2 minutes, the recommended preparation time is 2 minutes. For breath-holds longer than 2 minutes, the best preparation time to start with seems to be 3 minutes. Important to remark, there was no control of the depth of hyperventilation.

It is possible to reduce the total time required on the treatment machine even further when performing repeated L-DIBHs, as seen in the second phase of our study. Using the short schedule, a total preparation time of 6 minutes and 20 seconds led to a L-DIBH duration of more than 6 minutes in total, resulting in about a 1:1 preparation time and L-DIBH duration efficiency. However, the ultrashort schedule requires only 4 minutes of preparation time to obtain more than 6 minutes of L-DIBH.

Several factors determine the number and the length of breath-holds needed to complete a radiation treatment, such as the imaging used, the complexity of the treatment, the use of couch rotations and patient comfort. Using the data of this study, a tailor-made schedule for each patient can be made, taking into account all the above factors, to assure the most efficient treatment with the shortest preparation time and the optimal amount of DIBHs.

In conclusion, this investigation shows that there is a clear relationship between the preparation time using HNFO and the length of the L-DIBH. It is important to create the most optimal schedule for each patient in function of the required radiation treatment. In a next phase, this patient-specific approach will be tested in the classical radiotherapy chain.

Conflict of interest

No conflict of interest.

Disclosure

Liv Veldeman holds a Clinical Mandate of Foundation against Cancer. The PhD mandate of Max Schoepen and equipment were financed through grants FAF-C/2018/1190 and C_2020_1377 of the Foundation against Cancer. Annick Van Greveling is funded through a grant of Think-Pink.

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Chapter V: Prone radiotherapy

A. Introduction

At Ghent University Hospital, prone radiotherapy is the standard treatment position for patients requiring WBI without LNI. However, prone radiotherapy complicates LNI.

1. Development of prone-crawl breast couch

The previous results lead to the introduction of prone positioning at the Ghent University Hospital in 2008. A commercial prone breast board was acquired for positioning patients in prone positions with both arms elevated. This position will henceforth be called prone dive position due to both arms and hands being elevated above the head, like a diver hitting the water. However, this position results in the requirement of a support at both shoulders, and hence a limited beam access for LNI. To address the limited beam access the development of an in-house prone-crawl breast couch (PCBC) was started, which supports the ipsilateral arm alongside the torso of the patient. This resembles the crawl swimming pose, hence the name. The goals of the PCBC were better access to the regional lymph node volumes, increased setup accuracy and improvements in patient comfort.(143–145) As shown in Figure 7, the PCBC allows for greater beam access compared to prone dive position, allowing for a good coverage of the lymph node volumes.(27) The delineations guidelines were also adapted for prone LNI.(27)

2. Dosimetric advantages

As already mentioned in chapter two, prone radiotherapy leads to a reduction in the MHD and MLD.(71) Our research group has shown WBI on the PCBC to result in a similar MHD compared to supine position, for left and right sided patients, but a three to fivefold lower mean ipsilateral lung and integral lung dose.(90) Other research groups have confirmed these findings.(150) To minimize the MHD, prone positioning and DIBH can be combined. DIBH reduces MHD in both prone and supine positioning, with the lowest doses achieved by a combination of prone and DIBH.(107) These findings remain for the combination of WBI with LNI on the PCBC.(97) Nevertheless, these results were not yet validated on a group of patients before this dissertation. The preliminary dosimetric results formed the basis for the PROne versus SUpine irradiation with Randomized Fractionation schedule (PRO-SURF) study (NCT03280719).

3. Toxicity results

As mentioned in chapter two, prone radiotherapy has shown to produce less acute and two-year toxicity. The Ghent breast cancer radiotherapy group randomized 100 patients with large breasts between either supine or prone position, and published the results of acute toxicity in 2013. Prone

position reduced the risk of moist desquamation after radiotherapy by a factor of three, in addition to resulting in a significantly lower incidence of dermatitis, edema, and pruritus at 1 to 2 weeks after radiotherapy.(81) Veldeman et al. published the results for the 2-year late toxicity in 2016. Hyperpigmentation was less frequent in prone position, and cosmesis was better based on a photographic assessment using the BCCT.org software.(82) In 2022, Vespirini et al. from the Toronto Sunnybrook Regional Cancer Center in Canada confirmed the acute toxicity results from Ghent through a large phase III, multicentre, single blind randomized controlled trial for large breasted women (bra band ≥40 in and/or ≥D cup). Prone position led to a lower risk of moist desquamation compared to supine (26.9% vs 39.6%, $p<0.002$), which was also confirmed on multivariable analysis ($p<0.001$).(83)

4. Validating the use of prone radiotherapy

Although the results previously mentioned show a positive picture with regards to the use of prone WBI ± LNI, the implementation of the technique in daily practice remains limited. This chapter contains three publications on the use of prone radiotherapy: 1) the first publication uses the REQUITE consortium data to validate the advantage in toxicity and the reduction in MHD and MLD, 2) the second publication presents the five year results from the Ghent prone-supine RCT to validate the advantage of prone radiotherapy on long-term toxicity, and 3) the third publication presents the dosimetry and acute toxicity results of the PRO-SURF trial, a 4-arm randomized open-label trial comparing prone position (on the PCBC) and supine position for patients requiring adjuvant WBI and LNI.

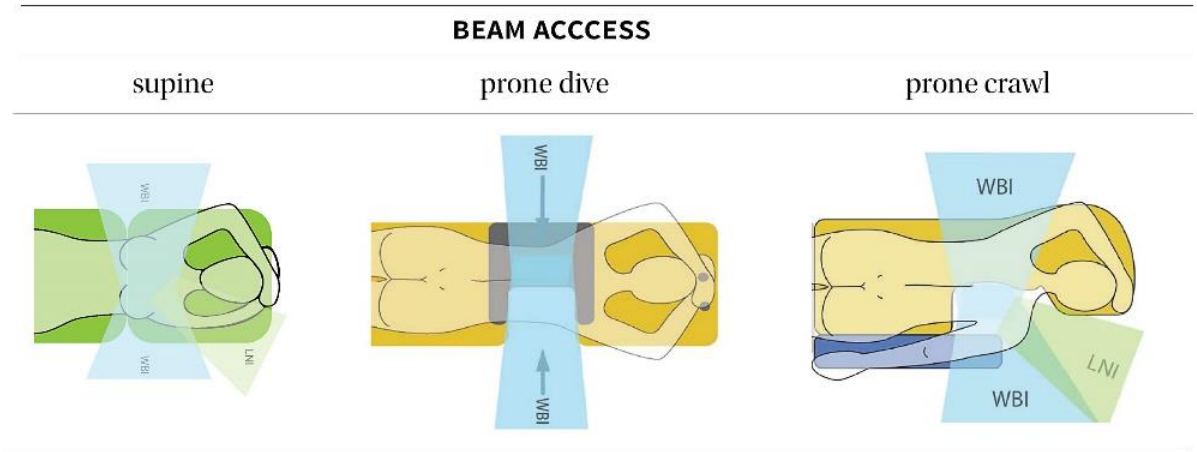

Figure 7: Prone crawl positioning allows an improved beam access by allowing anterior beams for the treatment of the lymph node regions. (Adapted from Schoepen M. Expanding the possibilities of prone crawl positioning for breast radiotherapy. [Ghent]: Ghent University; 2022.).

B. Matched case-control study using REQUITE data

Article 3: Comparison of prone and supine positioning for breast cancer radiotherapy using REQUITE data: dosimetry, acute and two years physician and patient-reported outcomes

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Reference:

Vakaet V, Deseyne P, Bultijnck R, Post G, West C, Azria D, et al. Comparison of prone and supine positioning for breast cancer radiotherapy using REQUITE data: dosimetry, acute and two years physician and patient-reported outcomes. Acta Oncol (Madr). 2023

Abstract

OBJECTIVE

Most patients after breast conserving surgery receive whole breast radiotherapy in a supine position. However, two randomized trials showed the superiority of prone over supine positioning in reducing acute toxicity. Furthermore, in most patients, prone positioning reduced doses to the organs at risk (OAR). To confirm these findings, we compared physician and patient assessed outcomes, photographic assessment and dosimetry between both positions using REQUITE data.

METHODS

REQUITE is an international multi-centre prospective observational study that recruited 2069 breast cancer patients receiving radiotherapy. Data on toxicity (CTCAE v4.0), health related quality of life (HRQoL) (EORTC QLQ-C30 and BR23) and dosimetry were collected, as well as a photographic assessment (analysed with BCCT.core software). A matched case control analysis compared patients treated prone (n=268) versus supine (n=493). Exact matching was performed for the use of intensity modulated radiotherapy, boost, lymph node irradiation, chemotherapy and fractionation, and nearest neighbour for breast volume. Primary endpoints were dermatitis at the end of radiotherapy, and atrophy and cosmetic outcome by photographic assessment at 2 years.

RESULTS

At the last treatment fraction, there was no significant difference in dermatitis ($p=0.28$) or any HRQoL domain, but prone positioning increased the risk of breast oedema ($p<0.001$). At 2 years, patients treated prone had less atrophy ($p=0.01$), and higher body image ($p<0.001$) and social functioning ($p<0.001$) scores. The photographic assessment showed no difference in cosmesis at 2 years ($p=0.22$). In prone position, mean heart dose was significantly lower for left-sided patients (1.29Gy vs 2.10Gy, $p<0.001$) and ipsilateral lung dose was significantly lower for all patients (2.77Gy vs 5.89Gy, $p<0.001$).

CONCLUSION

Prone is superior to supine positioning as it reduces late toxicities and lowers OAR doses. We recommend irradiation in prone position.

Introduction

Whole breast irradiation (WBI) after breast conserving surgery (BCS) results in better overall survival, but the benefit is partly undone by secondary heart disease and lung cancer.[1–4] Several methods to reduce organs-at-risk (OAR) dose have been developed including deep inspiration breath hold (DIBH), prone positioning and better planning techniques.[5] Usually, WBI is performed in supine position, but several studies have found better dosimetric results when treating in prone position, especially in patients with larger breasts.[6–9] A recent comparison of supine DIBH and prone position with free breathing found prone as the optimal position in 62% of patients, most notably for lung dose.[10] Besides better dosimetry, other advantages have been described, including lower rates of acute and late toxicity.[11–15] Two randomized trials compared the acute toxicity between both positions for large breasted women and both studies found a reduction in therate of acute toxicity.[14,16] Of these two trials, one trial also reported a reduction in late toxicity, but no results on quality of life.[15]

REQUITE (www.requite.eu) is a large prospective multicentre cohort study of patients undergoing radiotherapy for breast, prostate or lung cancer.[17] Over 2000 breast cancer patients were included and prospective data collection was done using standardized case report forms. Very detailed information is available for each individual patient including, but not limited to, fractionation, treatment techniques, and breast volume. To confirm the advantages of prone positioning, we performed a matched case-control analysis using data from the REQUITE breast cohort.[17] Our analysis compares the differences between prone and supine positions for toxicity and HRQoL, both acute and at 2 years. In addition, a dosimetric comparison was performed.

Methodology

STUDY POPULATION

REQUITE is an international multi-centre study using prospective standardized data collection with the aim to validate prediction models for late toxicity. From April 2014 until March 2017, the study recruited 4438 patients in 26 hospitals, of which 2069 were breast cancer patients (99% of target). The inclusion criteria were patients suitable for adjuvant radiotherapy (RT) after breast conserving surgery including patients receiving (neo-)adjuvant chemotherapy, with the last cycle at least 2 weeks before the start of WBI. All patients had planned potentially curable RT according to the local regimes. The choice of treatment position was based on the local treatment protocol. Exclusion criteria were mastectomy, prior RT in the same region, bilateral breast cancer, male breast cancer, partial breast irradiation, breast implants and bilateral breast cancer. Follow-up

was for at least 24 months, with longer follow-up encouraged. More detailed information on the REQUITE study and the patient characteristics of the breast cancer cohort can be found in a recent publication.[18]

MATCHING

Before matching, fractionation schedules were categorized as normofractionation (above 20 fractions), moderate hypofractionation (10-19 fractions), and strong hypofractionation (1-9 fractions). Each patient treated in a prone position was matched with 1 or, if possible, 2 patients treated in supine position, selected by means of a propensity scoring method without replacement. An exact method was used for lymph node irradiation (LNI), boost, intensity modulated radiotherapy (IMRT), chemotherapy and fractionation schedule, and a nearest neighbour method for breast volume.[19–22]

DATA COLLECTION

For the analysis, three time-points of interest were chosen: baseline, end of RT (acute toxicity) and 24 months after the end of RT. At baseline, demographics, comorbidity and treatment data were collected, including dosimetry. The physician assessed toxicity was assessed at all three time-points using the following CTCAE v4.0 terms: atrophy, oedema, skin ulceration, telangiectasia (inside and outside tumour bed), skin induration (inside and outside tumour bed), erythema, arm lymphoedema, pain and skin hyperpigmentation. HRQoL data were collected at all 3 time-points using the EORTC QLQ C30 [23] and breast specific QLQ BR23 [24] questionnaires. Since not all HRQoL questions are relevant in the comparison of prone and supine position, only the following scales were retained for the analysis: Physical Functioning, Social Functioning, Fatigue and Pain (QLQ C30), Body Image, Breast Symptoms and Arm Symptoms (QLQ BR23). A photographical assessment of breast cosmesis was done before RT and after 2 years using the BCCT.core software.[25] Dosimetry data were collected centrally through standardized operating procedures. The dosimetric analysis contained data on mean heart dose (MHD), mean lung dose (MLD), maximum skin dose, and the skin volume receiving a dose of >107% of the prescribed dose.

OBJECTIVES

The goal of the current analysis was to compare prone and supine positioning for 3 domains: 1) toxicity and cosmesis, 2) HRQoL and 3) dosimetry. Toxicity and HRQoL were separated in acute (at the end of RT) and late reactions (2 years). Before any analysis, to account for multiple testing, three primary endpoints were chosen: 1) acute dermatitis, 2) atrophy at 2 years and 3) photographic assessment at 2 years. Desquamation and ulceration were only analysed in the

acute setting. Atrophy, telangiectasia, fibrosis and hyperpigmentation were compared at 24 months. All toxicity measurements were dichotomized in no toxicity versus grade 1 or higher toxicity, except for acute dermatitis which was dichotomized between grade 1 or lower and grade 2 or higher toxicity (because 87% of all patients developed at least grade 1 dermatitis).

STATISTICAL ANALYSIS

R studio version 3.2.6 was used for all statistical analyses and data visualisation. To compare acute toxicity, acute and 24-months HRQoL and 24-months photographic assessment, the difference between baseline scores and the score after RT were calculated. A deterioration was defined as a worsening of at least one grade for physician assessed toxicity or cosmesis, and as a negative change of at least 10 points for HRQoL.[26] For the 24 months toxicity assessment, the baseline was not substracted. Cosmesis and toxicity outcomes were analysed using a Chi-Square test. HRQoL scores and dosimetry were compared using the Mann-Whitney U test. For the primary endpoints, an alpha level of 0.05 was chosen. To avoid type I errors due to the multiple tests, the Bonferroni correction was used for all secondary endpoints and for comparison of the baseline characteristics.

Results

Figure 1 gives an overview of the available data and the matching procedure, data was available for 2069 patients with missing data for one of the matching variables in 61 patients. In total, 2008 patients after BCS were matched, 292 were treated in prone and 1716 in supine position. After matching the number of patients was reduced to 761 (268 in prone and 493 in supine position). Table 1 shows the baseline characteristics before and after matching. Most patients treated in prone position were included in treatment centre A, whereas treatment centres B & C provided 45% of patients treated in supine position. After matching, statistically significant differences remain for age (57 vs 61 year, $p<0.001$), and treatment centre ($p<0.001$).

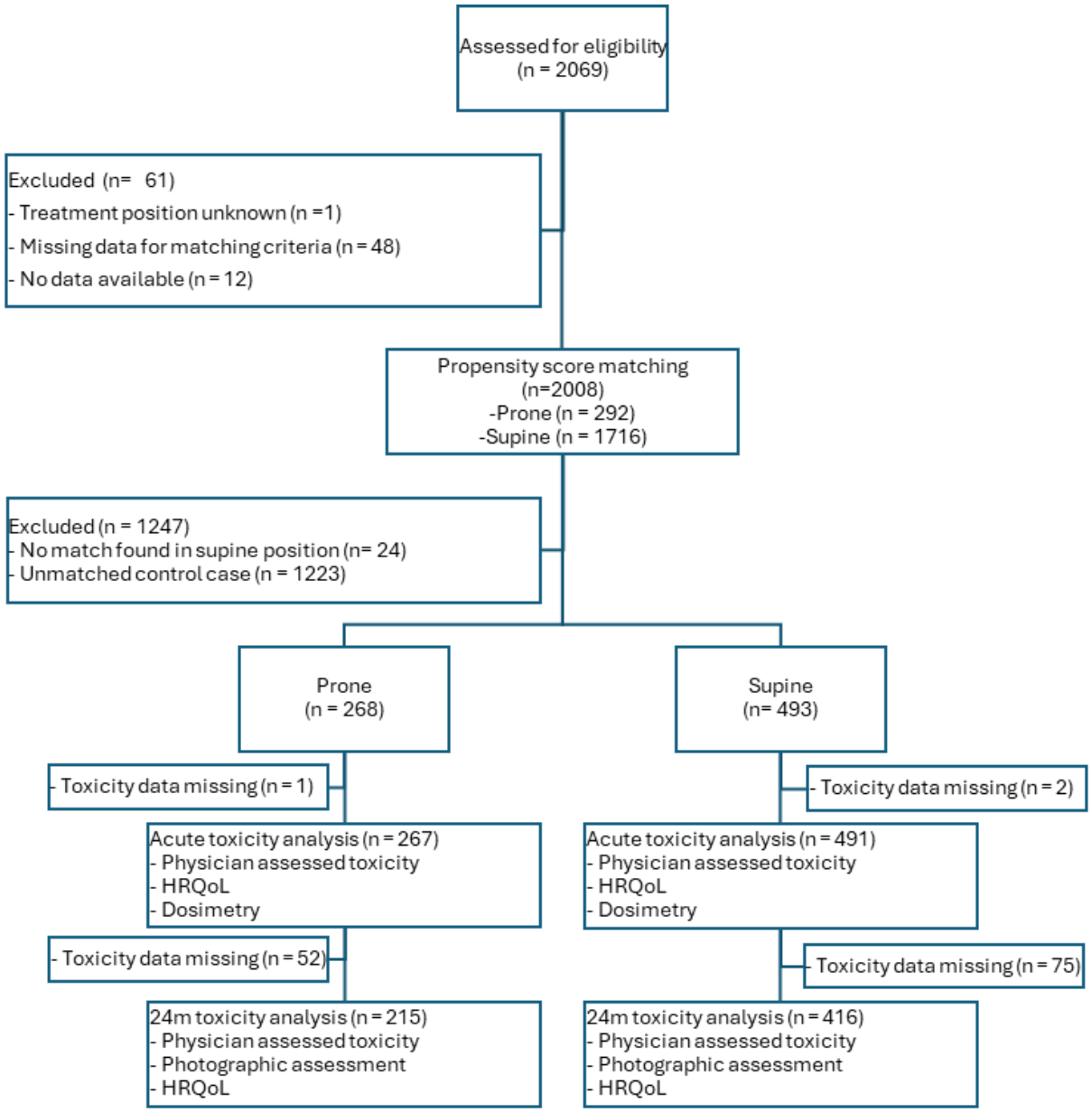

Figure 1: CONSORT diagram.

Table 1: Baseline characteristics of patients treated in prone and supine positions, before and after propensity score matching.

	Before matching			After matching		
	Prone N (%)	Supine N (%)	p-value	Prone N (%)	Supine N (%)	p-value
	N=292	N=1716		N=268	N=493	
Patient characteristics						
Age – years, mean	58	58	0.52	57	61	<0.001
BMI – mean	27	26	0.86	27	27	0.63
Breast volume – cc, mean	775	811	0.23	799	782	0.64
Smoking			0.76			0.94
Never	171 (58)	955 (56)		153 (57)	282 (57)	
Former	86 (30)	499 (29)		80 (30)	140 (28)	
Current	35 (12)	240 (14)		35 (13)	61 (12)	
Unknown	0 (0)	22 (1)		0	10 (2)	
Treatment centre						
Centre A	203 (70)	83 (5)	<0.001	179 (67)	21 (4)	<0.001
Centre B	41 (14)	58 (3)		41 (15)	28 (6)	
Centre C	7 (2)	428 (25)		7 (3)	152 (31)	
Centre D	7 (2)	337 (20)		7 (3)	42 (9)	
Other centres	34 (12)	810 (47)		34 (13)	250 (51)	
Treatment characteristics						
Axillary surgery			<0.001			0.03
SNB	236 (81)	997 (58)		215 (80)	304 (62)	
ALND	13 (4)	114 (7)		13 (5)	26 (5)	
ALND + SNB	13 (4)	167 (10)		12 (4)	31 (6)	
No axillary surgery	14 (5)	149 (9)		14 (5)	42 (9)	
Unknown	16 (5)	289 (17)		14 (5)	90 (18)	
Chemotherapy			0.73			0.69
NACT	24 (8)	165 (10)		23 (9)	37 (8)	
Adjuvant	65 (22)	366 (21)		47 (18)	78 (16)	
No chemotherapy	203 (69)	1185 (69)		198 (74)	378 (77)	
Hormone therapy			<0.001			0.008
Tamoxifen	145 (50)	600 (35)		138 (51)	204 (41)	
Aromatase inhibitor	88 (30)	705 (41)		77 (29)	195 (40)	
None	56 (19)	403 (23)		50 (19)	92 (19)	
Unknown	3 (1)	8 (0)		3 (1)	2 (0)	
Anti Her2 directed therapy			0.01			0.17
Yes	35 (12)	131 (8)		27 (10)	36 (7)	
No	252 (86)	1572 (92)		236 (88)	455 (92)	
Unknown	5 (2)	13 (1)		5 (2)	2 (0)	
Radiotherapy details						
Fractionation			<0.001			0.33
1 – 9 Fx	24 (8)	24 (1)		11 (4)	11 (2)	
10 – 19 Fx	221 (76)	706 (41)		210 (78)	390 (79)	
>20 Fx	47 (16)	986 (57)		47 (18)	92 (19)	
Lymph node irradiation			0.02			0.96
Yes	22 (8)	212 (12)		22 (8)	41 (8)	
No	270 (92)	1504 (88)		246 (92)	452 (92)	
Boost			0.75			0.59
Yes	200 (68)	1159 (68)		177 (66)	316 (64)	
No	92 (32)	557 (32)		91 (34)	177 (36)	
IMRT			<0.001			0.54
Yes	198 (68)	803 (47)		175 (65)	311 (63)	
No	94 (32)	913 (53)		93 (35)	182 (37)	

*ALND Axillary lymph node dissection, BMI body mass index, ER estrogen receptor, Fx fractions, IMRT intensity modulated radiotherapy, SNB sentinel node biopsy. * Significant after Bonferroni Correction p<0.003.*

TOXICITY AND COSMESIS

Figure 2 gives an overview of acute and 2-years toxicity. For acute toxicity, the proportion of patients experiencing at least one grade of deterioration is significantly higher for oedema (48% in prone vs 31% in supine, p<0.001). The primary endpoint of the proportion of patients with a deterioration (≥2 grades) for dermatitis is not statistically significant (16% vs 20%, p=0.28). At 2 years, the proportion of patients experiencing breast atrophy (primary endpoint) is significantly lower: 45% in prone and 56% in supine position (p= 0.013). For the secondary endpoints, the proportion of patients with at least grade I toxicity is not significantly different between both treatment positions. The photographic assessment, included in Table 2, found no difference in the risk of worse cosmesis at 2-years compared to baseline, both for arms on the hips and arms up.

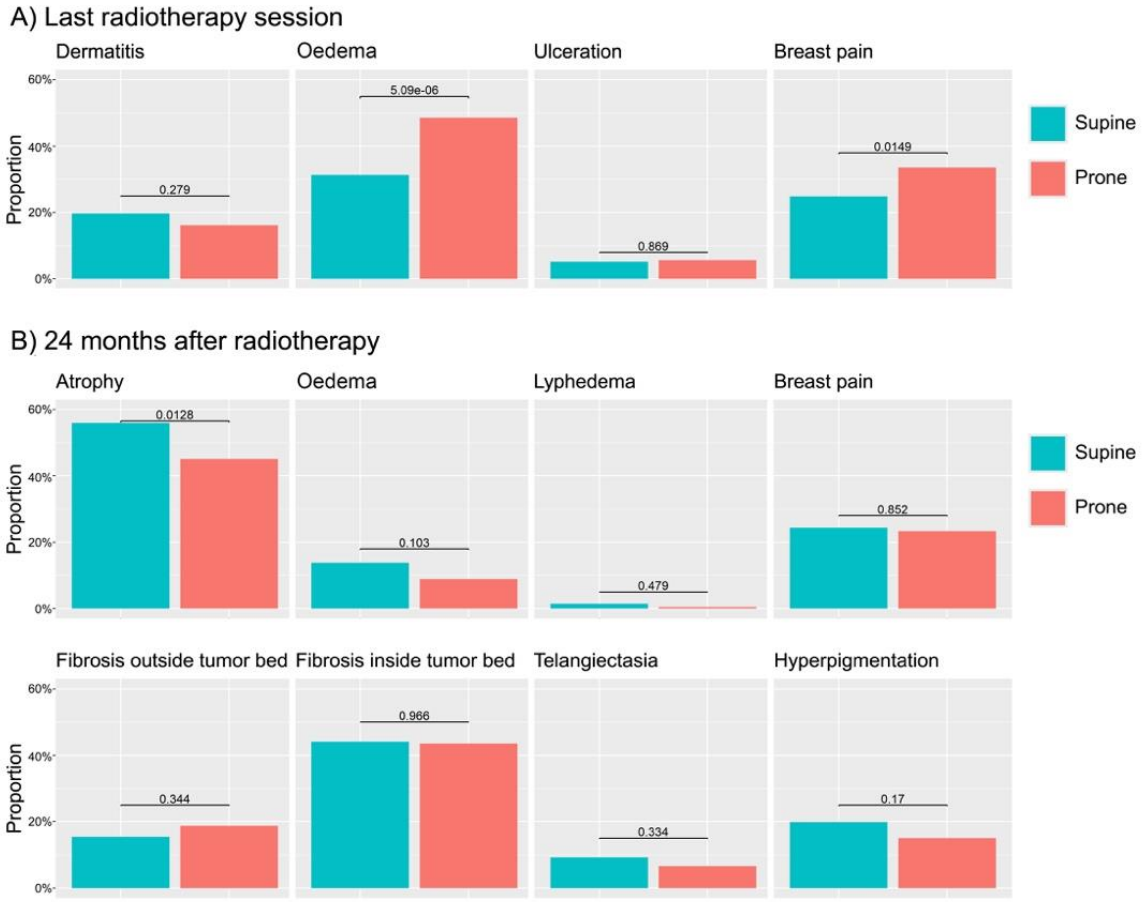

Figure 2: Comparison of physician assessed toxicity between prone and supine positions. A) Proportion of patients with a deterioration in toxicity at the end of radiotherapy compared to baseline with one category (oedema, ulceration and breast pain) or two categories for dermatatis. B) Proportion of patients experiencing grade I or higher toxicity at 2 years after radiotherapy.

Table 2: Photographic assessment at 24 months of deterioration of cosmesis compared to baseline for the photographs with a) both arms on the hips and b) both arms elevated.

	Prone (N= 198) n (%)	Supine (N= 390) n (%)	p-value
A) Arms on the hip			
No deterioration	148 (75)	275 (71)	0.50
1 category worse	37 (19)	89 (23)	
2 categories worse	12 (6)	26 (7)	
B) Arms up			
No deterioration	144 (73)	284 (73)	0.22
1 category worse	49 (25)	83 (21)	
2 categories worse	5 (3)	21 (5)	

HEALTH RELATED QUALITY OF LIFE

Figure 3 shows improvements or deteriorations of HRQoL from baseline, both acute and after 2 years. After RT, no significant difference in HRQoL between prone and supine position is found. At 2 years, body image (p=0.001) and social functioning (p=0.001) are significantly better in patients treated in prone position, with fewer patients experiencing a deterioration and a higher proportion of patient experiencing an improvement. The difference in body image compared to baseline is weakly correlated with the difference in social functioning (Spearman correlation coefficient rs=0.34).

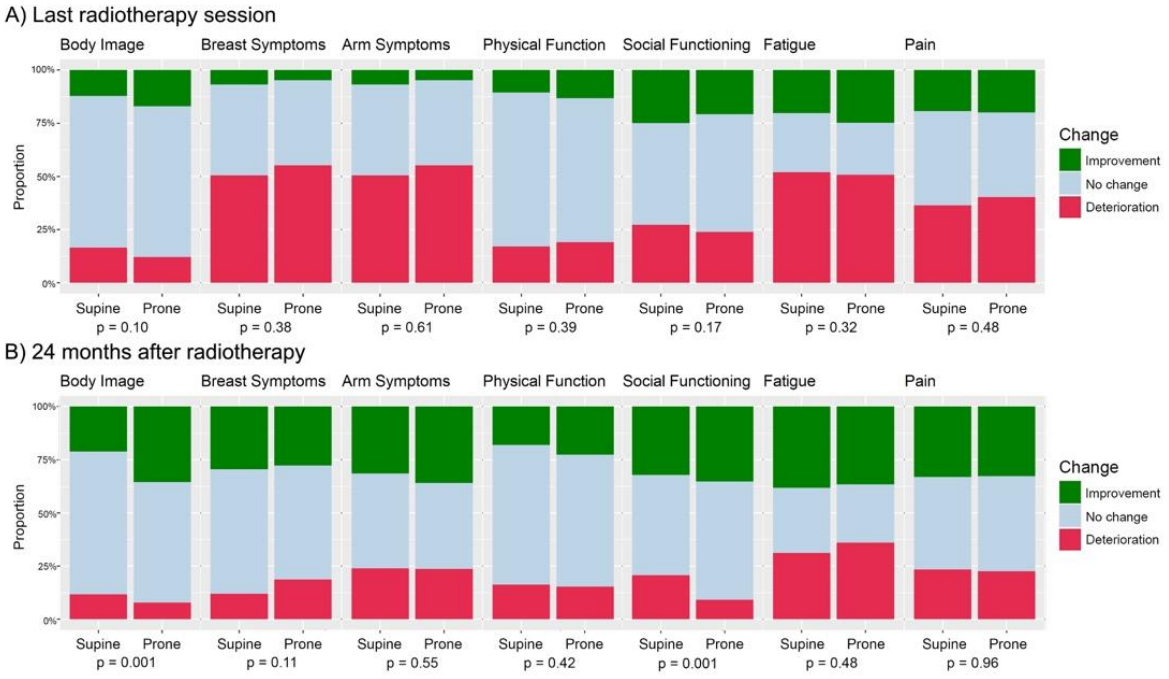

Figure 3: Proportion of patients, treated in prone or supine position, experiencing an improvement or deterioration of at least 10 points compared with baseline at A) the end of radiotherapy and B) 24 months after radiotherapy.

DOSIMETRY

Figure 4 shows the MHD for left and right-sided patients and the ipsilateral MLD. On the one hand, the median MHD for left-sided patients is 1.29Gy in prone position and 2.10Gy in supine position ($p<0.001$). On the other hand, for right-sided patients median MHD is significantly higher in prone (0.60Gy vs 0.40Gy, $p<0.001$). A 3.11Gy lower median MLD is found for prone position, compared to supine position (2.77Gy vs 5.89Gy, $p<0.001$).

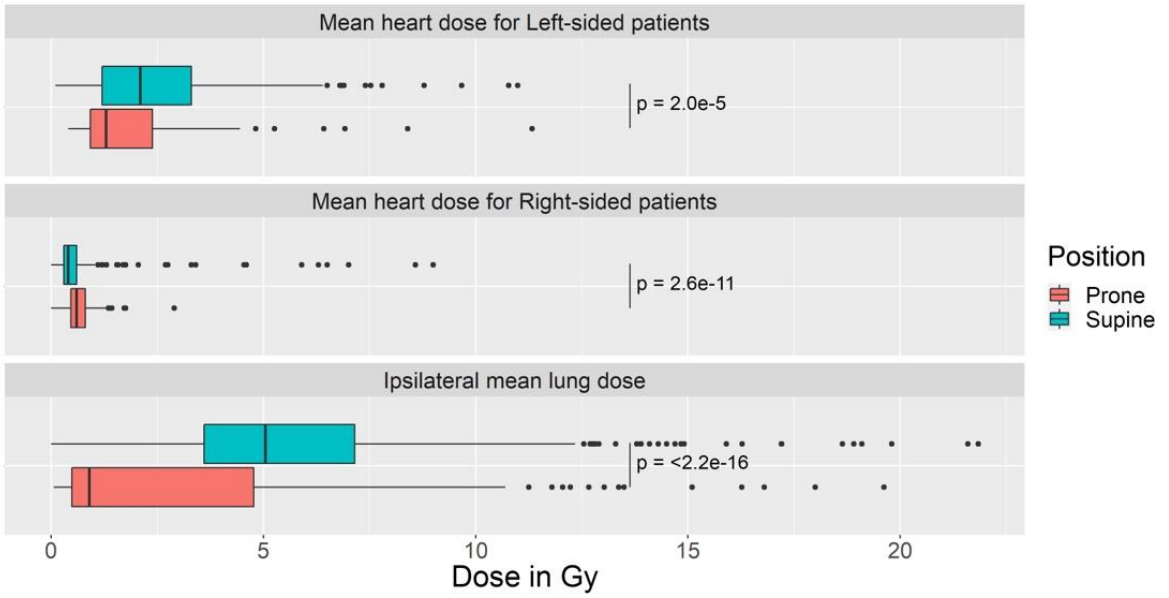

Figure 4: Mean heart dose, shown separately for left- and right sided breast cancer patients, and ipsilateral mean lung dose for all patients.

Discussion

The dosimetric advantages of prone positioning have been known for a long time, yet the application in daily clinical practice remains limited.[6–8,10,27] Other potential advantages, like reduced toxicity and improved HRQoL remain underreported. Only one randomized controlled trial (RCT) has compared acute and late toxicity between prone and supine position in women with large breasts.[11–13] This RCT showed positive results at all three time-points (acute, 2 years and 5 years). The risk of acute toxicity, measured both at the end of WBI and 1 to 2 weeks thereafter, was lower for prone compared to supine positioning for the following toxicity domains: desquamation (or ulceration), dermatitis and oedema.[12] Recently a second single blind RCT confirmed the lower risk of desquamation after WBI in prone position.[14] In contrast, the present analysis of acute toxicity did not find any advantage for prone positioning. On the contrary, prone positioning resulted in a significantly higher risk of oedema. However, acute toxicity was only measured at last day of irradiation, while it is known the highest rates of acute toxicity are seen 2

to 8 weeks after irradiation, depending on fractionation.[28,29] Also, fraction of patients treated in prone positioning is radiotherapy centre dependent and most prone patients were included from a single institution, hence resulting in a risk of bias due to scoring differences between institutions. Finally, previous RCTs only allowed patients with large breast sizes, which is a risk factor for acute toxicity.[6,19,20,30] In contrast our analysis included patients of all breast sizes, like small breasted patients with a low risk of acute toxicity in both positions. A hypothesis for the increased risk of oedema is the increased gravitational pull in prone position. The higher rate of oedema did not result in any differences in the acute patient reported outcomes.

In contrast to the acute toxicity results, our 2-year results do confirm the lower risk of breast atrophy (45% vs 56%, p= 0.013) found in the only RCT reporting late toxicity, despite our analysis including patients with small breasts.[11] However, these findings were not confirmed in the photographical assessment. All RT centres took photographs which were assessed centrally using the BCCT.core software.[31] The HRQoL items body image and social functioning were significantly better in prone position at 2 years. The better patient satisfaction with their body image could be a result of the lower risk of atrophy. Besides a weak correlation with body image (rs =0.34), the difference in social functioning might be due to other differences. These factors influencing HRQoL include age (supine patients are on average 4 years older), use of hormone therapy, cultures between treatment centres or other factors not used in matching, due to the choice for toxicity as the primary endpoints.[32,33]

The current analysis supports the reduced MHD and ipsilateral MLD in prone compared to supine position. [6–8,10] Median MHD for left-sided patients is 39% lower in prone compared to supine position. The 0,81Gy difference in MHD between both positions should lead to a 6 percent reduction in the increase in the rate of major coronary events after radiotherapy, according to Taylor et al.[2] In contrast to the MHD reduction for left-sided patient, prone resulted in a 0.2Gy higher median MHD for right sided patients. Nevertheless, the median MHD in both positions for right-sided patients is low (0.6Gy in prone, and 0.4Gy in supine position). Besides heart disease, a second cause radiation-related mortality in breast cancer patients is secondary lung cancer. A SEER analysis even found that for women treated between 1983 and 1992, there was evidence for secondary lung cancer mortality, but not for cardiac mortality.[4] Taylor et al. found an excess relative risk for lung cancer of 0.11 per Gy.[34] The risk is most prominent after the first decade. In prone-treated patients, the median ipsilateral MLD was more than halved from 5.89 to 2.77 Gy.

A recent analysis comparing prone free breathing with supine DIBH, found a dosimetric gain for prone position in 62% of patients.[10] The UK HeartSpare Stage IB Study also compared prone

free breathing and supine DIBH, using a cross-over design in patients requiring left-sided WBI with an estimated breast volume of at least 750cm^3.[35] The authors concluded that supine DIBH resulted in better heart sparing and higher set-up accuracy, and was preferred by patients. Nevertheless, prone resulted in a 10-fold decrease in ipsilateral MLD (3.73Gy vs 0.34Gy, $p<0.001$). Hence, the question becomes: should the focus be on MHD or MLD reduction, in particular for smokers?[4,34] The most promising technique is probably the combination of prone position with DIBH, a combination which has been described to be feasible and of great potential.[27,36,37] Unfortunately, data on DIBH were not collected in the REQUITE study.

Despite the advantages of prone position, implementation of the technique in daily clinical practice remains limited. Only 2 centres in the REQUITE study used the prone position on a regular basis. Potential reasons for the limited use of the prone position are the superiority of supine DIBH over prone free breathing for MHD (even though prone DIBH probably is the most optimal technique), the greater set-up errors in prone position resulting in larger PTV margins, the misconception that the benefits of prone position only apply to patients with large breast size and prone positioning being less comfortable for patients. Since prone positioning is more complex, training for the technologists is required, but after being accustomed to the technique, treatments can be given in 20 minutes or less.[35,38]

The main limitation of the current analysis is the overrepresentation of patients from one single treatment centre, contributing for 67% of all prone patients, which could have biased the results. The other 7 out of 9 main participating centres treated only a very limited percentage of patients in a prone position (less than one in ten). Physician assessed toxicity has been shown to be highly susceptible to interobserver variability.[39] Another limitation is the difference in age, with supine-treated patients being on average 4 years younger. This discrepancy was accepted since literature does not show a strong connection between age and acute toxicity.[19,22,40] In contrast, age does impact HRQoL and late toxicity which could influence the results.[41] Nevertheless, scoring was done prospectively using standardized instruments at specific intervals and dichotomized to minimize inter-observer discrepancies.[18] Also, observer independent measurements were included like HRQoL and photographic assessment.

Based on our current findings, prone is superior to supine positioning: it lowers the risk of atrophy at 2 years, improves body image at 2 years and lowers ipsilateral MLD and MHD for left-sided patients. The higher risk of breast oedema at the end of RT had no impact on patient reported outcomes or late toxicity. Therefore, we recommend use of prone positioning for WBI.

Conflict of interest

Ghent University owns the patent application entitled Radiotherapy Board and Couch [WO2015144654A1] filed on March 25, 2014 for which LV is listed as inventor. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Disclosure

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C. Five-year data of the randomized prone-supine trial for WBI without LNI

Article 4: 5-year outcomes of a randomized trial comparing prone and supine whole breast irradiation in large breasted women

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Reference:

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Abstract

INTRODUCTION

Prone position for whole breast irradiation (WBI) results in lower rates of toxicity and reduced ipsilateral mean lung and heart doses. No randomized trials comparing toxicity and cosmesis at 5 years, comparing prone and supine positioning, are available.

METHODS

In this phase II open-label trial, one-hunderd patients, with large breast size requiring WBI were randomized between prone and supine position. Physician-assessed toxicity (retraction, fibrosis, edema, telangiectasia, pigmentation changes) was scored yearly, for a total of 5 years, and photographs were taken at 5 years to assess cosmesis. The data was analyzed longitudinally and cross-sectionally.

RESULTS

Longitudinal analysis shows lower grade 2 late toxicity in prone position. The results of at least grade I physician-assessed toxicity at 5 years are similar between respectively supine and prone position for retraction (56% vs 54%), fibrosis outside the tumourbed (33% vs 24%), tumourbed fibrosis (49% vs 46%), edema (11% vs 8%), telangiectasia (8% vs 3%) and breast pain (6% vs 8%), using cross-sectional analysis. However, the risk of pigmentation changes in prone position (0% vs 19%) 5-years after radiotherapy was significantly lower. Cosmesis was good or excellent in 92% and 75% of patients in prone and supine position respectively. 5-year overall survival is 96% in both groups.

CONCLUSION

Prone position results in reduced rates of late toxicity.

Introduction

Compared with supine positioning, radiation therapy in prone position, in general, delivers a lower ipsilateral mean lung dose, mean heart dose (MHD) and left-anterior-descending-coronary-artery (LAD) dose, especially in patients with large breasts.[1–7] Therefore, ASTRO guidelines recommend prone positioning as one of the options to reduce heart dose, in addition to deep inspiration breath-hold (DIBH) and heart blocks. [8] In a minority of patients, prone position can result in a higher heart dose.[1,9,10] However, a large reduction in ipsilateral lung dose is seen in all patients, regardless of breast volume and laterality.[1,4] Another advantage is the effect that the unique anatomy and shape of the breast in prone position results in unfolding of the skin folds as well as a better dose distribution and homogeneity, so that hotspots and acute toxicity are reduced.[11–13] Our study is the only randomized controlled trial (RCT) comparing whole breast irradiation (WBI) in prone and supine position, and confirms the expected lower toxicity resulting from prone positioning, both in the acute phase and after 2-years.[13,14] Other trials have reported 5-year toxicity in prone position, but no comparison of both positions has been published.[15,16] The current update compares the results for late toxicity, cosmesis and disease free survival, 5 years after closure of patient enrollment.

Methodology

This study is a phase II, open label, RCT comparing prone and supine radiotherapy. [14] The study was approved by the local ethics board and registered on www.clinicaltrials.gov (NCT00887523). One hundred women with European cup size C or more, eligible for WBI after breast conserving surgery, were included between December 2010 and December 2012. All patients were lymph node negative at baseline. Detailed inclusion and exclusion criteria, prone set-up procedure, constraints and dosimetry have been previously published. [13] All patients received a hypofractionated schedule of 40.05Gy in 15 fractions, followed by a sequential boost of 10Gy in 4 fractions, if indicated according to the treating physician. A 2-beam tangential field IMRT technique was used in the prone group and a 6-beam IMRT technique in the supine group, with a multibeam IMRT boost in both arms.

Physician-assessed toxicity was scored before WBI, every 6 months in the first 2-years after WBI, and yearly afterwards. The toxicity was scored by the treating radiation oncologist, using the Late Effect of Normal Tissue-Subjective, Objective, Medical Management and Analytical evaluation (LENT-SOMA) scale.[17] As previously described, standardized digital photographs were taken

yearly and analyzed using the commercially available BCCT.core (Breast Cancer Conservation Treatment. cosmetic results) software of the INESC Porto Breast Research Group.[14,18]

For the cross-sectional analysis of the prone and supine toxicity at 5 years, the Fisher's exact test was used, comparing the proportion of patients experiencing grade 1 or higher toxicity according to the LENT-SOMA scale. For the longitudinal analysis of the grade 2 late toxicity, Generalized Mixed Models were built, with treatment position as the fixed effect, and patient and follow-up moment as random effects. For cosmesis the photographic assessment and resulting BCCT.core classification were compared between both study arms. To eliminate the influence of baseline differences in breast cosmesis, the baseline classification was subtracted from the 5-year classification. The Fisher's exact test was used to compare the proportion of patients experiencing a deterioration compared to baseline, between both arms. All analyses and visualizations were done in RStudio (version 3.6.2).

Results

Five-years physician-based toxicity was available in 73 patients and photographs in 70 patients. Twenty-one patients were lost to follow-up since the last update (10 supine vs. 11 prone). Table 1 shows the baseline characteristics of the patients analysed in the cross-sectional analysis at 5 years. Table 2 shows the results of this cross-sectional analysis at 5-years. No significant differences in physician-assessed toxicity were found, except for pigmentation changes ($p=0.005$), in favour of prone positioning. Figure 1 gives an overview of the proportion of patients with any grade 2 or higher toxicity throughout the follow-up.

Table 1: Baseline characteristics tables of the patients included in the 5-year cross-sectional analysis

Characteristics		Treatment group	
		Supine N= 36	Prone N= 37
Age (y)		62 (36 – 78)	58 (39 – 78)
BMI		28 (19 – 44)	27 (19 – 38)
Cup size	C	19	19
	D	13	12
	E	3	4
	≥F	1	2
Breast volume (cc)		623 (191 – 980)	571 (243 – 876)
T-stage	Is	2	3
	1a	0	3
	1b	10	7
	1c	15	17
	2	9	7
ALND	No	29	33
	Yes	7	4
Chemotherapy	No	30	27
	Yes	6	10
Hormone therapy	No	4	5
	Yes	32	32
Boost	No	9	12
	Yes	27	25

Numerical values indicate number of patients, unless otherwise indicated. Mean (range) was used to express BMI, age and breast volume. Abbreviations: BMI, body mass index, T-stage, tumour stage, boost, sequential boost.

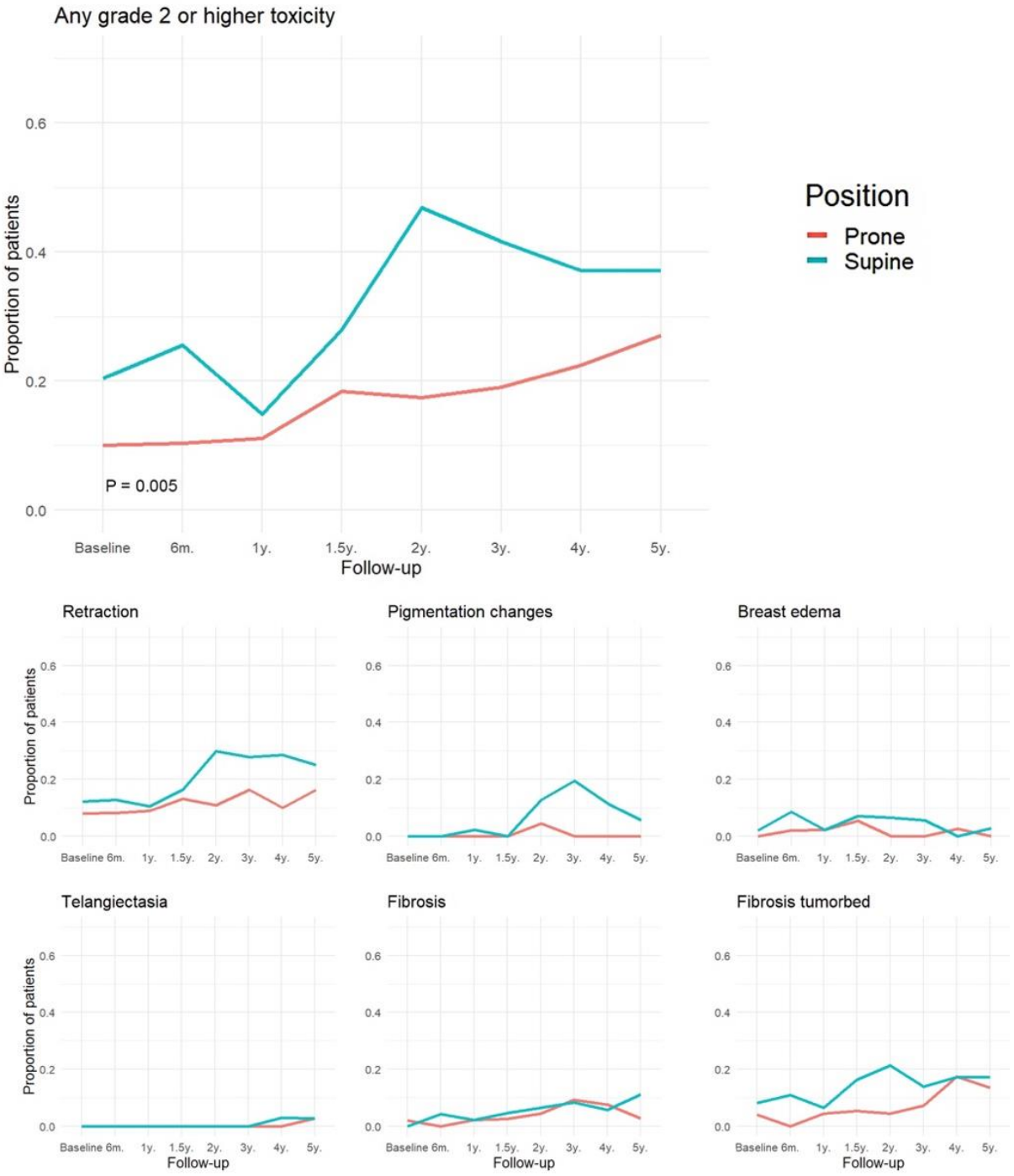

Figure 1: Longitudinal analysis of late grade II or higher toxicity according to the LENT-SOMA scale, comparing prone and supine position.

During the longitudinal analysis of grade 2 toxicity, prone positioning resulted in lower overall toxicity compared to supine positioning (p = 0.005). Table 2 shows an overview of the 5-year photographic assessment. No significant difference in the deterioration of breast cosmesis was found between both groups. According to the BCCT.core classification, cosmesis 5 years after radiotherapy was good in both arms with a good or excellent result in 75% and 92% of patients, in supine and prone respectively. The evolution of the toxicity is similar between both groups with breast oedema decreasing during follow-up, and fibrosis outside the tumour bed increasing over time. Grade 2 breast retraction reached a maximum at 2 years in supine (30%) and 3 years in prone (16%) position and remained stable afterwards. Grade 2 pigmentation changes peaked at 3 years in supine (19%) and 2 years in prone (4%) position, decreasing again afterwards. Finally, 5-year overall survival is 96% in both arms, as seen in Figure 2. At 5 years, no patients relapsed in the prone arm, although one patient developed a metastasized angiosarcoma, and two patients relapsed in the supine arm, one patient had a concurrent locoregional and distant relapse, and, one patient had a distant relapse.

Table 2: Cross-sectional analysis of the 5-year late toxicity. A) shows grade I or higher toxicity according to the LENT-SOMA scale. B) shows a comparison of breast cosmesis using photographs and scored using the BCCT.core software. a) Shows cosmesis results at 5 years, and b) shows the deterioration in cosmesis classification from baseline. Photographs were taken and analyzed in two positions: with both arms down and both arms up.

A. LENT-SOMA Toxicity grade I or higher at 5 years (N=73)

	Supine N (%)	Prone N (%)	OR (95% CI)	P-value
Breast retraction	20 (56)	20 (54)	0.94 (0.34 – 2.6)	1
Breast fibrosis	12 (33)	9 (24)	0.65 (0.20 – 2.0)	0.45
Breast fibrosis inside tumour bed	17 (49)	17 (46)	0.90 (0.32 – 2.5)	1
Breast edema	4 (11)	3 (8)	0.71 (0.10 – 4.6)	0.71
Breast telangiectasia	3 (8)	1 (3)	0.31 (0.006 – 4.1)	0.36
Pigmentation change	7 (19)	0 (0)	0 (0 – 0.60)	0.005
Breast pain	2 (6)	3 (8)	1.49 (0.16 – 19)	1

B. Photographic assessment at 5 years (N=70)

	Arms down		Arms up	
	Supine N (%)	Prone N (%)	Supine N (%)	Prone N (%)
a) BCCT.core classification				
Excellent	11 (34)	19 (50)	9 (28)	18 (47)
Good	13 (41)	16 (42)	10 (31)	11 (29)
Fair	5 (16)	1 (3)	8 (25)	2 (5)
Poor	3 (9)	2 (5)	5 (16)	7 (18)
b) Deterioration in BCCT.core classification at 5 years, compared to baseline				
None	17 (55)	26 (68)	17 (55)	24 (63)
1 categorie worse	13 (42)	12 (32)	8 (26)	8 (21)
2 categories worse	1 (3)	0 (0)	6 (19)	6 (16)

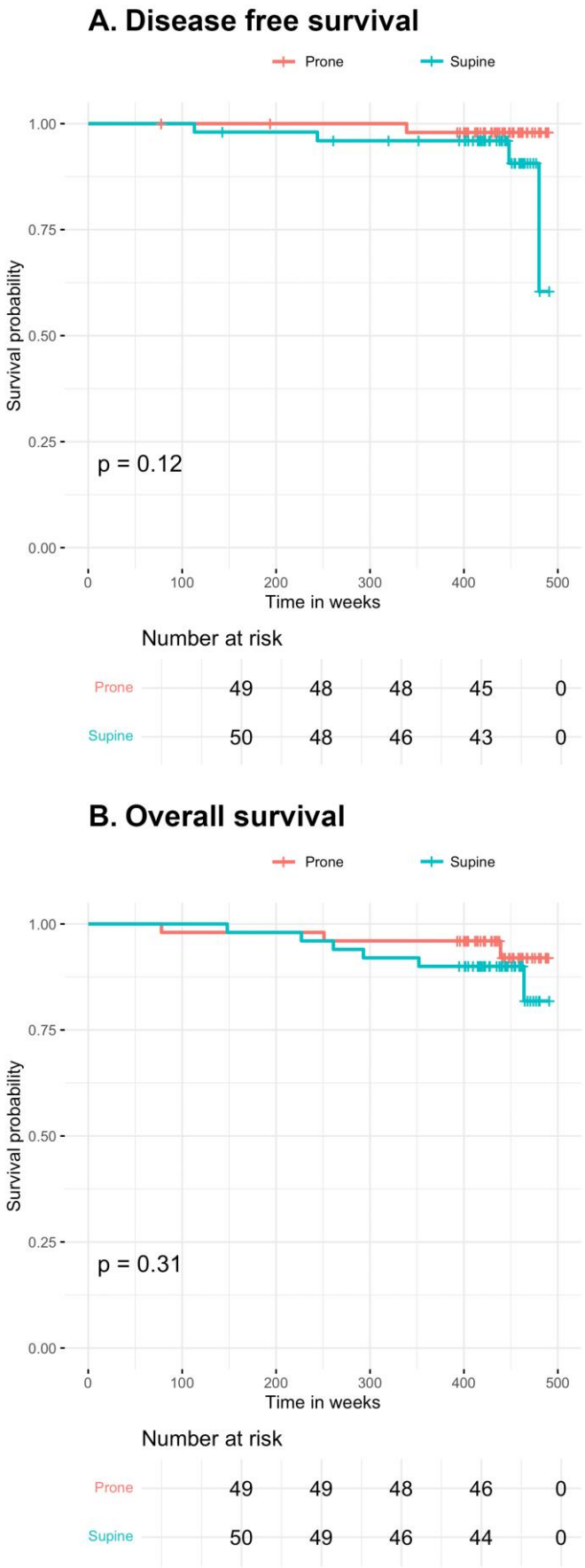

Figure 2: Kaplan-Meier curve for the A) disease free survival and B) overall survival.

Discussion

Currently, prone position is the standard of care at our department, due to lower ipsilateral lung and heart dose, fewer hot-spots, and significantly lower acute and late toxicity.[1–7,13,14] Our study is the only RCT comparing late toxicity and cosmesis between both treatment positions, as the results from the Canadian RCT (NCT01815476) are not yet published.[19] Prone and supine positioning show different levels of breast toxicity at 5 years in general. Prone positioning resulted in a lower risk of pigmentation changes and in lower grade 2 late toxicity throughout the 5-year follow-up. The advantage of prone positioning in the photographic assessment seen after 2 years has decreased after 5 years.[14] Disease free survival and overall survival are similar in both groups.

Other trials have compared prone and supine position target and organs at risk dosimetry, based on computed tomography simulation scans in both positions.[1–7] All studies found prone position was superior for lung sparing, hence reducing the risk of secondary lung cancer.[20] Based on dosimetric comparison, Lymberis et al. chose to treat 94 out of 100 patients in prone position: 100% of right sided and 87% of left sided breast cancer patients.[4] The same research group published on 5-year physician appraised cosmetic results – without photographic assessment – in an additional 314 patients treated in prone position, using the same fractionation schedule in 15 fraction with a marginally higher dose of 40.5Gy compared to 40.05Gy in our study.[15] Similar to our study, they reported a very low rate of grade 2 pigmentation changes of 1% throughout follow-up for prone position. Comparative data with supine position were not available, but we observed in our trial an increased rate of grade 2 pigmentation changes in supine position, reaching a 19% difference at 3 years. There is an important difference in breast retraction between both studies: 5% grade 2 retraction during follow-up versus a maximum of 30% in supine and 16% in prone position in our cohort. However as illustrated by the FAST-FORWARD trial, physicians may underscore the rate of retraction. They observed a physician assessed grade 2 retraction rate of 5%, while 28.5% of patients reported grade 2 retraction.[21] In our study retraction was scored on photographs using dedicated analysis software, which should result in a more consistent scoring compared to other trials. Other possible explanations for the difference may be the fact that we only included large breasted women and that our boost rate was 3 times higher (75% vs 25%).

The publication of the UK HeartSpare Stage Ib study showing a lower mean heart dose, higher comfort and better reproducibility, with supine positioning combined with DIBH compared to prone positioning without DIBH, negatively affected broad implementation of prone

positioning.[10] Difficulties in prone radiotherapy are shoulder positioning, underarm discomfort and shoulder tension.[1,10,22] But prone breast board technology has improved resulting in higher patient comfort and position reproducibility.[23,24] Furthermore, the reduction in lung doses in prone position cannot be ignored.[1,4] Also, prone position and DIBH can be combined.[3,25] The combination leads to the lowest heart and lung doses.[26] Of note is that chest wall and clip motion during treatment are strongly reduced in prone position, as respiration occurs through posterior chest wall excursion instead of ventral chest wall excursion.[3] Finally, prone position allows for good dosimetric results with a simple tangential field technique, without the need for multibeam IMRT treatments.[12] So despite the fact that positioning is more difficult, prone breast radiotherapy remains a performant technique due to the above mentioned benefits.

The main limitation of our study is the limited number of patients due to the phase 2 design of our trial. A larger trial, randomizing 378 patients has recently finished accrual, but it is not clear whether late follow-up will be published.[19] At the moment, our study remains the only trial comparing late toxicity for prone and supine positions.

Funding statement

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Conflict of interest

None of the authors have any disclosures to report.

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D. Result of the randomized PRO-SURF trial for WBI with LNI

Article 5: Prone breast and lymph node irradiation in 5 or 15 fractions: a randomized 2x2 design comparing dosimetry, acute toxicity and set-up errors

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Reference:

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Abstract

OBJECTIVE

Prone whole breast irradiation (WBI) results in lower dose to organs at risk (OARs) compared to supine position, especially lung dose. However, the adoption of prone position for WBI + lymph node irradiation (LNI) remains limited and data on LNI in 5 fractions is lacking. Although the study was ended prematurely for the primary endpoint (breast retraction at 2-years), we decided to report acute toxicity for prone and supine position and, 5 and 15 fractions. Additionally, dosimetry and set-up accuracy between prone and supine position were evaluated.

METHODS

A randomized open-label factorial 2x2 design was used for an acute toxicity comparison, between prone and supine position and, 5 and 15 fractions. The primary endpoint of the trial was breast retraction, 2 years after treatment. In total 57 patients were evaluated. Dosimetry and set-up errors were compared between prone and supine position. All patients were positioned on either our in house developed prone crawl breast couch (PCBC) or a Posirest-2 (Civco, USA).

RESULTS

No difference in acute toxicity between prone and supine position was found, but 5 fractions did result in a lower risk of desquamation (15% vs 41%, $p = 0.04$). Prone positioning resulted in lower mean ipsilateral lung dose (2.89Gy vs 4.89Gy, $p<0.001$), mean thyroid dose (3.42Gy vs 6.61Gy, $p= 0.004$), and mean contralateral breast dose (0.41Gy vs 0.54Gy, $p=0.007$). No significant difference in mean heart dose (0.90Gy vs 1.07Gy, $p=0.22$) was found. Set-up accuracy was similar between both positions.

CONCLUSION

Unfortunately, the primary endpoint of the trial was not met due to premature closure of the trial. Acceleration in 5 fractions resulted in a lower risk of desquamation. Prone positioning did not influence acute toxicity or set-up accuracy, but did result in lower ipsilateral mean lung dose, thyroid dose and contralateral breast dose.

Introduction

Whole breast irradiation (WBI), with or without lymph node irradiation (LNI) results in lower risk of local recurrence and breast cancer mortality, but a higher risk of heart, lung and contralateral breast cancer.[1,2] LNI generally leads to an increase in the mean heart dose (MHD), although the MA.20 trial and EORTC 22922 trial did not show an increase in long-term heart toxicity.[3,4] WBI in prone position after breast conserving surgery (BCS), with our without LNI, can reduce these risks, due to lower ipsilateral mean heart, lung and contralateral breast doses.[5-10] Furthermore, previous studies showed reduced skin toxicity (acute and late) and better cosmesis for prone position.[5-8,11-14] Most prone support devices or treatment tables obstruct the anterior beams for the supraclavicular lymph nodes (LNs), in addition to decreased comfort for the patient and reduced reproducibility compared to the supine treatment position.[15] To eliminate these concerns, the new prone crawl position was introduced and an adapted prone crawl breast-couch (PCBC) developed, allowing anterior beam access.[16] Preliminary dosimetric results are encouraging, showing good breast and nodal coverage, combined with reduced ipsilateral lung, thyroid and contralateral lung doses in prone crawl compared to supine position.[17]

Another recent trend in breast cancer irradiation is accelerating the treatment to 5 fractions. Previous acceleration trials only included small numbers of patients receiving LNI, which were not separately analysed.[18,19] In general, acceleration in 5 fractions leads to lower acute toxicity, and less deterioration of health-related quality of life (HRQoL), without increasing ipsilateral breast tumour recurrence.[18,20-22] Although prone position and acceleration in 5 fractions seem promising, clinical endpoints of both techniques have not yet been sufficiently investigated in patients receiving LNI. Therefore, a 4-arm RCT was initiated using a 2 x 2 full factorial design, comparing prone and supine position, and 5 and 15 fractions in patients referred for WBI + LNI. Since the only RCT comparing prone and supine position for WBI without LNI found a reduction in the rate of breast retraction at 2 years in prone position, breast retraction was chosen as primary endpoint for this trial.[13] The first results of the UK FAST trial showed similar breast retraction rates for WBI in 5-fractions compared to normofractionation in 25 fractions.[22] For the sample size calculation, a superiority design was used for the prone/supine comparison and a non-inferiority design for the 5 fractions/15 fractions comparison. Unfortunately, the study had to be prematurely closed due to regulatory difficulties in expanding the study multi-centric and the COVID-19 pandemic halting further inclusion. This present article describes the acute toxicity, dosimetry and set-up accuracy.

Methodology

The PROne versus SUpine irradiation with Randomized Fractionation schedule (PRO-SURF) study (NCT03280719, registered at www.clinicaltrials.gov) is a 4-arm randomized open-label trial for female breast cancer patients ≥ 18 years, treated with breast conserving surgery (BCS) requiring adjuvant WBI and LNI according to a multidisciplinary decision. The study compares prone and supine position and 5 and 15 fractions, in a 2x2 full factorial design. Exclusion criteria are: mastectomy, bilateral irradiation, distant metastasis, previous irradiation for breast cancer, a life expectancy below 2-years, pre-existing conditions making toxicity evaluation difficult (e.g. skin disorders), pregnancy or breast feeding, and patients unlikely to comply with the protocol. The study protocol was approved by the hospital's ethics board. The primary endpoint of the trial is breast retraction, 2 years after WBI + LNI. Secondary endpoints are acute and late breast toxicity (other than breast retraction), cosmesis, and health related quality of life, locoregional and distant tumour control, dose/volume parameters of target and organs at risk (OARs), and setup accuracy. The PRO-SURF study was powered to find a 15% lower risk of breast retraction at 2-years according to positioning and fractionation. In order to compare prone and supine position 340 patients are required. This was extrapolated from the data of the RCT comparing prone and supine WBI [13], assuming a 50% rate of breast retraction at 2 years in supine treated patients receiving LNI.[23] Independence of the effect of treatment positioning and fractionation was assumed, allowing a second sample size calculation. Based on the FAST trial, similar 2-year breast retraction rates were expected for 5 and 15 fractions.[22] Therefore, a non-inferiority analysis was done, with a 15% increase in breast retraction considered unacceptable, resulting in 350 patients for both arms combined. All analysis were done with an alpha of

0.05 and a power of 0.8. Patients were included in the trial from August 2017 until July 2020. Unfortunately, due to regulatory difficulties in expanding the study multi-centric and the COVID-19 pandemic halting further inclusion, premature termination was decided at an inclusion of 61 patients.

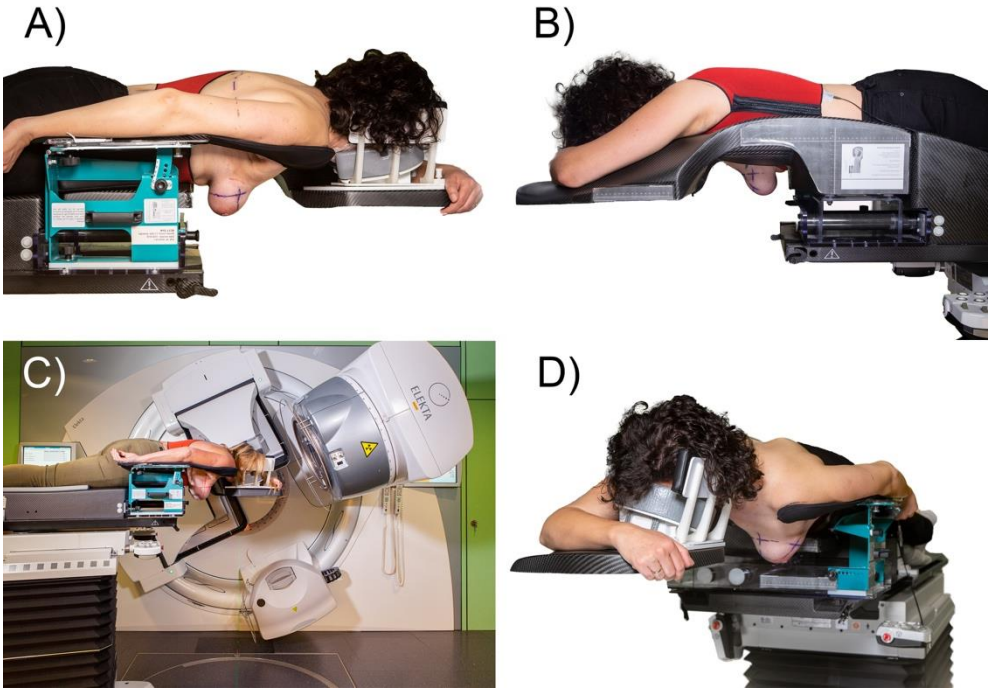

Figure 1: Overview of positioning on in house developed prone crawl breast couch.

POSITIONING DEVICE

As previously described, our PCBC was developed in house.[16,24] As seen in Figure 1, the PCBC supports the arm at the treated side using an adjustable armrest and the contralateral hemi-thorax, contralateral breast and shoulder are positioned on a wedge shaped support. The treated breast and its regional LNs are positioned between the armrest and the wedge. In contrast, most breast boards use a prone position with both hands above the head of the patient and support the ipsilateral shoulder region, preventing the use of cranial beams. The PCBC does allow anterior and cranial beams angles for targeting of the lymph node regions I-IV and internal mammary LNs (Figure 1 c and d).[17,25] Based on the randomization, patients were treated either in prone position on the PCBC, or in supine position using the Posirest-2 (Civco, USA).

RADIOTHERAPY

A computer-generated randomization was used to assign patients in 4 groups: Prone & 15 fractions, Prone & 5 fractions, Supine & 15 fractions, and Supine & 5 fractions. Based on the randomization, WBI was delivered either 5 days a week in 15 fractions of 2.67Gy with a simultaneously integrated boost (SIB) to the tumour bed of 15∗3.12Gy, or in 5 fractions of 5.7Gy over 10 to 12 days, with a SIB of 5*6.2Gy. LNI was delivered either in 15∗2.67Gy or 5∗5.4Gy. All patients underwent computed tomography (CT) imaging with iodine contrast (if no contra-indications and sufficient venous access) for treatment planning. The clinical target volume (CTV) for WBI was delineated as proposed by the ESTRO guidelines, the regional LNs were delineated according to the PROCAB guidelines (which were adapted for prone positioning).[26,27] The Feng

et al. guidelines were used for the delineation of the whole heart and left anterior descending coronary artery (LAD). Apex, left and right lungs, brachial plexus, contralateral breast, thyroid and esophagus were individually delineated by a single researcher (VV). Plan optimization in prone position has been previously described.[17,25] In short, a non-coplanar multiple overlying partial volumetric modulated arc therapy (VMAT) technique was used and optimized using GRATIS (Sherouse-on-Hudson Medical Physics, High Falls, NY) with in-house expansions, as described previously.[28] In supine position, a multi-beam static intensity modulated radiation therapy (IMRT) technique was used and optimized in Raystation 6 (Raysearch laboratories, Stockholm, Sweden).[29]

Final dose calculations were done on a Pinnacle 9.8 treatment planning system (Philips Healthcare, Fitchburg, WI) for prone and supine position. The homogeneity index (HI) of the different target volumes was calculated using the formula: D5/D95. For comparison of the dose to the OARs, the linear quadratic model was used to calculate the equivalent dose in 2Gy fractions (EQD2) using an alpha/beta ratio of 3 using the following formula with D mean total dose and #Fr number of fractions:

$$EQD2 = \mathrm{D} * \left(\frac{\frac{\mathrm{D}}{\#\mathrm{Fr}} + 3}{2 + 3} \right)$$

TOXICITY ASSESSMENT

Physician-assessed acute toxicity was scored at baseline and at 2-4 weeks after the end of treatment, using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 toxicity scoring system. Study data were collected using REDCap electronic data capture tools hosted at Ghent University Hospital.

SET-UP ACCURACY

Daily cone-beam CT was performed, both in prone and supine position and the daily shift required was recorded. The negative of the laterolateral shift was taken for patients in both positions with left-sided breast cancer, to detect systematic errors to the medial or lateral side. This information was used to calculate the overall mean error (M), the standard deviation (SD) of the systematic error (Σ), and the SD of the random error (σ). The van Herk formula was used to calculate the PTV margin: 2.5* Σ + 0.7 * σ.[30] To compare the random errors between both treatment positions, the mean of the individual SD was calculated.

STATISTICAL ANALYSIS

The statistical package R-studio (version 3.6.2.) was used to analyse the data. All data were analysed in a per-protocol-analysis (PPA). Acute radiotherapy-related toxicity was defined as toxicity that deteriorated by one grade or higher, compared to the baseline evaluation. Differences in toxicity between prone and supine positioning, and between 5 and 15 fractions, were analysed by performing a Chi-square test with a significance level of $p < 0.05$. The intention-to-treat analysis, performed for acute toxicity, and did not show different results to the PPA. A dosimetric analysis was done between prone and supine position, HI was compared using the Mann-Whitney U test, dose to OARs was compared using a multivariate linear model (adjusted for fractionation and laterality). For comparison of the set-up accuracy, the overall mean error and the mean of the individual standard deviation (for individual random error), in all three axes, were compared in prone and supine position using a Student-t test.

Results

In total, 61 patients were enrolled and randomly assigned to all four treatment arms. Three patients withdrew informed consent, two patients in Supine & 5 fractions and one patient in Prone & 5 fractions. One patient in Prone & 15 fractions did not receive the allocated treatment by a decision of the treating physician, and was treated in Prone & 5 fractions. In total, 58 patients were included in the dosimetry analysis and 57 patients in the acute toxicity analysis, since one patient did not return for the planned follow-up visit. Median number of days until acute toxicity evaluation were: 16 days for Prone & 15 fractions, 17 days for Supine & 15 fractions, 14 days for Prone and 5 fractions, and 19 days for Supine and 5 fractions. Table 1 shows the baseline characteristics in all four treatment arms. No significant differences in baseline characteristics between all four treatment arms were found.

Table 1: Baseline characteristics.

		Prone & 15 fractions N= 16	Supine & 15 fractions N=14	Prone & 5 fractions N=16	Supine & 5 fractions N=12	p-value
Age –mean (range)		56 (32-72)	52 (36-70)	53 (42-66)	55 (34-70)	0.80[a]
Body mass index – mean (range)		24 (19-36)	27 (21-37)	26 (18-41)	24 (15-32)	0.50[a]
Breast volume (cc) – mean (range)		688 (165-1885)	845 (417-1548)	802 (242-1686)	752 (280-1191)	0.75[a]
Ki67 (%) – mean (range)		19 (1-80)	29 (5-60)	26 (5-90)	41 (1-99)	0.13[a]
Number of positive lymph nodes – mean (range)		2 (0 – 11)	3 (0-7)	2 (0-9)	2 (0-7)	0.79[a]
Lymph node irradiation	Level II-IV	8 (50)	6 (43)	8 (50)	6 (50)	0.98[b]
	Level I-IV	8 (50)	8 (57)	8 (50)	6 (50)	
Boost	No	0 (0)	0 (0)	0 (0)	1 (8)	0.27[b]
	Yes	16 (100)	14 (100)	16 (100)	11 (92)	
Smoking	Current	0 (0)	1 (7)	2 (13)	1 (8)	0.82[b]
	Former	7 (44)	6 (43)	5 (31)	3 (25)	
	Never	9 (56)	7 (50)	9 (56)	8 (67)	
Side	Left	9 (56)	8 (57)	6 (38)	8 (67)	0.51[b]
	Right	7 (44)	6 (43)	10 (63)	4 (33)	
Location	Upper quadrants	12 (75)	12 (86)	10 (63)	6 (50)	0.19[b]
	Central	3 (19)	1(7)	3 (19)	1 (8)	
	Lower quadrants	1 (6)	1 (7)	3 (19)	5 (42)	
Type	Ductal	15 (94)	14 (100)	12 (75)	8 (67)	0.06[b]
	Lobular	1 (6)	0 (0)	4 (25)	3 (25)	
	Other	0 (0)	0 (0)	0 (0)	1 (8)	
Her2Neu	Positive	3 (19)	3 (21)	1 (6)	1 (8)	0.63[b]
	Negative	13 (81)	11 (79)	15 (94)	11 (92)	
Estrogen receptor status	Negative	2 (13)	2 (15)	2 (13)	4 (33)	0.51[b]
	Positive	14 (88)	11 (85)	14 (88)	8 (67)	
Progestron receptor status	Negative	2 (13)	3 (23)	5 (31)	5 (42)	0.34[b]
	Positive	14 (88)	10 (77)	11 (69)	7 (58)	
pT	0 (0)	0 (0)	0 (0)	0 (0)	1 (8)	0.044[b]
	1b	0 (0)	0 (0)	1 (6)	1 (8)	
	1c	4 (25)	3 (21)	11 (69)	4 (33)	
	2	9 (56)	7 (50)	3 (19)	2 (17)	
	y0	2 (13)	1 (7)	1 (6)	2 (17)	
	y1a	1 (6)	0 (0)	0 (0)	0 (0)	
	y1b	0 (0)	1 (7)	0 (0)	2 (17)	
	y1c	0 (0)	1 (7)	0 (0)	0 (0)	
	yIs	0 (0)	1 (7)	0 (0)	0 (0)	
pN	1a	9 (56)	5 (36)	11 (69)	7 (58)	0.19[b]
	1mi	1 (6)	0 (0)	0(0)	0 (0)	
	2a	2 (13)	4 (29)	3 (19)	1 (8)	
	3a	1 (6)	0 (0)	0 (0)	0 (0)	
	X	0	1 (7)	1 (6)	0	
	y0	2 (13)	1 (7)	0 (0)	3 (25)	
	y1a	0 (0)	3 (21)	0 (0)	0 (0)	
	y2a	0 (0)	0 (0)	0 (0)	1 (8)	
	yX	1 (6)	0 (0)	1 (6)	0 (0)	

Axillary surgery	Planned ALND	2 (13)	7 (50)	4 (25)	6 (50)	0.30[b]
	SNB	6 (38)	3 (21)	6 (38)	2 (17)	
	SNB plus ALDN	8 (50)	4 (29)	6 (38)	4 (33)	
Adjuvant Chemo	No	6 (38)	5 (36)	7 (44)	8 (67)	0.40[b]
	Yes	10 (63)	9 (64)	9 (56)	4 (33)	
NACT	No	13 (81)	10 (71)	15 (94)	8 (67)	0.27[b]
	Yes	3 (19)	4 (29)	1 (6)	4 (33)	
Trastuzumab	No	13 (81)	11 (79)	15 (94)	11 (92)	0.63[b]
	Yes	3 (19)	3 (21)	1 (6)	1 (8)	
Cardiovascular disease	No	10 (63)	11 (79)	10 (63)	8 (67)	0.77[b]
	Yes	6 (38)	3 (21)	6 (38)	4 (33)	
Diabetes	No	16 (100)	12 (86)	15 (94)	12 (100)	0.27[b]
	Yes	0 (0)	2 (14)	1 (6)	0 (0)	
Thyroid disease	No	15 (94)	11 (79)	16 (100)	10 (83)	0.21[b]
	Yes	1 (6)	3 (21)	0 (0)	2 (17)	
Rheumatoid arthritis	No	14 (88)	11 (79)	11 (69)	11 (92)	0.40[b]
	Yes	2 (13)	3 (21)	5 (31)	1 (8)	

[a]One-way ANOVA, [b]Fisher's Exact test
ALND axillary lymph node dissection, NACT neo-adjuvant chemotherapySNB sentinel node biopsy

DOSIMETRIC COMPARISON BETWEEN PRONE AND SUPINE POSITION

As seen in Table 2, prone position resulted in better mean ipsilateral lung (2.89Gy vs 4.89Gy, p<0.001), contralateral breast (0.41Gy vs 0.54Gy, p=0.007) and thyroid dose (3.42Gy vs 6.61Gy, p=0.004). MHD was low in both groups, and not significantly different (0.90Gy vs 1.07Gy, p=0.22). The dose homogeneity index (HI) was not statistically different for the PTV of the boost (1.09Gy vs 1.10Gy, p=0.87) and whole breast (1.12Gy vs 1.11Gy, p=0.51). However, dose homogeneity in prone position was lower for the PTV of the treated LNs (1.16Gy vs 1.12Gy, p<0.001). The difference in HI is statistically significant for the lymph node regions II-IV (1.16Gy vs 1.12Gy, p<0.001), but not for the level I axillary nodes (1.14Gy vs 1.13Gy, p=0.49). The accidental level I mean dose when level I was not part of the target volume, is more than halved in prone compared to supine position (18Gy vs 45Gy, p<0.001). Including level I significantly increases the MHD from 0.84Gy to 1.10Gy (p=0.05) and the ipsilateral mean lung dose (MLD) from 3.41Gy to 4.11Gy (p = 0.001). When level I is included in the target volume, the MHD increased from 1.07Gy in prone to 1.13Gy in supine position (p=0.42). Without level I, the MHD increased from 0.70Gy in prone to 1.01Gy in supine position (p= 0.12). MLD increased from 3.26Gy in prone to 5.14Gy in supine (p<0.001) with level I inclusion, and from 2.46Gy in prone to 4.59Gy in supine (p<0.001) without level I inclusion in the target volume.

Table 2: Dosimetric comparison of prone and supine position

A) Organs at risk - EQD2 (Gy)			
Organs	Prone (n = 32) Mean (+/-sd)	Supine (n =26) Mean (+/-sd)	Adjusted P-value*
MHD	0.90 (0.57)	1.07 (0.54)	0.22
LAD	1.74 (1.68)	3.18 (3.77)	0.09
MLD	2.89 (0.83)	4.89 (1.14)	<0.001
Contralateral breast	0.41 (0.20)	0.54 (0.18)	0.007
Thyroid	3.42 (2.84)	6.61 (4.69)	0.004
Esophagus	0.98 (0.59)	0.92 (0.59)	0.49
B) Target volumes - Homogeneity index			
PTV volume	Prone (n = 32) Mean (+/-sd)	Supine (n =26) Mean (+/-sd)	Unadjusted P-value
Boost	1.09 (0.03)	1.10 (0.02)	0.87
Whole breast (excl. Boost)	1.12 (0.06)	1.11 (0.03)	0.51
Lymph nodes	1.16 (0.05)	1.12 (0.08)	<0.001
- Level II-IV	1.16 (0.05)	1.12 (0.06)	<0.001
- Level I Ɨ	1.14 (0.06)	1.13 (0.05)	0.49

ACUTE TOXICITY COMPARISON

Figure 2 shows the differences in acute toxicity based on positioning and fractionation. The percentage of patients with an increase of ≥1 grades of dermatitis from baseline is non-significantly higher in prone compared to supine positioning (80% vs 66%, p = 0.35). Acceleration in 5 fractions results in a significantly lower risk of an increase of ≥1 grades of desquamation from baseline, compared with hypofractionation in 15 fractions (15% vs 41%, p = 0.04).

Three patients experienced grade 3 pain, two in supine (8%) (one in Supine & 5 fractions and one in Supine & 15 fractions) and one patient (3%) in Prone & 15 fractions. Two patients developed grade 3 dermatitis, one in Prone & 15 fractions (3%) and one in Supine & 15 fractions (4%).

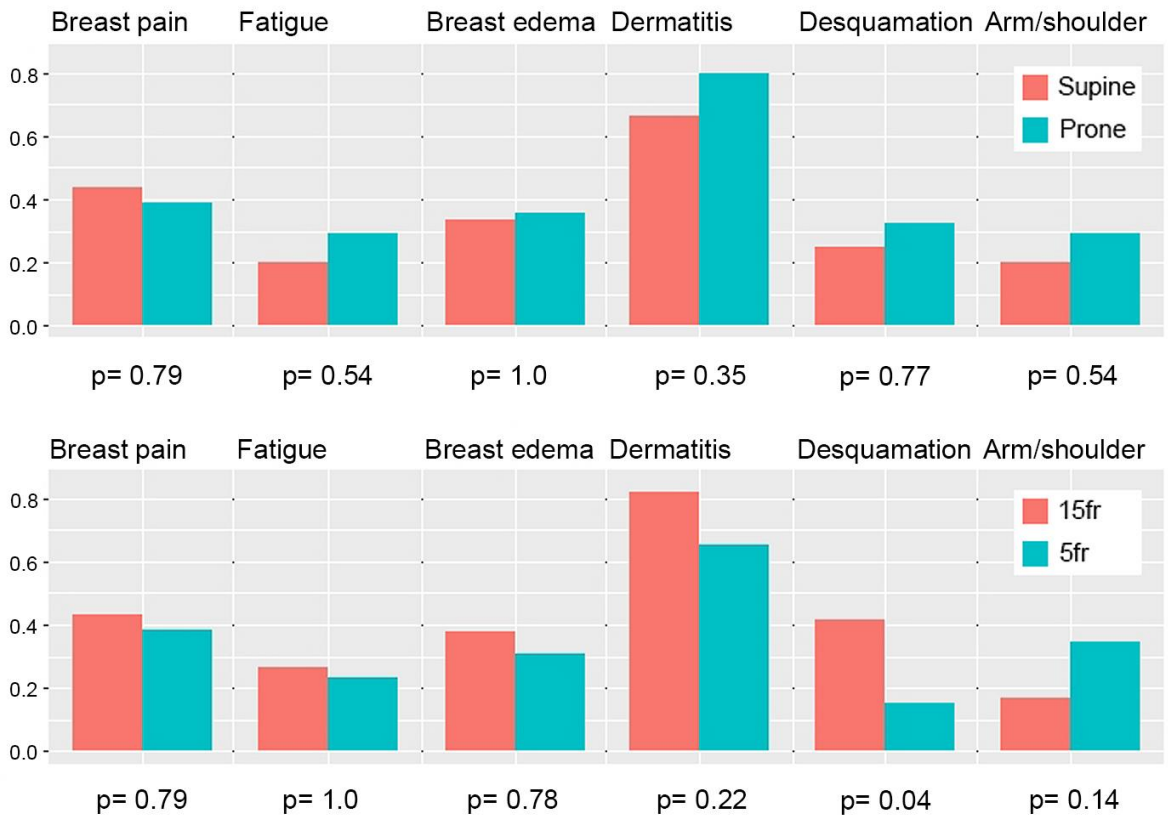

Figure 2: Proportion of patients with a deterioration in acute breast toxcity at 2-4 weeks after radiotherapy, compared with the baseline evalution. A) Shows the comparison between the prone and supine postion, and B) shows the comparison between 5 and 15 fractions.

COMPARISON OF SET-UP ACCURACY BETWEEN PRONE AND SUPINE POSITION

Table 3 shows the overall mean error (M), mean of the individual SD, SD of the systematic error (Σ), and SD of the random error (σ) for prone and supine position. The difference in the mean shift in the cranio-caudal direction is significant (-0.8mm for prone and 2.5mm for supine position, $p<0.001$). The mean individual SD in the latero-lateral direction is also significantly different (4.9mm for prone and 2.5mm for supine position, $p<0.001$). Using the van Herk formula, the latero-lateral margins are higher in prone position (14.3mm vs 9.1mm for supine position) and the cranio-caudal margins are higher in supine position (8.9mm for prone vs 12.0 for supine position).

Table 3: Set-accuracy comparison between prone and supine position. The van Herk formula requirements (in mm), the mean of the individual standard deviation of shifts, and calculated PTV margins according to prone or supine positioning.

	AP			LL			CC		
	Prone (n =32)	Supine (n =26)	p	Prone (n =32)	Supine (n =26)	p	Prone (n =32)	Supine (n =26)	p
Overall mean error (M)	-2.2	-2.7	0.51	0.4	1.7	0.19	-0.8	2.5	<0.001
Mean individual SD	3.4	2.7	0.07	4.9	2.5	<0.001	3.4	3.2	0.98
SD of the systematic error (Σ)	2.6	3.5		4.1	2.9		2.4	3.8	
SD of the random error (σ)	3.8	2.9		5.9	2.7		3.9	3.4	
Required margins	9.2	10.1		14.3	9.1		8.9	12.0	

AP antero-posterior; CC cranio-caudal; LL latero-lateral; SD standard deviation

Discussion

Unfortunately, the PRO-SURF trial was prematurely ended due to difficulties expanding the trial multicentric and the COVID-19 pandemic. Therefore, the trial is underpowered for the primary endpoint of detecting breast retraction at 2-years. However, the trial remains the first RCT for WBI with LNI, randomizing for treatment position and fractionation. Other RCTs did not include patients with LNI.[21,31,32]

Beginning with dosimetry, our trial shows a lower lung dose for prone positioning compared to supine positioning. Taylor et al. has found a 0.11 excess relative risk for the development of lung cancer per Gy mean lung dose (MLD).[10] Even though there is a continued emphasis on cardiac mortality after breast cancer radiotherapy, an analysis of the SEER database has found increased radiation related mortality for lung cancer, but not for heart disease, in patients treated between 1983 and 1992.[33] This is especially the case for patients with a high baseline risk of lung cancer, like smokers.[34] Our results are in line with our own data and other research groups, showing lung dose reductions in prone position for WBI with and without LNI.[5,7,9,12,17,25,35] A systematic review of the lung doses published between 2010 and 2015 showed an average ipsilateral MLD of 11.7Gy for WBI (or chest wall) with LNI using IMRT in supine position, which is higher than our 4.9Gy ipsilateral MLD in supine position.[36] The 2.89Gy ipsilateral MLD in prone position with LNI is similar to the previously published ipsilateral MLD of 2.5Gy in prone position without the inclusion of LNI.[36] Contralateral breast and thyroid doses are also significantly lower in prone position. The reduction in contra-lateral breast dose could be caused by the tilt of the patient on the PCBC (Figure 3). At last, MHD is low in both positions and not significantly

different. When only MHD is considered, Bartlett et al. found voluntary deep inspiration breath-hold (DIBH) to be superior over prone free breathing for WBI without LNI.[37] A recent analysis compared WBI without LNI in prone free breathing with supine DIBH and found a dosimetric gain, in 62% of patients for prone position, balancing both MHD and MLD-differences. The advantage was more commonly found in patients with high pendulousness and a moderately large breast.[38] These results also confirm our dosimetry data collected before the start of the PRO-SURF study.[17]

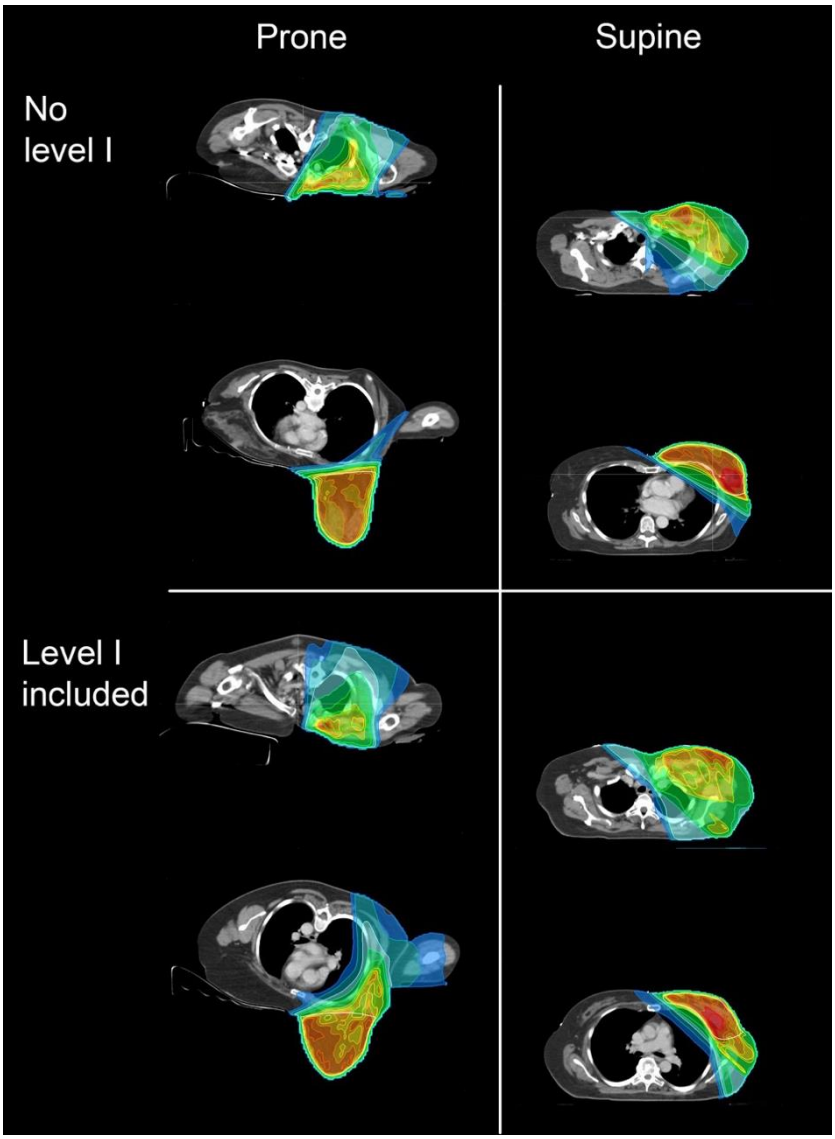

Figure 3: Transverse dose distributions in prone and supine position, with and without the inclusion of level I in the target volume.

Around half the patients in the trial required level I lymph node irradiation (52%), for the other half of the patients (48%) the dose to level I was accidental. In prone position, the mean D50 to level I decreased significantly from 46Gy to 18Gy when level I was not included in the PTV, as described before (Figure 3).[39] Several studies have found a protective effect of WBI on the risk of axillary

recurrence after sentinel node biopsy, although the accidental level I dose is generally considered inadequate for microscopic disease control.[40,41] Therefore, it has become common practice to exclude level I from the RT target volumes after a representative axillary dissection to reduce the risk of arm lymph edema. It is unknown whether the accidental dose to level I contributes in the reduction of local or distant recurrence after axillary dissection.

In a previous RCT comparing prone and supine WBI without LNI in 100 patients with large breasts, lower acute and late toxicity was observed in prone compared to supine position.[12-14] The current PRO-SURF trial, including patients requiring LNI, does not show any difference in physician assessed acute toxicity. Due to the premature closure, the trial was not powered to detect a difference. The HI for WBI in prone and supine position (1.12Gy vs 1.11Gy, p=0.51) is similar to the publication of Barlett et al. (1.09Gy vs 1.10Gy, p=0.87) and Varga et al. (1.14Gy vs 1.10Gy).[37,42] One potential reason for worse HI for LNI, is the use of a cranio-caudal beam for LNI in prone position (Figure 1c), resulting in a long path-length. Previous research has shown this beam arrangement is ideal for internal mammary node irradiation, but might be unnecessary when this target volume is not included.[25]

With regards to fractionation, physician assessed acute toxicity was reduced in the group receiving accelerated radiotherapy in 5 fractions, compared to the group with hypofractionation in 15 fractions (Figure 2b), in line with previous trials.[18,21,22] The difference was only significant for desquamation, probably because the study was underpowered. Compared to other trials we report higher dermatitis in all arms, due to the inclusion of grade I dermatitis in the results. Also, only physician assessed toxicity was reported in this trial, no HRQoL results are available. WBI with LNI in 5 fractions is feasible and safe with regards to acute toxicity. The results of the FAST-FORWARD trial, excluding the patients with LNI in the analysis, are reassuring with regard to late toxicity, ipsilateral breast relapse (showing non-inferiority) and disease free survival at 5-years.[32] However, this trial only allowed a sequential boost and used a daily fractionation scheme with a lower dose per fraction (5.2Gy per fraction). All patients in our study received a SIB, which has been shown to result in lower acute toxicity and equal 2-year toxicity.[43-45] Further research is required to determine the influence of 5 fractions combined with a SIB on late toxicity, including the risk of lymphedema, and the risk of recurrence after WBI with LNI.

All prone patients were positioned on our in house developed PCBC. The main advantage of the PCBC for LNI, is higher comfort compared to other positioning devices and better access to the supraclavicular LNs without any obstruction, due to positioning of the arm beside the patient and supporting the tip of the shoulder.[16,46] Previous studies comparing prone and supine

positioning have found lower set-up accuracy in prone position.[37,47] The SuPr trial found margins of between 12 and 16mm for prone and 10mm for supine position.[47] They found the greatest uncertainty in prone position in the antero-posterior (AP) direction (for clip based matching), and larger margins for prone in all directions compared to supine position. The UK HeartSpare study Stage IB also found larger margins in all directions for prone positioning.[37] In contrast, our study found smaller margins for prone positioning in the AP direction and cranio-caudal direction, but larger margins in the latero-lateral direction compared to supine positioning. Potential reasons for the differences with previous studies are the improvements in set-up precision using our new PCBC, compared with older positioning devices, and the high level of experience with prone radiotherapy in our department. Recently, neighboring radiotherapy centres successfully implemented prone-crawl positioning on our PCBC for breast only radiotherapy. Radiotherapy departments adopting PCBC should determine the local set-up precision and adapt their margins accordingly.

In conclusion, WBI and LNI is feasible in prone crawl position. Prone position results in a lower MLD, thyroid and contralateral breast dose, a similar MHD and a comparable set-up precision compared to supine position. Dose coverage of all LN levels is good in both positions, although the study confirms the lower accidental level I dose in prone position. Significantly reduced acute desquamation is observed in 5 fractions.

Conflict of interest

Wilfried De Neve, Bruno Speleers and Liv Veldeman are co-inventors of the Prone Crawl Breast Couch of which Ghent University owns the patent entitled *Radiotherapy Board and Couch*.

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Chapter VI: Preoperative radiotherapy

A. Introduction

Neo-adjuvant radiotherapy (NART), meaning radiotherapy before surgery, was commonplace before the emergence of neoadjuvant chemotherapy (NACT) as a means to downstage the tumour in inoperable breast cancer.(151) Table 3 shows an overview of studies describing the use of NART for the treatment of breast cancer. The inclusion of patients in NART trials started around 1970, with many trials publishing results around 1990. In these trials NART was often followed by mastectomy, although many authors already mentioned the potential to improve the rate of BCS. Pierquin et al. started treating patients from 1961 with NART followed by BCS. The study resulted in an increase in the indications for BCS in Paris.(152) The combination of NART and NACT was also investigated, resulting in the publication of several papers.(153,154) Lately, the interest in NART is returning, due to the improvements in radiotherapy techniques, hypofractionation and the potential immunostimulatory effect.

The FAST-FORWARD trial shows that the survival after accelerated hypofractionation in five fractions is non-inferior (and potentially even superior) to hypofractionated radiotherapy in five fractions. This allows the delivery of radiotherapy within one week, compared to the historical five weeks.(31) The RCT of Recht et al. determined an increase in the risk of distant metastasis by delaying chemotherapy by at least five weeks to deliver the radiotherapy first.(155) However, given the current accelerated hypofractionation treatments in five fractions, the delay in chemotherapy due to radiotherapy should be minimal. Besides the RCT of Recht et al., data on the optimal treatment sequence is limited. Population based trials did, however, link a shorter overall treatment time (OTT) to better survival outcomes.(156–159) The POP-ART trial was an effort to revive the use of NART in the era of accelerated hypofractionation, and to shorten the OTT by eliminating the delay for wound healing between surgery and adjuvant radiotherapy. The primary outcome was a reduction in OTT, and secondary outcomes were safety and feasibility.

Table 3: Non-systematic literature overview of publications describing the use of neo-adjuvant radiotherapy, with or without the use of (concomitant) chemotherapy

Study Sort	Reference	FU	Patient count	Period of inclusion	NARCT	Control	Random	Dose in Gy	Daily Dose in Gy	Boost (SIB/SEB)
1. Cohort Study	Pierquin , 1990	15 years	245	1961-1974	No	No	No	45	1.80	Brachy SEB
1. Cohort Study	Jacquillat, 1990	5 years	252	1980-1986	Yes, VTMF	No	No	23 or 45	5.75 or 1.80	
1. Cohort Study	Touboul , 1992	5 years	82	1982-1987	No, sandwich	No	No	45	1.96	Brachy and SEB
1. Cohort Study	Touboul , 1996	7 years	97	1982-1990	No, sandwich	No	No	45	1.96	Brachy and SEB
1. Cohort Study	Boelke , 2013	>15 years	315	1991-1998	Yes, EC/AC/Mitoxantrone	No	No	50	2.00	Brachy
1. Cohort Study	Formenti , 1997	early	35	1993-1996	Yes, 5-FU	No	No	50	2.00	
1. Cohort Study	Colleoni , 1998	early	32	Before 1998	No	No, Escalation to CT responder	No	50 + 10	2.01	SEB
1. Cohort Study	Ayrus , 2000	early	73	NA	Yes, EC	Yes, NART lower pCR than NACT alone	No	50	2.02	SEB
1. Cohort Study	Adams , 2010	5 years	105	1997-2009	Yes, paclitaxel	No	No	50	2.03	SEB
1. Cohort Study	Formenti , 2010	5 years	105	1997-2009	Yes, paclitaxel	No	No	45	1.80	SEB
1. Cohort Study	Skinner , 1997	2 years	36	1997	Yes, 5-FU	No	No	?	?	No
1. Cohort Study	Skinner , 1999	early	29	1999	Yes, taxol	No	No	45	1.80	No
1. Cohort Study	Alvarado , 2009	5 years	112	2000-2003	Yes, FAC of AC + RTCT	No	No	50	2.00	SEB
1. Cohort Study	Chakravarthy , 2006	2 years	38	2000-2004	Yes, taxol	No	No	46.8	1.66	No
1. Cohort Study	Baltodano , 2017	early	77902	2005-2011	NA	No	No	NA	NA	NA
1. Cohort Study	Palta , 2010	early	17	2007-2009	No	PBI Planning-study	No	15	15.00	PBI
1. Cohort Study	Nardone , 2014	3 years	21	2009-2011	Yes, Anthracycline/Taxol	No	No	9.6 => 50,4	0.40 => 2.00	No
1. Cohort Study	Zinzindohoué , 2016	6 months	94	2010-2012	No	No	No	?	?	
1. Cohort Study	Thiruchelvam , 2017	12 wks to 1.5 yrs	19	Before 2016	No	No	No	?	?	NA
2. Matched Case	Brackstone , 2017	5 years	32	2009-2011	Yes, EC + Taxol	Yes, NART/CT vs NACT, betere pCR	No	45	1.80	SEB
3. Clinical Trial	Daveau , 2011	10 years	100 vs. 65	1985-1999	No	Yes, Surgery vs No Surgery	No	45	1.82	No
3. Clinical Trial	Kao , 2005	early	33	1995-2003	Yes, RT + taxol	No	No	60 - 70	2.00	No
3. Clinical Trial	Formenti , 2003	early	44	1997-2000	Yes, paclitaxel	No	No	45	1.80	SEB
3. Clinical Trial	Bollet , 2006	early	59	2001-2003	Yes, 5FU + vinorelbine	No	No	50	2.00	SEB
3. Clinical Trial	Bollet , 2012	7 years	51	2001-2003	Yes, 5FU + vinorelbine	No	No	50	2.00	SEB
3. Clinical Trial	Ishitobi , 2014	early	29	2009-2011	No, however Ais	No	No	50	2.00	?
4. RCT	Wallgren , 1978	5 years	960	1971-1976	No	Yes, NART vs post-op RT vs no RT	Yes	45	1.80	No
4. RCT	Wallgren, 1986	10 years	960	1971-1976	No	Yes, NART vs post-op RT vs no RT	Yes	45	1.81	No
4. RCT	Semiglazov , 1994	5 years	271	1985-1990	Yes, TMF	Yes, NARCT vs NART	Yes	60	2.00	No

CT chemotherapy, EC Epirubicine/Cyclofosfamide, FAC Fluorouracil/Adriamycin/Cytoxan, FU follow-up, NA not applicable, NACT neo-adjuvant chemotherapy, NART neo-adjuvant radiotherapy, PBI partial breast irradiation, pCR pathologic complete response, RCT randomized controlled trial, RT radiotherapy, SEB sequential boost, TMF Thiotepa/Methotrexate/5-fluorouracil, VTMF vinblastine/thiotepa/methotrexate/5-fluorouracil

B. Potential survival benefit

Surgery results in a reduction in the blood flow around the tumour due to tissue damage. The resulting hypoxic state could increase the resistance of tumour cells to radiotherapy, leading to a diminished response to an equal dose post-operatively compared to pre-operatively.(160) For rectal cancer, another type of adenocarcinoma, the advantage of pre-operative radiotherapy was established in a RCT published in 1993.(161) Fryckholm et al. randomized patients to five fractions of NART (25.5Gy in one week) or prolonged post-operative radiotherapy (60Gy in seven or eight weeks) and found a lower local recurrence rate for short course NART (13% vs 22% at five years). Later, the German Rectal Cancer Study Group compared preoperative versus postoperative chemoradiotherapy for high-risk disease.(162) Although the postoperative chemoradiotherapy group received an additional boost of 5.4Gy (1.8Gy/fraction), the risk of local relapse was halved in the group receiving pre-operative chemoradiotherapy (6% vs 13% at five years). Finally, the OPRA trial for rectal cancer could provide insight in the optimal sequencing of radiotherapy and chemotherapy.(163) Induction radiotherapy followed by consolidation chemotherapy showed a higher rate of rectum sparing compared to induction chemotherapy followed by radiotherapy.

Besides cancer of the rectum, other tumours are also managed with NART. The use of NART is common for esophageal cancer. A recent analysis of the SEER database showed superior survival outcomes for neo-adjuvant chemoradiotherapy compared to adjuvant chemoradiotherapy.(164) Furthermore, a recent meta-analysis confirmed the superiority of neo-adjuvant treatment compared to adjuvant treatment in a direct comparison for the treatment of esophageal cancer.(165) The only RCT for soft tissue sarcomas that compared NART to adjuvant RT reported a slightly better overall survival for NART, at the cost of more wound complications post-surgery.(166) Finally, neo-adjuvant chemoradiotherapy has shown promising survival results in pancreatic cancer and is currently under investigation.(167–169) Overall, NART has shown promising results in different tumour types and further investigation is warranted if the advantage of NART is present in the treatment of breast cancer.

C. Aesthetic outcomes

The delivery of NART has been investigated in the realm of breast reconstruction and oncoplastic surgery in order to improve the aesthetic outcomes. Three main reasons are mentioned in literature. After a mastectomy and adjuvant radiotherapy, a waiting time is recommended before breast reconstruction to reduce the risk of complications and improved aesthetic outcomes.

NART facilitates the immediate reconstruction in patients undergoing a mastectomy, and probably contributing to a better cosmetic result by avoiding flap irradiation and the associated risk of fibrosis and flap contraction.(170) Notable are the results of the PRADA trial, a prospective, multicentre, non-randomized, feasibility study that investigated NART after NACT but before epigastric perforator flap reconstruction.(171) PRADA confirmed the hypothesis that NART followed by reconstruction was feasible and technically safe. Secondly, induction radiotherapy for locally advanced breast cancer should allow better downstaging and hence a higher rate of skin-sparing mastectomy. A higher rate of breast conserving surgery has been found after NACT, as should be the case after NART.(172) Thirdly, the tumour can be more precisely targeted since it is still visible at the time of radiotherapy (simulation), especially the boost volume that is often enlarged by the presence of seroma.(160,170) Therefore, there is less uncertainty at the moment of contouring, smaller margins can be applied around the GTV for the CTV expansion and the online imaging can visualize the tumour, resulting in better positioning of the patient. The risk of geographic loss, especially regarding the use of oncoplastic surgical techniques with the according tissue rearrangement, should be lower in the NART setting. Finally, the breast volume irradiated to the highest boost dose, that has the highest risk of fibrosis, is removed during surgery. These factors predict better aesthetic outcomes after surgery and have resulted in a large number of trials investigating NART.

D. Preoperative accelerated radiotherapy

Article 6: Safety of pre- or postoperative accelerated radiotherapy in 5 fractions: a randomized pilot trial

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Abstract

OBJECTIVE

Neo-adjuvant radiotherapy (NART) for breast cancer has shown promising survival results in retrospective trials. However, there are some obstacles such as a chemotherapy delay, an increased overall treatment time (OTT) and the risk of increasing surgical morbidity. Accelerated radiotherapy (RT) in 5 fractions allows to deliver NART in a very short time span and minimizes the delay of surgery and chemotherapy. This trial investigates this NART schedule for safety, feasibility and OTT.

MATERIAL AND METHODS

Twenty patients eligible for neo-adjuvant chemotherapy (NACT) and breast conserving surgery, were randomized between NART before NACT or NACT and postoperative RT. In both arms, RT treatment was given in 5 fractions to the whole breast with a simultaneously integrated boost (SIB) on the tumour(bed). Lymph node irradiation was given concomitantly in case of lymph node involvement. OTT was defined as the time from diagnosis to last surgery in the intervention group, while in the control group the time between diagnosis and last RT-fraction was used. In the intervention group NACT-delay was defined as time between diagnosis and start of chemotherapy.

RESULT

20 patients were included, and 19 patients completed treatment. OTT was significantly shorter in the intervention group (mean 218 days, range 196-253) compared to the control group (mean 237, range 211-268, $p = 0.001$). The difference in mean duration from diagnosis to the first treatment was a non-significant 4 days longer (31 vs 27 days, $p = 0.28$), but the start of NACT after diagnosis was delayed by 21 days (48 vs 27 days, $p < 0.001$). NART did not result in additional surgery complications.

CONCLUSION

This pilot trial is the first to report on accelerated NART in 5 fractions with SIB. NART before NACT resulted in a shorter OTT with good safety results.

Introduction

Neo-adjuvant chemotherapy (NACT) has recently become the standard of care for selected high-risk early breast cancer patients, not only for tumour downstaging, but also for response monitoring.[1] In case of residual disease after NACT, better oncological outcomes are observed with treatment escalation, in Her2-positive and triple negative breast cancer (TNBC).[2,3] NACT also leads to a higher rate of breast conserving surgery (BCS), but at the risk of higher local recurrence in older studies (inclusion from 1983 to 2002).[4] Historically, the role of tumour downstaging to increase the rate of BCS was reserved for neo-adjuvant radiotherapy (NART), showing satisfactory cosmetic results and low complication rates.[5-9] In contrast, potential disadvantages of NART are a delay of NACT, an increase in the overall treatment time (OTT), and a higher risk of surgical morbidity. Recent advances in breast cancer radiotherapy (RT) could provide a solution. Accelerated RT in 5 fractions did not increase the risk of local relapse at 10 and 5-years in the recently published FAST and FAST-FORWARD trials, respectively.[10,11] Moreover, acceleration in 5 fractions resulted in lower acute toxicity with similar late toxicity, better health related quality of life (HRQoL), and OTT.[10,12-14] The European Society of Medical Oncology (ESMO) guidelines recommend a radiotherapy boost to the tumourbed in patients with a high risk of recurrence [1], as is often the case in patients receiving NACT. In the FAST-FORWARD trial, the boost was given in additional fractions after whole breast radiotherapy, adding at least one week to the treatment.[10] A further decrease in OTT can be achieved by a simultaneously integrated boost (SIB) to the tumour(bed) in the treatment without decreasing cosmesis or increasing acute and late toxicity.[15-17] Using NART in 5 fractions with SIB should result in even a shorter OTT, since the waiting time between surgery and RT is omitted. Treatment delays, not only between symptoms and diagnosis, but also between diagnosis and surgery or start of NACT, have been associated with worse survival for aggressive tumours like TNBC, although the causality remains questionable.[18-27] Consequently, changing treatment sequences should not result in a delay between diagnosis and the surgery or the first treatment. To confirm the theoretically shorter OTT and acceptable toxicity after NART, the pre- or post-operative accelerated radiotherapy (POP-ART) randomized pilot trial was undertaken. To our knowledge, this is the first study investigating radiotherapy in 5 fractions in the neo-adjuvant setting. This report details the differences in treatment durations between both groups, in addition to differences in surgery complications, mastectomy rate, radiotherapy toxicity and response rate.

Materials and methods

PATIENTS

The full protocol of the POP-ART trial has previously been published.[28] Twenty female breast cancer patients (≥18 years of age) eligible for NACT according to multidisciplinary decision, were randomized between NART followed by NACT and surgery (intervention group) or NACT followed by surgery and postoperative RT (control group). All patients were treated at Ghent University Hospital. Potential reasons for proposing NACT to patients included triple negative or Her2-positive biology or downsizing of large tumours. A written informed consent was obtained from all patients before enrollment in the trial. Exclusion criteria were distant metastasis, inflammatory breast cancer, multifocal tumour lesions, lobular carcinoma, a history of breast cancer, chemotherapy, RT, or reconstructive breast surgery, planned mastectomy and patients unfit for NACT treatment.

TRIAL DESIGN

The trial was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The protocol was approved by the local ethics commission and registered at clinicaltrials.gov (NCT03783364). Figure 1 shows an overview of the treatment sequence in both arms with the predicted duration for each part. In the intervention arm the port-a-cath placement was completed within 7 days after the ending of NART, followed by NACT shortly afterwards. According to the protocol, the time was equal for NACT and recovery between both treatment arms.

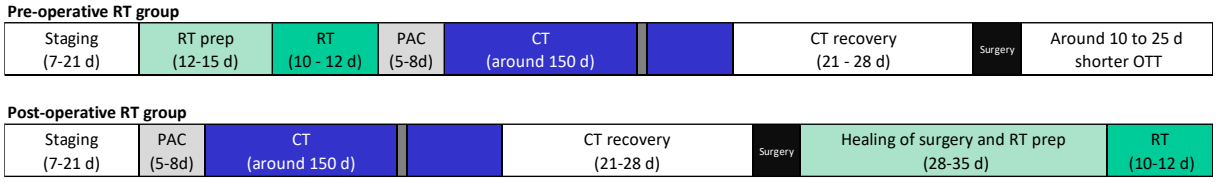

Figure 1: Schematic overview of the time schedule in both treatment arms.
CT: chemotherapy; RT: radiotherapy; PAC: port-a-cath; RT prep: radiotherapy preparation; OTT: overall treatment time.

TREATMENT PROCEDURES

All patients received extensive imaging before any treatment including ultrasound-guided tissue biopsy and marking of the tumour using a clip, magnetic resonance imaging (MRI) of the breast, and either fine needle aspiration cytology (FNAC) in case of a suspicious lymph node or sentinel node biopsy (SNB) if no lymph node involvement was seen during imaging.

The chemotherapy and surgical protocols were the same in both treatment arms. NACT consisted of 4 cycles of epirubicin (90 mg/m^2) and cyclophosphamide (600 mg/m^2) every 2 or 3 weeks,

followed by 12 weekly cycles of paclitaxel with or without carboplatinum. In case of Her2 amplified tumours, lymph node negative patients received trastuzumab every 3 weeks, concomitantly with paclitaxel, whereas lymph node positive patients received treatment with a combination of trastuzumab and pertuzumab. Chemotherapy adaptation based on treatment toxicity or tumour response was allowed, to allow best current practice.

RT was given in 5 fractions up to a total dose of 28.5Gy (5.7Gy per fraction) to the whole affected breast with a SIB up to 31 Gy (6.2Gy per fraction) on the tumour(bed). In case of pathologically confirmed lymph node involvement (either on SNB or FNAC), the level I-IV axillary lymph nodes were irradiated to 27 Gy (5.4 Gy per fraction). RT was delivered over 10-12 days with at least one day interval between fractions. In the intervention arm the SIB was delineated using the gross tumour volume (GTV) based on MRI and expanded by a 5mm clinical target volume (CTV) margin and a 5mm planning target volume (PTV) margin. Around this PTV, a dose fall-off region of 1.5 cm was created receiving a minimum dose of 27.08 Gy with 95% receiving at least 27.9 Gy. In the control arm, the SIB was delineated using a CTV based on the surgical clips, histology report and all available pre-operative information. A dose fall-off region of 2 cm around this CTV was defined, receiving a minimum dose of 27.08 Gy with 95% receiving at least 27.9 Gy. The axillary lymph node regions were delineated using the PROCAB guidelines.[29] Level I was included at the discretion of the treating physician. Breast-only RT was delivered in prone position, breast + nodal RT was delivered in supine position.

BCS was always attempted, unless genetic testing during treatment demonstrated a high genomic risk for breast cancer. In this case, bilateral mastectomy was performed. In case of pathologically confirmed lymph node involvement (either on FNAC or SNB), an axillary dissection was performed.

ENDPOINTS

The primary endpoints of the trial are: 1) safety, 2) feasibility, and 3) overall treatment time (OTT). Secondary endpoints include tumour response, therapy compliance, and treatment complications.

OTT was measured from the first pathologic confirmation of the diagnosis until the last day of RT in the control arm, or the day of the last surgery in the intervention arm. Tumour response to neo-adjuvant treatment was evaluated using the pathological complete response (pCR) rate. The rate of patients finishing all 4 EC cycles and 12 paclitaxel cycles was measured. Patients were followed until 6 months after surgery (intervention arm) or RT (control arm) to determine any treatment complications or any additional surgeries including mastectomy. Acute RT toxicity was

determined two to four weeks after the last fraction, using standardized questionnaires previously published.[12]

STATISTICAL ANALYSIS

All analyses were done on an intention-to-treat (ITT) basis. The study was powered to detect a 14-day difference in OTT between both groups, with 80% percent power at an alpha level of 0.05 using a two-sided Student's t-test. The proportion of patients requiring mastectomy, with surgical complications or achieving a pCR was compared using a 2-sided Fisher's Exact test (to account for small numbers).

Results

Of the 20 patients randomized, 19 patients were analyzed in the OTT analysis. One patient (without lymph node involvement) in the control group was excluded from analysis since she did not receive RT due to progression during NACT (a "rescue" mastectomy was performed). Table 1 shows the baseline characteristics in both groups. One patient randomized to NART crossed over to the NACT arm due to uncertainty about lymph node involvement during staging.

Table 1: Baseline Characteristics

	Intervention group	Control group	p-value
	N=10	N=9	
Age - mean (range) – yr	55 (31 – 67)	54 (41 – 64)	0.89
BMI - mean (range)	26,1 (19,3 – 37,0)	25,6 (22,8 – 33,9)	0.82
Laterality			
Left	3 (30%)	3 (33%)	0.88
Right	7 (70%)	6 (67%)	
cTNM classification			
T1cN0	2 (20%)	0 (0%)	0.41
T1cN1	1 (10%)	1 (11%)	
T2N0	5 (50%)	5 (56%)	
T2N1	1 (10%)	3 (33%)	
T3N1	1 (10%)	0 (0%)	
Tumour diameter on pre-treatment MRI – mean (range) - mm	3,4 (1,9 – 5,7)	3,4 (1,4 – 6,5)	0.97
Lymph node irradiation			
Yes	4 (40%)	5 (56%)	0.82
No	6 (60%)	4 (44%)	
Clinicopathological subtype			
Luminal A	1 (10%)	0 (0%)	0.82
Luminal B	2 (20%)	2 (22%)	
Her2+	3 (30%)	3 (33%)	
Basal like	5 (50%)	4 (44%)	

Table 2 gives an overview of the duration in days from diagnostic biopsy to the start of the first treatment, start of NACT, surgery and the end of treatment. OTT was significantly shorter in the intervention group (mean 218 days, range 196 – 253) compared to the control group (mean 232, range 211 – 268, p=0.03). The difference in mean duration from diagnosis to the first treatment was a non-significant 4 days longer (31 vs 27 days, p=0.28) in the intervention group. The start of NACT after diagnosis was delayed by on average 21 days in the intervention arm (48 vs 27 days, p<0.001).

Table 2 Treatment durations according to the number of days from diagnostic biopsy for each individual patient

Patient number	First treatment	Start NACT	Surgery	Last treatment
Intervention group (n=10)				
2†	22†	22†	175†	220†
4	34	49	222	222
6	27	43	223	223
8	27	48	204	204
10	33	50	208	208
12	45	62	214	228*
15	24	56	200	200
17	32	50	229	229
19	29	49	198	253*
20	31	48	196	196
Mean (sd)	31 (6)	48 (10)	207 (16)	218 (12)
Control group (N=9)				
1	37	37	197	239
5	29	29	189	234
7	25	25	200	252
9	27	27	188	233
11	41	41	218	268
13	21	21	166	211
14	22	22	177	241
16	18	18	172	217
18	21	21	174	241
Mean (sd)	27 (8)	27 (8)	187 (16)	237 (17)

† Patient did not receive NART but adjuvant radiotherapy
** Patient received additional surgery*
NACT: neo-adjuvant chemotherapy; NART: neo-adjuvant radiotherapy

An overview of pCR, chemotherapy, surgery and RT details is found in table 3. The proportion of patients with a pCR was similar between both groups (6/10 vs 6/9, p=1.0). NART did not result in a lower percentage of patients finishing the complete NACT treatment (7/10 vs 4/9, p=0.37). All patients had good wound healing

Table 3: Neo-adjuvant treatment response rate, surgery and radiotherapy details

	Intervention group	Control group	P-value
Pathological complete response	N=10	N=9	
Yes	6 (60%)	6 (67%)	1.0
No	4 (40%)	3 (33%)	
Chemotherapy			
Finished all EC and Taxol treatments			
Yes	7 (70%)	4 (44%)	0.37
No	3 (30%)	5 (56%)	
Surgery			
Mastectomy rate			
Yes	1 (10%)	2 (22%)	0.58
No	9 (90%)	7 (78%)	
Second surgery			
Yes	2 (20%)	2 (22%)	1.0
No	8 (80%)	7 (78%)	
Use of antibiotics 3 weeks after surgery			
Yes	3 (30%)	0 (0%)	0.21
No	7 (70%)	9 (100%)	
Radiotherapy			
CTV boost volume in CC (mean (sd))	38 (25)	33 (11)	0.59
PTV WBI-volume in CC (mean (sd))	713 (333)	793 (304)†	0.62

†The data of only 7 patients is available, since 2 patients received a mastectomy after NACT
NACT: neo-adjuvant chemotherapy treatment; PTV planning target volume

Discussion

The POP-ART trial is a pilot trial demonstrating NART in 5 fractions before NACT is feasible and does not lead to a longer OTT. On the contrary, due to eliminating the waiting time between surgery and the start of RT, the resulting OTT is on average 14 days shorter. Compared to other studies, a relatively short OTT in both treatment arms was achieved by using a RT schedule in 5 fractions, delivered over 10 to 12 days. The RT schedule in 5 fractions is still experimental, although the results from the YO-HAI5, FAST and FAST-FORWARD trials are promising.[10-12] The UK FAST trial (5 fractions over 5 weeks) and FAST-FORWARD trial (5 fractions over 5 days) showed, compared to 25 or 15 fractions, no significant differences in relapse rates or survival as expected based on radiobiology, nor an increase in normal tissue toxicity after 10 years and 5 years, respectively.[10,11] However, less than 4% of patients included in the FAST and FAST-FORWARD trials received NACT. For the 5-fractions schedule over 10-12 days no long-term randomized evidence exists. An interim analysis of the YO-HAI5 study, randomizing between 5 fractions over 10-12 days and 15 fractions over 3 weeks, showed less acute toxicity [12] and better short-term

HRQoL for the 5 fractions schedule.[14] A matched-case analysis with patients treated in 15 fractions, showed less 2-year toxicity except for fibrosis outside of the tumour bed.[30]

Generally, the beginning of the cancer treatment was not delayed (31 vs 27 days), but the start of NACT was delayed by around 20 days due to RT preparation and delivery. If NACT were to be given first, some of the advantages of NART, like better targeting of the high dose region or the induction of an immune response, might get lost. A solution is giving chemotherapy and radiotherapy concomitantly, which has been done in several trials in the adjuvant setting.[8,31-35] However, the combination of accelerated RT in 5 fractions with concomitant chemotherapy has never been tested before and might lead to an increase in toxicity. The only randomized trial including 716 patients, comparing concomitant and sequential radio- and chemotherapy after surgery, resulted in no advantage of adjuvant concomitant chemo-radiotherapy for disease free survival or overall survival, but an increase in grade 2 or greater late side effects.[36,37] However, the node-positive subgroup did seem to have a significantly better locoregional control after concomitant chemo-radiotherapy.

NART has historically been used for downstaging to increase the rate of BCS, especially in locally advanced breast cancer.[5-8,34,38-41] The addition of NART to NACT could result in a higher rate of pCR, although our study was too small to determine this difference. A recent propensity score matched case-control analysis of 32 patients, receiving concomitant NART and docetaxel after neo-adjuvant FEC, found a significant increase in pCR from 14% to 22% by adding NART.[35] These pCR rates are a lot lower than in our study , most likely since they included mostly Luminal A and B patients. Further studies are required to investigate if NART results in a higher pCR, which could result in better survival outcomes.[42]

Other potential advantages of NART are better targeting of the dose, higher biological effectiveness of RT and the induction of an anti-tumour immune response.[43] Firstly, delineation of the tumour in situ (GTV), instead of the postoperative tumour bed, should reduce the high dose volume to healthy tissue, improving cosmesis and reducing radiotherapy toxicity. The use of NART has been found to reduce the PTV volume in partial breast irradiation.[44] This difference was not reflected in the CTV or PTV boost volumes between both treatments in our study. However, in the NART arm on average 21% of the PTV boost volume compromised of the GTV, i.e. malignant tissue that will be surgically removed. Moreover, the chance of accurate boost delineation is higher when the tumour is still visible on the imaging.

Secondly, NART has shown signs of higher effectiveness through better local control, and possibly even survival, in other tumour types.[45-48] Retrospective studies in breast NART

support this hypothesis of better outcomes after NART, although recent prospective data are lacking.[6,38] From a radiobiology perspective, the intact vasculature, lower hypoxia and reduction in radioresistant tumour clones would be expected to result in better radiosensitivity. Thirdly, NART can induce antigen release, increasing the presence of antigen-presenting cells and stimulating T-cell response.[49]

The main disadvantage of NART, in combination with NACT, is the uncertainty of the influence of NART on treatment escalation after NACT. Recent trials have shown advantages when escalating treatment after incomplete response, in TNBC and Her2+ tumours.[2,3] Further research is required to better select patients requiring adjuvant systemic treatment using biomarkers or liquid biopsies, evolving from the approach of using the patients as their own tumour model. Nevertheless, these techniques are not yet ready for prime time.[50] Liquid biopsies, to detect extracellular vesicles, have been collected for future research. A major challenge of NART is predicting which patients require axillary RT. A negative axilla on imaging does not preclude the finding of a positive sentinel node at the time of surgery. A pre-SLNB is one solution, but it is difficult to schedule and requires 2 surgical procedures. Another potential disadvantage of sequential NART is the NACT delay. In our trial the average duration between the first fraction of NART and the first cycle of NACT was only 19 days, although NACT after diagnosis was delayed, on average, by 21 days. To our knowledge no studies are published investigating the impact of NACT delay on survival. In the adjuvant setting, CT delays above 30 days have been associated with worse overall and disease free survival, especially in TNBC.[25,27] In an umbrella trial, Khorana et al. found a significant impact of time to treatment initiation with any treatment modality.[19] As mentioned previously, treatment initiation was not significantly different between both arms (31 vs 27 days).

Although this feasibility study could have been a single arm trial, this pilot trial is the first study to use a 5-fraction RT schedule in the neo-adjuvant setting, showing that the combination is feasible and leads to no excess acute toxicity, although it has a limited sample size of 20 patients. Furthermore, the combination of NART in 5 fractions and modern NACT consisting of anthracyclines and taxanes is achievable. However, many questions regarding NART in 5 fractions in combination with NACT remain unanswered. Radiotherapy in 5 fractions has not been investigated in a population of patients with breast cancer who received NACT. Therefore, future more evidence is required to confirm this protocol is safe in terms of survival in this population. The optimal sequence of current (neo-)adjuvant treatments remains uncertain.[51] NART results in a shorter OTT since the waiting time after surgery can be reduced and post-operative complications do not result in delays of treatment. Often RT cannot be delivered within 8 weeks

from the first surgery, as was the case in the control arm for 2 patients requiring a mastectomy and additional surgery, which has been correlated with worse disease free and overall survival.[23] In the NACT setting, further investigation is required to determine the impact of NART, with or without immunotherapy, on pCR and survival. Hence, our pilot trial was underpowered for these outcomes. Increasing pCR can potentially result in a de-escalation of adjuvant treatment, especially in the setting of Her2+ and TNBC.[2,3] Several trials are investigating this scenario, notably the NeoChack-Ray trial (NCT03875573) investigates the impact on pCR from adding RT and immunotherapy to NACT in luminal B patients. Also, the PANDoRA trial (NTC03872505) compares non-anthracycline-based NACT and immunotherapy with our without NART for pCR.[52] Furthermore, concomitant delivery of NACT and NART, in an accelerated 5-fraction schedule with SIB, could be investigated to further reduce OTT, but increased acute and long-term toxicity are to be expected.

This pilot trial confirms that accelerated NART in 5 fractions with simultaneously integrated boost (SIB) is feasible and results in a shorter OTT without excess acute toxicity.

Conflict of interest

During the conduct of this work, Liv Veldeman was recipient of a Clinical Mandate of Stand up to Cancer (Flemish Cancer Society). None of the other auteurs have a conflict of interest. Katrien Vandecasteele holds a postdoctoral mandate for fundamental, translational and clinical research by the Foundation against Cancer.

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Disclosure

None of the authors has any disclosures to report.

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Chapter VII: Discussion

A. The current breast cancer landscape

Fortunately, the breast cancer survival is improving rapidly. Recent evaluations in the UK show a reduction in the 5-year risk of death from 14.4% for a diagnosis between 1993 and 1999 to on average 4.9% with a diagnosis between 2010 and 2015. Therefore, breast cancer patients can live long and healthy lives after the diagnosis.(173) The implication is a need to minimize the long term treatment related side effects. This thesis presented several concepts to reduce the side effects related to breast cancer radiotherapy: prone positioning, NART and the combination of DIBH with complex planning techniques. This chapter will add some final remarks on the strengths and weaknesses of each individual technique and an overarching conclusion.

B. Is prone radiotherapy better for WBI?

Prone radiotherapy is the current standard of care in the Ghent University Hospital for WBI without LNI. This decision is supported by the publications presented in this thesis together with the doctoral theses of several of my colleagues (including but not limited to dr. Bert Boute, dr. Max Schoepen, dr. Pieter Deseyne and dr. Michael Stouthandel).(174–176) This body of evidence strongly supports the usage of prone positioning, but the actual uptake of the technique worldwide remains poor. Unfortunately, the exact reasons are not well investigated, although with the combination of common sense and the scientific literature, a fair assumption can be made.

From a treatment perspective, a first potential reason could be the larger set-up errors reported in literature. Several publications, including papers from our radiotherapy department, have shown lower set-up accuracy in prone position compared to supine, especially in the laterolateral direction.(48,74,177) However, our in-house developed PCBC resulted in significantly lower set-up errors in the latero-lateral direction compared to the previous breast board (by putting the patient in a prone dive position), resulting in acceptable errors compared to those reported in supine position.(178) The previous findings of more difficult latero-lateral positioning in prone positioning were confirmed in the PRO-SURF trial (for WBI with LNI), since the set-up errors were higher in prone compared to supine position.(179) A second reason is the reduced comfort from lying in prone position.(48,74) Again, the crawl position on the new PCBC offered a clear advantage over the previous breast board and could (at least partially) negate this disadvantage.(178) A third potential reason is the reduced lymph node access, but, as mentioned previously, prone crawl positioning allows similar beam access compared to a standard supine position with both arms elevated (see Figure 7).(175,180)

From an economic perspective, the introduction of prone WBI incurs several costs for the radiotherapy department. Firstly, an investment is required in a prone positioning device. Several options are available, and due to strict European legislation, all options are fairly expensive.(175) The second obstacle is the lack of staff training. Due to the limited penetration of prone positioning, experience is lacking throughout the RTT-workforce. Therefore, implementing prone positioning into daily practice is likely to result in a learning phase before the optimal results are achieved.(181) (180)Finally, treatment times in prone position have generally been longer compared to supine position, in the range of one to three minutes for each individual patient.(48,74,182)

Looking through the glasses of a radiation oncologist, several additional concerns could be cultivated. The heartspare 1B study found better heart sparing with DIBH compared to prone positioning for left-sided breast cancer patients.(74) Also, historically prone WBI was reserved for large breasted women, because the lower rate of radiation dermatitis was especially relevant in this patient group.(183) Finally, the delineation guidelines were developed for supine positioning.

Yet, from the perspective of the patient, prone positioning is most commonly the treatment position of choice.(76,184) With the use of the appropriate positioning device, like the PCBC, the set-up error can be lowered, comfort is acceptable and the lymph nodes can be accessed.(178,185) Although no difference was found in the MHD between prone and supine position in the first randomized trial comparing both positions (MHD_{supine} 2.0Gy vs MHD_{prone} 1.5Gy, p=0.08), a three-fold lower in MLD was found for prone positioning (MLD_{supine} 3.8Gy vs MLD_{prone} 1.1Gy, p<0.001).(81) The main weaknesses of this RCT were the single centre nature of the trial, the relatively small number of patients, and the possibility of suboptimal (no use of DIBH) treatment techniques in supine position. Therefore, the REQUITE consortium, an international group of large radiotherapy centres collecting prospective standardised data, was consulted to secure real-life data of breast cancer patients treated in prone and supine position. A matched case control-design was used to compare the MHD and MLD within the data of the REQUITE consortium. In total, the study recruited 2069 breast cancer patients in 26 large (or university) hospitals.(186) A lower median MHD for left sided patients was found in prone position (1.29Gy in prone position vs 2.10Gy in supine position, p<0.001), versus a marginally higher MHD in prone position for right sided patients (0.60Gy in prone position vs 0.40Gy in supine position, p<0.001). Additionally, MLD was more than halved in prone (2.77Gy) compared to supine position (5.89Gy, p<0.001).(187) A common misconception is the fact that prone positioning or DIBH are mutually exclusive. DIBH in prone position retracts the heart from the breast.(98) A feasibility trial in our centre for DIBH in prone position demonstrated a significant reduction in MHD for WBI without

LNI, from 2.2Gy in prone position without DIBH to 1.3Gy with the combination of prone position and DIBH ($p<0.001$).(107)

Furthermore, lower acute and 2-year late toxicity was found in two RCT's.(81,82) This thesis adds the updated 5-year results of the first RCT to the medical literature, confirming the improvement in toxicity at long-term.(188) The first RCT comparing prone and supine positioning started recruiting patients in December of 2010 and finished in December of 2012. The acute toxicity results were published in 2013 and they demonstrated a 3-fold reduction in moist desquamation (chi-square $p=0.04$, Fisher's exact test $p=0.07$), lower incidence of dermatitis ($p<0.001$), and edema ($p=0.005$). These results were recently confirmed in a publication by Vesprini et al., in the second RCT comparing both positions, originated in Canada. The Canadian trial also found a significant, although less distinct, difference in the risk of moist desquamation (40% of patients treated in supine, compared to 27% of patients treated in prone position, $p<0.001$).(83) Of notice is that both RCT's only included large breasted patients (the Ghent trial required European cup size C or higher, the Canadian trial required bra band ≥40 in and/or ≥D cup). This thesis used REQUITE data to confirm these findings in women with all breast sizes using a matched case-control design.(187) However, at the moment of the last treatment fraction, no significant difference in dermatitis or the risk of desquamation could be determined. Potential reasons for the discrepancy between both RCT's and the case-control analysis include the moment of measuring acute toxicity, since toxicity is highest in the weeks following WBI (+/-LNI), the risk of bias due to one centre providing the majority of prone treated patients and the reduction in statistical power due to allowing women with small breast in the analysis, with a low risk of toxicity in both positions. Nevertheless, like the late toxicity results from the Ghent RCT, the REQUITE analysis concluded that prone resulted in a lower risk of atrophy at two years with a better body image using HRQoL. This analysis was the first to include the patient's perspective in a prone vs supine comparison.

After the initial investment for a prone positioning device and proper training of the RTT's, the RT sessions could take a few minutes longer in prone compared to supine position. Our in-house cross-over trial found an increase from 19.4 to 21.2 minutes, very similar to the 3-minute difference in the heartspare 1B study (from 17 minutes towards 20 minutes).(182) However, at first these results will not be achievable because of a learning curve of around 5 to 10 patients that will require a longer set-up duration and more substantial patient shifts.(181) New technology could further shorten treatment slots and improve set-up accuracy. Notably, SGRT could improve the patient setup, requiring fewer verification imaging (and associated dose) and hence speed up treatments, although this potential advantage has not yet been established.(189)

Prone causes difficulties for SGRT since the target volume is not visible from the ceiling mounted cameras. Also, the introduction of 6-MV O-ring linear accelerators could greatly reduce the time required for each treatment, compensating the additional time required for the prone positioning. Using this type of accelerator, researchers at the Perelman Center in Pennsylvania (USA), found an average total room time for breast radiotherapy (from leaving the gowned waiting area to return) of 14.3 minutes in supine position with DIBH, and 13.1 minutes in prone position without DIBH, only a couple of minutes higher compared to treatments in supine position without DIBH (on average 11.6 minutes).(190)

To conclude, in my opinion, the advantages of prone positioning, especially when combined with DIBH if necessary, far outweigh the disadvantages. Extensive scientific literature is available to support this claim.(80) This thesis further increased this body of evidence, generally favouring the use of prone position for WBI. Hopefully, this will lead to an increase in the worldwide adoption of the technique.

C. Expanding prone radiotherapy use

As mentioned previously, the advantages of prone radiotherapy were mostly studied in patients requiring WBI without LNI.(83,188) The treatment of the lymph nodes is complicated on most commercial prone positioning devices since the anterior beam-access is often blocked by the positioning device. The solution was the introduction of the in-house developed PCBC that allows a far greater beam-access to the lymph node areas compared to the other available commercial devices (see Figure 7).(175,180) Secondly, the planning experience for the treatment of WBI with LNI was limited until recently.(90,97) Thirdly, the change in position from supine to prone (crawl) position could introduces changes in the anatomical position of the regional lymph nodes. Thiel-embalmed specimens were positioned in prone crawl position an thoroughly scanned using both a CT- and MRI-scanner to adapt the supine delineation guidelines.(27,191) Fourthly, the reproducibility of prone crawl position for WBI with LNI was unknown, especially when combining prone (crawl) position with DIBH.(100) After the groundwork in previous trials, the first patient trial could be started and formed a part of this thesis.

Dosimetry studies showed an advantage for the use of prone(-crawl) compared to supine position for WBI with LNI including the IMN. Using non-coplanar VMAT plans, the average MHD was not significantly different between both positions (5.6Gy for supine and 4.3Gy for prone position, $p=0.16$), but again, the lung dose was halved (5.91Gy for supine and 2.90Gy for prone position, $p=0.002$). This resulted in an estimated 3% difference in the cumulative 30-year risk of either cardiac death or lung cancer death for a smoking patient between both positions (without DIBH

in either position) for WBI with LNI including the IMN, or a more modest 0,2% difference for non-smokers without cardiac risk factors.(192)

Like for WBI-only, DIBH can be combined with prone position for WBI with LNI. Again similar to WBI only, the combination of prone-crawl positioning with DIBH for WBI with LNI (including the IMN) further reduces MHD from 4.55Gy without DIBH, towards 2.54Gy with DIBH ($p<0.001$). Adding DIBH to prone position resulted in a further estimated 1% difference in the cumulative 30-year risk of either cardiac death or lung cancer death for a smoking patient, and again a 0,2% improvement for non-smokers without cardiac risk factor.(97) These patients requiring WBI with LNI are also obtain the highest benefit of a prolonged DIBH (L-DIBH), as will be demonstrated in the next paragraph.

Additionally, an improvement in the 2-year breast retraction for prone crawl WBI with LNI was anticipated. To validate this claim, a new RCT was started at our department. The PRO-SURF (PROne versus SUpine irradiation with Randomized Fractionation schedule) trial was established and included patients from August 2017 until July 2020. The PRO-SURF study was powered to find a 15% lower risk of breast retraction at 2-years according to positioning of the patients. Besides the difference in breast retraction based on treatment position, the study was additionally powered to detect the absence of higher breast retraction with more aggressive hypofractionation in 5 fractions (using a non-inferiority design to exclude a 15% difference of breast retraction at two-year). In total 350 patients were required for both endpoints. Unfortunately, due to regulatory difficulties in expanding the study multi-centric and the COVID-19 pandemic halting further inclusion, premature termination was decided at an inclusion of 61 patients.(179)

Although the trial was ended prematurely, the dosimetric gains could be examined in an actual treatment setting. Again, prone positioning resulted in a halving of the ipsilateral MLD (2.89 vs 4.89 Gy; $P < .001$), without a significant difference in MHD (0.90 vs 1.07 Gy; $P = .22$). As mentioned, the trial was underpowered for the (acute) toxicity analysis, but did demonstrate a lower risk of desquamation with hypofractionation in 5 fractions. This corresponds to the lower acute toxicity found in trials comparing hypofractionation in 15 and 5 fractions, including our own YO-HAI5 trial.(56,104)

Overall, the advantage of prone positioning regarding the OAR dose remains definitely clear, but the advantage on acute or late toxicity, like for WBI without LNI, remains to be determined. Unfortunately, the odds of a future trial investigating this question are very slim.

D. L-DIBH development

As mentioned previously, DIBH more than halves the MHD for left sided breast cancer patients requiring WBI, with or without LNI (Figure 5).(71) Most patient can achieve DIBH durations of around 30 seconds, resulting in around 3 to 5 DIBHs to deliver a high quality WBI treatment, and around 10 DIBHs for WBI with LNI.(69,110) To reduce the number of DIBHs required from a patient and increase her comfort, prolonged DIBHs were developed.(135,136) However, none of the initial techniques have found their way into routine clinical practice.

To increase the probability of introducing the technique in clinical practice, an iterative co-creation method was chosen for the Hyperventilation Oxygenation to prolong Breath hold in Breast cancer Irradiation Treatment (HOBBIT) study. Our methodology was based on the Stanford BioDesign Process, a systematic procedure for developing Innovating Medical Technologies.(193) The framework contains three phases: 1) Identify, 2) Invent, 3) Implement. The identify phase concluded several shorter consecutive L-DIBHs are more interesting compared to a single 5 minute L-DIBH. All identified stakeholders were consulted for feedback throughout the development phase, the co-creation part of the process, in order to increase the knowledge base, accelerate innovation, and foster stakeholder commitment. The identified stakeholders include: the patients, the RTTs that would use the technique day in and day out, radiation oncologists, medical physicists, and an anaesthesiologist (to assure the safety). This is in line with the WHO people-centred care framework from 2016, entailing a partnership between health professionals, and patients.(194) The patient has always been at the heart of my PhD research, with their perspectives—or those of volunteers—playing a pivotal role in shaping our results. For example, while L-DIBH durations were comparable between the mechanical ventilator and the Optiflow device, subsequent research prioritized the Optiflow. This decision was partly informed by volunteers who described it as less restrictive compared to the mechanical ventilator. Also, we actively engaged several patients as participants for our L-DIBH research, seeking their feedback to validate the technique and understand their experiences. Encouragingly, the responses have been overwhelmingly positive. However, selection bias remains a concern, as not all patients approached were willing to participate. Moreover, in our department's latest hypofractionation trial, patient-reported outcomes in the form of HRQoL, have supplanted physician-reported measures as the primary outcome. There is a growing emphasis in academia, supported by funding agencies, on involving patients throughout the research lifecycle.(195) While this approach offers clear benefits, it also entails significant challenges, such as developing patient-centred communication, conducting outreach, and assembling a committed cohort of

participants. Despite these demands, I firmly believe that aligning our research with patient aspirations addresses questions of greater real-world relevance, ultimately justifying the effort.

We started the development with establishing the primary goal that our innovation needed to accomplish: a safe and repeatable 2 minutes and 30 seconds L-DIBH. Secondary goals included simplicity, minimal overall treatment time (including the set-up time required for L-DIBHs) and optimal patient comfort. The development was iterative, since the knowledge from the last examination cycle was carried over to the next cycle, until no clear progression of our goals was achievable.(196) The development cycle was finished by validating the technique in a group of breast cancer patients. The median L-DIBH duration of our group of patients was 3 minutes and 9 seconds. The results showed that repeating the protocol on the same day resulted in an increased L-DIBH duration. Furthermore, median L-DIBH durations also improved for each consecutive day of the examinations (four in total), showing a clear learning curve. Generally, we found all participants (volunteers and patients) to have at least a doubling of the mean DIBH duration. Large patient-specific variation remains with our technique with an interquartile range of 1 minute and 44 seconds. Currently, we have no clear indication of patient specific factors that predict long or short L-DIBH durations, and this should be further investigated during the implementation phase.

At the latter part of my time as a fulltime PhD student, the first steps in the implementation phase were made. A standard breast radiotherapy treatment consists of three stages that require a DIBH: 1) the imaging stage (around one minute in duration), 2) the first tangential beam (around two minutes in duration), and 3) the second tangential beam (around two minutes in duration).(109) Between these phases of a normal WBI delivery, downtime is available for hyperventilation and oxygenation. These three phases of treatment inspired the creation of the second HOBBIT study, to investigate shorter consecutive L-DIBHs, first for imaging and then twice for the beam delivery. For all three consecutive L-DIBHs we aimed for a two-minute duration. Eight out of eleven volunteers achieved the goal of three successive L-DIBHs of at least 2 minutes duration four times in a row (on two different days). The exceptions were one volunteer failing to reach 2 minutes for the second L-DIBH and one volunteer failing twice in the same sequence to reach the goal of 2 minutes, and finally one volunteer in the short preparation group that needed to sneeze at the beginning of the third L-DIBH. In total 93% of all attempts successfully reached two minutes.

During implementation, treatments using a L-DIBH will require a patient tailored approach based on the individual L-DIBH duration achievable by the individual patient. Three main steps in the

journey of the patient are: 1) informing, 2) training and 3) treatment. The communication should focus on creating trust between the health care professionals and the patient. The safety guards should also be communicated to the patient to reduce the stress as much as possible. The procedure should be clearly explained to the patient to prevent any confusion at a later stage (an instruction video could be useful). Secondly, in the training phase, the patient should perform a normal DIBH under guidance by the healthcare professional, followed by the first sensation of HFNO admission. After the patient feels confident with the HFNO equipment, the first round of hyperventilation followed by an L-DIBH can be started. Every L-DIBH duration should be noted, and the health care professional should not be discouraged by the first L-DIBHs durations being shorter (due to the strong learning effect). At least three L-DIBHs should be performed to get a good understanding of the L-DIBH durations the patient can achieve. The beam-on time is highly dependent on the required treatment, and the L-DIBH schedule should be adapted. Before the actual treatment, a dummy run seems recommended, both for the patient and the health care providers, especially at the beginning of the implementation of L-DIBH. Finally, during the treatment phase, the first L-DIBH should be used for the positioning of the patient (and verification imaging). During the matching of the treatment position to the position during CT-simulation the patient can restart the hyperventilation with HFNO. After matching and hyperventilation with HFNO, the first L-DIBH for radiotherapy delivery can be performed. Most breast plans contain at least two beams, and a new hyperventilation with HFNO followed by a L-DIBH is required for the second beam (during which the gantry will move around 180 degrees, taking around 30 seconds). The duration of hyperventilation can be discussed with the patient, but initially we would recommend at least two minutes of hyperventilation before the first L-DIBH, followed by at least 45 seconds of hyperventilation before the first and second beam. The research shows that a longer duration of hyperventilation, generally, results in longer L-DIBH durations. Hence, if a longer beam on-time (for each beam) is required for the optimal treatment, this should result in a longer hyperventilation duration for the patient. L-DIBH duration is not clearly linked with the hyperventilation frequency, so the patient could change the frequency based on individual preference.

My final work as a fulltime PhD student was the quantification of the motion during L-DIBH, necessary before the implementation in the clinic. The main shortcoming of our research on DIBH prolongation was the lack of spatial information gathered. Although the measurement of the $etCO_2$ during L-DIBH allows the detection of any expiration during the breath-hold. This measurement does not give any direct indication on the stability of the anatomy during L-DIBH, or the reproducibility of the individual L-DIBHs. To quantify the motion in three dimensions MRI

images were created during L-DIBH. Ten female volunteers were scanned during L-DIBH both in prone and supine position. The volunteers performed three consecutive L-DIBHs in both positions to assess the intrafraction motion, the primary endpoint of the study. Secondary endpoints include the dosimetric impact (MHD and MLD) of a L-DIBH in both positions.(197) We also performed a pilot trial on the influence of abdominal or thoracic respiration on the MHD reduction. A recent trial by Matsumoto et al. suggests a significantly lower MHD and MLD for an abdominal respiration, for patients treated in supine position.(198)

E. Alternative L-DIBH and respiratory support techniques

As mentioned in the previous paragraph, the HOBBIT trial resulted in a new and simple protocol for L-DIBHs. Other researchers have previously established methods to prolong DIBH duration, an overview can be found in Chapter IV. Three main methods can be distinguished: oxygen, mechanical (hyper)ventilation, and non-invasive high frequency percussive ventilation (HFPV). The delivery of additional oxygen, resulting in hyperoxia, has long been established as a simple and effective method to improve DIBH duration.(129) This result has also been corroborated in the context of radiotherapy.(142) Hyperventilation is well known in the worldwide breath-holding competitions.(199) The combination of both techniques resulted in the protocol described by Roth et al. and Parkes et al.(135,136) However, both authors used mechanical ventilators to induce hyperventilation which require skill to master, and require a leak free seal around the face mask. The HOBBIT protocol creates a simplification of both techniques by using HFNO (high frequency nasal oxygen) and voluntary, instead of forced, hyperventilation by letting the patient follow the rhythm of a metronome. As mentioned in the previous paragraph, a large variation in L-DIBH duration is found, requiring small individual adaptation of the technique for each patient. Since the UK Heartspare stage IA, comparing ABC and voluntary DIBH, found no large differences besides a preference by patients and RTTs for voluntary DIBH, combined with a shorter set-up time for voluntary DIBH, I do think the HOBBIT protocol is superior to the previous techniques. The HFNO set-up only takes seconds and the hyperventilation protocols are fairly short. Nevertheless, no direct comparison of the techniques by Roth et al./Parkes et al. and the HOBBIT protocol is available, so this is solely opinion based.

An alternative use of the mechanical ventilator, besides the induction of hyperventilation, is the regulation of breathing and the induction of repeatable short DIBHs. A RCT at the Cliniques Universitaires Saint-Luc (Brussels, Belgium) by Vander Veken et al. compared mechanically induced DIBH and voluntary DIBH guided by SGRT.(200) Both techniques provided equal reproducibility and stability, but MHD and lung dose parameters were lower in the mechanically-

induced DIBH. Further research is required to determine the difference in MHD and MLD between mechanically-induced short DIBHs and voluntary L-DIBH using the HOBBIT protocol.

Another method to achieve a form of a L-DIBH is the use of high frequency percussive ventilation (HFPV), using small tidal volume and high frequency pulses for ventilation, inducing a apnea-like suppression of the respiratory motion.(138) A L-DIBH duration of over 10 minutes is achievable, and the feasibility during adjuvant breast radiotherapy, lung cancer treatments, and Hodgkin lymphoma treatments has been shown.(138,140) However a recent publication compared a L-DIBH technique with an 8-minute 100% Oxygen breathing preparation (with 5 minutes of controlled hyperventilation) to HFPV. L-DIBH resulted in a smaller variability in lung volume and higher precision in the position of lung structures compared to HFPV.(201)

Finally, in 2018 Kil et al. presented a case report on the use of continuous positive airway pressure (CPAP) for a left-sided post-mastectomy patient requiring adjuvant radiotherapy.(202) CPAP is a positive airway pressure ventilator, which keeps the airways continuously open and can create thoracic changes resembling a DIBH. The combination of CPAP and DIBH can result in even better heart and lung sparing.(203) Similar to CPAP, HFNO creates a higher positive end-expiratory pressure (PEEP) compared to no device or an O_2-mask, although the difference in the level of PEEP between CPAP and HFNO is substantial (around 1.5cmH_20 for HFNO vs 10.3cmH_20 for CPAP, in a bench model with a manikin).(204) How this difference in PEEP will translate into the heart and lung sparing capacity of HFNO supported DIBH versus CPAP supported DIBH needs to be determined still.

F. Neo-adjuvant radiotherapy

Until now, the discussion mainly focused on principles to improve breast radiotherapy. The next paragraph will focus on the role of radiotherapy within the breast cancer landscape. During my PhD research, significant changes were made to the treatment of early breast cancer. These include the expansion of neo-adjuvant (chemo)therapy, the introduction of immune-checkpoint inhibitors (ICI) and a move towards more personalized medicine. The first wave followed the publication of the CREAT-X trial (2017) and KATHERINE (2019) trials.(205,206) Both trials randomized patients after NACT to an additional agent in case of residual disease at the time of the operation. Later in 2020, Keynote 522 instituted the role of ICI in the setting of early TNBC.(207) Finally, the publication of the TAILORx, RxPONDER and MINDACT trials led to the introduction of gene-expression profiles (GEP) in clinical practice.(208–210) During the POP-ART trial the introduction of GEP in our hospital was gradual due to the lack of reimbursement at that time (now a GEP is reimbursed based on criteria set by the RIZIV).

In this changing landscape, the POP-ART pilot trial was held, between November 2018 and August 2020. The trial re-introduced the old idea of neo-adjuvant radiotherapy in aggressive types of breast cancer. Historically the decision for neo-adjuvant treatment was mostly based on anatomical extent but in the POP-ART trial, immunohistochemistry (ER-status and Her2-status) were also considered.(152,211) Most patients eligible for NACT were allowed to participate in the trial, which was powered to show a difference in the OTT between both treatment sequences (NART followed by NACT or NACT followed by adjuvant radiotherapy). NART in 5 fractions resulted in a 19 day shorter OTT compared to adjuvant radiotherapy in 5 fractions, at the cost of a 21 day delay in the initiation of NACT.(212) Both radiotherapy and chemotherapy delay can significantly impact oncological outcomes. A recent publication by Yung et al. found a decrease in breast cancer specific mortality from delaying both radio- and chemotherapy by more than 8 weeks (or 56 days).(156) One publication combining multiple prospective clinical trial did show a difference between initiation of chemotherapy within 20 days compared to 21 until 86 days.(157) An extensive literature review did not find any significant results for an even shorter interval to chemotherapy initiation, that resulted in a significant difference in oncological outcome, although it did show a significantly higher risk from a treatment-related delay for triple negative breast cancer due to a delay of four weeks (or more).(158,159) Randomized research is very unlikely, due to difficulties in recruiting, logistics as well as ethical issues.

In general, shorter OTT seems superior, although the overall trend seems to be a longer time to the initiation of adjuvant treatment, potentially due to the increased request for additional testing.(213) Gene expression profile (GEP) tests, that determine the aggressiveness and hence the appropriateness of chemotherapy treatment, often take weeks to provide a result, delaying chemotherapy initiation. At the moment, radiotherapy is not dependent on the results of GEP (or other additional testing) and a short 5 fraction treatment could be delivered in the meantime further reducing the OTT. NART can reduce the OTT by removing the waiting time that is required for wound healing between surgery and radiotherapy. As mentioned previously, our POP-ART trial did confirm this finding. However, another very similar phase I feasibility and safety trial with an identical name was performed in Belgium at the same time, the POPART trial from the Vrije Universiteit Brussel.(212,214) Both POP(-)ART trials used very similar fractionation schedules in five fractions: 28.5Gy in five fractions every other day with a SIB of 31Gy in Ghent versus 25Gy in five consecutive days with a SIB of 30Gy in Brussels. However, the Ghent trial performed NART before NACT, whereas the Brussels trial performed NART 2 to 8 days before surgery in a group of patients at a lower risk of recurrence. The Brussels group found wound complications in 5 of the 14 patients treated with NART with three patients developing a fistula (with one patient requiring

additional surgery), compared with 3 out of 10 patients requiring antibiotics post-surgery in the Ghent trial. The frequency of complications could be considered high, although both trials showed manageable toxicity. One reason for the high rate of complications in the Brussels POPART trial would be the short interval to surgery. Further research is required to determine if an additional waiting period results in lower rates of toxicity. Our trial only performed surgery around six months after NART due to all patients also receiving NACT, this could potentially explain the lower severity of post-operative complications.

An alternative to potentially reduce the surgical complication risk of NART, whilst still harvesting the advantages of neo-adjuvant treatment, would be the treatment of only a part of the breast with accelerated neo-adjuvant partial breast irradiation (NAPBI). PBI requires a higher level of precision regarding the (initial) location of the tumour, therefore NAPBI could be superior due to the tumour still being in place allowing for better targeting and smaller treatment volumes. Since 2013, around seven trials have reported on the use of accelerated NAPBI, generally in patients with low risk breast cancer.(170) Bosma et al. reported the results of 133 patients treated with NAPBI using two fractionation schemes: 40Gy in 10 fractions or 30Gy in five fractions (similar to SIB dose is Brussels POPART trial).(215) Only 15 patients developed post-operative complications (11%), and 82% of patients were (very) satisfied with the cosmetic outcome 5 years after treatment. Notably, three recurrence developed in the needle biopsy track, prompting the removal of the biopsy track in the last two years of the trial. Other NAPBI trials have attempted to even further reduce the number of fractions below five using SBRT. The first report of SBRT for breast cancer was reported in 2012 in the phase I trial by Bondiau et al. that investigated the safety of five levels of dose escalated SBRT to the tumour in three fractions during the NACT treatment (not delivered on the same day), followed by conventional WBI after the surgery.(216) SBRT was well tolerated an a pCR was found 36% of patients in dose levels III to V. Afterwards, Horton et al. performed a similar dose escalation trial for single fraction SBRT treatments, but most patients did not receive an adjuvant WBI treatment.(217) Again the tolerance was good, even for a single fraction of 21Gy, with no acute dose-limiting grade 3 or 4 radiation-related toxicities or wound dehiscence and good cosmetic outcomes. The SIGNAL study positioned patients in prone position to deliver a single fraction of 21Gy to the breast and reported no significant toxicity with excellent cosmetic outcomes.(218) The latest phase I trial tested NAPBI for small hormone sensitive breast cancers, up to a dose of 34Gy in a single fraction, using a MRI and linear accelerator combination, or robotic radiosurgery or cobalt stereotactic breast unit.(219) The rate of pCR or near complete response were drastically higher for 34Gy (93% pCR) compared to 30Gy

(38%). Overall, NAPBI could become a treatment option to reduce toxicity and increase the cosmetic outcomes for early breast cancer with a good prognosis.

For high risk TNBC the Keynote 522 resulted in ICI becoming the standard of care in the neo-adjuvant treatment.(207) The combination of ICI with radiotherapy could induce antigen release, increasing the recruitment of antigen-presenting cells and stimulating T-cell responses.(220) Since the start of the POP-ART trial, another Belgian trial started investigating NAPBI, three fractions of 8Gy with an SBRT technique, in early stage luminal B breast cancer: the NeoCheck-Ray trial (NTC03875573). The goal of the radiotherapy in this trial is an improvement in rate of response by adding NAPBI to NACT with ICI (Durvalumab with or without Oleclumab). The PANDoRA trial (NCT03872505) is randomizing patients with TNBC to receive NACT, including ICI durvalumab, with or without NAPBI using SBRT (again three times 8Gy). The primary endpoint is also the response after neo-adjuvant treatment. One of the secondary endpoints in de POP-ART trial was the change in tumour infiltrating lymphocytes after NART. Unfortunately, due to the small sample size in the trial (20 patients) and the loss of certain samples (some due to the COVID pandemic), no definitive conclusions could be made. A trial based in the Cedars-Sinai medical center (Los Angeles, USA) will further investigate the impact of NART in combination with ICI (NCT03366844).(221)

In the last decade, many novel systemic agents have been approved. The list of Her2-targeted therapy was expanded with a large number of antibody-drug conjugates (ADCs), namely Trastuzumab-Emtansine, Trastuzumab-Deruxtecan, and Sacituzumab Govitecan.(222) The landscape of hormone sensitive breast cancer saw the introduction of CDK4/6 inhibitors Palbociclib, Ribociclib and Abemaciclib, and of the PI3Kα-specific inhibitor Alpelisib.(223) Patients with a germline BRCA mutation now have access to Olaparib or other PARP inhibitors. Finally, ICI have found their way in the treatment of breast cancer.(207) By the time of writing, the list is probably already outdated. Certain new agents could exacerbate the radiotherapy side-effects on heart and lungs, and both long-term follow-up for clinical trials and careful postmarketing surveillance are required to determine any synergistic effects with radiotherapy. ESTRO recently published multidisciplinary consensus guidelines on the integration of radiotherapy with new systemic treatments for breast cancer.(224) These guidelines emphasise the importance of considering radiotherapy parameters and comprehensive quality assurance in clinical trials assessing novel systemic therapies for breast cancer. Although CDK4/6 inhibitors and PARP inhibitors have shown promising safety data when combined with radiotherapy, further research is warranted. PI3K and mTOR inhibitors have shown safety signals warranting caution, and discouraging their combination with radiotherapy. ICI and Her2-targeted treatments (non-

ADC's) can be safely administered alongside radiotherapy. Trastuzumab-Emtansine (an ADC) appears safe during adjuvant radiotherapy, but the guidelines recommend not to combine both treatments due to the limited data. Other emerging tyrosine kinase inhibitors and ADCs should not be combined with concurrent radiotherapy. Finally, since the normal tissue complication probability is a function of the radiotherapy dose delivered to the organ at risk, the techniques described in this thesis are especially relevant in combination with novel systemic agents to reduce the risk of adverse events.

Finally, as was already mentioned in Chapter VI, NART could allow for better breast reconstruction results after mastectomy. A recent publication of an Italian expert Delphi consensus round summarizes the main controversies.(225) Firstly, the increase in the use of oncoplastic techniques results in more difficulties to deliver a boost to the tissue that was in contact with the tumour, something that can easily be achieved with NART. Good marking of the tumour bed is essential for adjuvant radiotherapy after oncoplastic BCS. The best technique for breast reconstruction and timing in patients requiring adjuvant radiotherapy after mastectomy remains to be established. As mentioned previously, the PRADA trial (NCT02771938) has already published results showing a breast reconstruction is feasible and technically safe after NART.(171)

The use of NART in combination with NACT, like performed in the POP-ART, should improve the rate of pCR. However, it is uncertain if the results of the CREAT-X trial (2017) and KATHERINE (2019) trials are still valid after the combination of NART and NACT.(205,206) Both trials escalate treatment if no pCR is reached after NACT. It is uncertain if a pCR after NART plus NACT is equal to a pCR after only NACT. If so, the need for additional adjuvant treatments after a neo-adjuvant treatment can be reduced with the use of NART. Otherwise, NART could result in the undertreatment of certain patients.

G. Future perspectives

1. Expansion of prone positioning

Throughout the thesis, many advantages of prone radiotherapy were mentioned. Clearly, potential pitfalls are present, despite most of them being addressed by my or previous published research. Nevertheless, the adoption of prone positioning remains minimal. In my opinion, more effort is required to increase the use of prone breast radiotherapy. Firstly, the lower risk of acute toxicity is known through two RCTs.(81,83) Secondly, the REQUITE publication showed that the dose delivered to the lungs is significantly lower, the median MLD was more than halved in this

cohort of patients from high volume centres. Thirdly, this PhD thesis provided additional evidence on the advantage of prone position in the prevention of late side effects. Previous publications focused only on the difference between the MHD. The UK Heartspare Stage IB trial found a lower MHD with the use of DIBH compared to the use of prone position. However, both techniques can be combined. This results in the lung sparing capacity of prone position being combined with the heart sparing capacity of DIBH.(97) Although the advantages are known, the uptake of the technique remains very low.

The following list contains the main arguments mentioned against the use of prone position, according to my own experiences: 1) cost-price of buying equipment for prone positioning, 2) the steep learning curve at all levels of the radiotherapy department, 3) the requirement to support both prone and supine position at the same time, 4) bad compatibility between prone position and SGRT, and 5) more urgent innovations that require attention. These points are not based on thorough data analysis, but could still provide insight into the slow adoption of prone.

The introduction of prone position for breast cancer patients necessitates a capital investment into the equipment required. Several platforms are available, but these are not cheap due to the high administrative burden of the European medical device regulation, which is required to bring a new system to market (resulting in reduced competition). Not only is the price high, the system is of limited use for other pathologies requiring radiotherapy. Yet, due to breast cancer patients representing a large number of all patients for each radiotherapy clinic, a prone positioning device should see a fair amount of use throughout the day. The learning curve for RTT's, planners and medical physicists of around 5 to 10 patients has already been mentioned.(181) More research is required to provide the optimal training protocols for the implementation of prone radiotherapy in a new treatment centre, for each of the different disciplines involved in the treatment of patients. Owing to the high number of breast cancer patients requiring radiotherapy treatment, the recruitment of around 10 patients for the training phase should be swift.

Not all patients support the treatment in prone position, mostly due to a reduced mobility that inhibits the patients getting to the treatment position safely. Nevertheless, most patients in our radiotherapy department are treated in prone position (for WBI) and the use of supine position is limited, although it is required to retain the knowledge of treating in supine position for this small group of patients with bad mobility. SGRT is another reason to avoid prone positioning, since the target volume (the breast) is not clearly visible to the ceiling mounted cameras in prone position. Research is required to determine the optimal position of the SGRT cameras. Finally,

radiotherapy continuous quickly changing, hence requiring continuous adaptation to remain at the forefront of the field.

Overall, each treatment centre should make an individual decision to support, or not, the delivery of radiotherapy to the breast in prone position. Hopefully, this thesis can provide an overview of the advantages of the technique, and by giving an overview of the hurdles, overcome the anxiety of implementing a new technique in the department. An in depth investigation in the reasons for the lack of adoption of prone positioning seems opportune. Based on these results, further training programs could be developed to reduce the burden of implementing a new technique.

2. Use-cases for L-DIBH

The PhD thesis mainly focused on the use of DIBH for MHD reduction in left-sided breast cancer patients. Nevertheless, the use of DIBH has been found effective in a far wider range of patients.(226) ABC breath-holding has been studied for the delivery of stereotactic body radiotherapy (or SBRT, a radiotherapy treatment that delivers a low number of high dose fractions to the target with a high precision) to the lung or liver.(227,228) Contrary to the use of DIBH in breast cancer, tumour immobilization is of key importance in lung or liver cancer. Both lung and liver lesions can move dramatically during the respiratory cycle, requiring large margins around the tumour to ensure a complete irradiation of the tumour. The healthy organs can be spared due to the reduction in margins around the tumour from immobilization during DIBH. In the setting of primary lung cancer treatments, using a long (non-SBRT) schedule, the clinical benefit has already been established.(229) The STIC project, run between 2004 and 2008, found lower acute pulmonary toxicity, and pulmonary, cardiac, and oesophageal late toxicities, especially with DIBH techniques. Most current lung cancer patients have a history of smoking, resulting in a lower lung capacity and more difficulties to perform a DIBH. The support technique from the HOBBIT trial could provide a solution.

Secondly, the risk of radiotherapy toxicity needs to be reduced in the utmost way for patients with mediastinal Hodgkin lymphoma, since it is a supremely curable disease frequently encountered in younger patients with a long life-expectancy. The most important risks in this group of patients are the secondary cancer risk and the risk of heart toxicity. Like in breast cancer, DIBH can significantly reduce MHD and MLD.(230) For patients with both Hodgkin lymphoma and non-Hodgkin lymphoma (a similar disease found in elder patients compared to Hodgkin lymphoma), DIBH did not result in a reduction of radiation pneumonitis.(231) However, the consensus view is that the correlation between MLD and secondary lung cancer risk, found in breast cancer patients, should remain intact for patients suffering from (non-)Hodgkin lymphoma.(67) For

optimal dose conformity, complex IMRT (or other advanced radiotherapy techniques like protons radiotherapy) are often given, to minimize the treatment risks. An L-DIBH technique could allow these complex techniques to be combined with DIBH. The MAASTRO clinic has recently published the clinical experience and DIBH stability of using HFNO, like in our protocol, for DIBH in patients with mediastinal lymphoma.(132) HFNO resulted in a doubling of DIBH duration, with good stability, allowing the reduction of the treatment margins. This resulted in a considerable MHD, MLD, oesophagus and healthy breast dose reduction. The same group found HNFO also increased L-DIBH duration in locally advanced lung cancer patients.(133)

Thirdly, reducing respiratory motion in liver, lung, and renal cancers leads to a smaller PTV volume and, consequently, a reduced dose to healthy organs. Liver SBRT particularly benefits from motion management techniques, which help meet dose constraints, ensure low toxicity rates, and enable dose escalation.(232) The recent paradigm shift in treating oligometastases has further heightened interest in liver SBRT. However, tumour motion during voluntary DIBH can still reach up to 1 cm in a single breath-hold.(233) Our L-DIBH protocol using HFNO shows potential to reduce this intrafraction motion, though additional research is necessary to confirm its effectiveness.(202) Lung cancer patients may also benefit from reduced tumour motion. Recently, colleagues from the Université Catholique de Louvain published results from a prospective feasibility trial that evaluated the use of MANIV for lung and liver SBRT. Their findings demonstrated accurate intrafraction tumour repositioning for lung tumours.(234) Another approach for managing motion in lung cancer is the use of continuous positive airway pressure (CPAP), which can increase lung volume by 32% and reduce tumour motion by 5 mm.(235) Unfortunately, the PEEP provided by HFNO is likely too low to achieve this effect, necessitating further research to validate its use. Lastly, models predict improved renal function through motion management, though this too requires additional investigation.(236)

Fourthly, proton radiotherapy is far less forgiving than radiotherapy using photon beams. Due to the high conformity of proton radiotherapy, and the physical properties of the charged particles, the risk of overshoot or undershoot in case of motion of the tumour is higher for proton radiotherapy, compared to photon radiotherapy.(95) One method to increase the robustness, is an additional margin around the target, but this could negate the advantages of the state-of-the-art proton radiotherapy. Furthermore, the delivery of proton radiotherapy, generally, takes longer compared to photon radiotherapy. The introduction of the L-DIBH could provide a solution. Emert et al., from the Paul Scherrer institute that has access to proton radiotherapy, has compared L-DIBH (combining oxygenation and hyperventilation) with HFPV in 21 healthy subjects on multiple 1.5 T MRI scans.(201) L-DIBHs were long enough to allow proton radiotherapy, and the variability

in lung volume was smaller and the position of lung structures more precise for L-DIBHs compared to HFPV. Our research group has shown that the lowest MHD for left-sided WBI with LNI including the IMN is achieved with the combination of DIBH and proton radiotherapy, although the absolute reduction in MHD due to DIBH is smaller in proton compared to photon radiotherapy due to the higher conformity of proton radiotherapy.(97) On the other hand DIBH increased the MLD for proton plans due to a larger dose spread in the low density cavities of the lung. Without DIBH the heart can function as a dose absorber in front of the lungs, whereas in DIBH the heart is retracted from the chest wall and more dose is delivered to the lungs.

Finally, previous research mostly focused on L-DIBH support through the delivery of oxygen, the induction of hypocapnia or mechanical ventilation, but these are not the only available techniques. Besides the physiological parameters that govern our breathing, a long voluntary DIBH is more difficult for patients in a bad mood since emotions play an important role in the perception of breathlessness.(123) Research found that negative affectivity leads to more symptoms of breathlessness in asthma patients (both adults and children). These findings are corroborated by our own experiences during the execution of the HOBBIT trial, where a negative (or positive) mood of the participant could have an impact on his/her L-DIBH duration, although we did not objectively measure these effects. Consequently, positively influencing the psychology of our patient could lead to improvements in (L-)DIBH durations. Although previous research has shown that reading, mental calculations or performing a basic task can improve DIBH durations, no research is available in the context of radiotherapy or L-DIBH.(123–125) Another method to reduce stress, and improve L-DIBH durations, is the training of the patients.(126) Our research clearly showed an improvement in L-DIBH duration for each day of the examination and each consecutive L-DIBH during a single session. Further optimization of (L-)DIBH durations could potentially be achieved through better training of the patient, since forming an interesting research topic for future projects.(128)

Further research is required on the implementation of L-DIBHs into daily practice. The first steps have already been performed at the Cliniques Universitaires Saint-Luc (Brussels, Belgium) with the implementation of a mechanical ventilator in the treatment room.(200) They also compared two methods to achieve a DIBH, voluntary or supported by a mechanical ventilator, and found an advantage on dosimetric parameters for the mechanical ventilator. However, the final choice of breathing management tool in a clinic will be based on more than just the dosimetry parameters: investment cost, education requirements for RTTs, regulatory difficulties (in Belgium nurses are allowed to deliver oxygen without an additional licence, but they are not allowed to independently operate a mechanical ventilator without additional training), patient comfort, ease of use, overall

treatment time and the requirement of L-DIBH due to long beam-on times, are just a few of the considerations before starting breathing management.(169)

As already mentioned, co-creation involving RTT's and patients was used to increase the likelihood of a quick implementation, but further research is still required before the introduction of the technique in the clinic. The co-creation resulted in the simplification of the previously described techniques that often require a full-face mask, which should allow patients with mild claustrophobia to also perform the technique. The implementation of a new technique is not just a question of technique, as much as an economical one. Many innovations don't see the timely introduction into daily practice due to a lack of training, desirability, feasibility, clear goals and processes and the complexity of a project.(237) For a further roll-out to other hospitals, the first important step is communication between the radiotherapy departments to share know-how, either through face-to-face meeting, or online resources.(238) Secondly, full implementation plans are recommended for each department, and a plan for our department was developed based on the implementation protocol by the MAASTRO clinic in the Netherlands. Thirdly, the hands-on training of the personnel is required, by trainers experienced with the technique. In the beginning, consultancy in the department from RTTs already familiar with the technique seems optimal. The training program should be based on the already existing programs, like the mechanical ventilator training program by Parkes et al. taught in the Netherlands by RTTs to other RTTs.

3. Neo-adjuvant radiotherapy

In the changing early breast cancer landscape, NART still needs to find its place. There are multiple theoretical advantages including increasing the response after neo-adjuvant treatment, inducing an antigen release that can boost the effectiveness of ICIs, or reduce the side effects of radiotherapy due to smaller margins for the boost-volume. Due to hypofractionation or the use of stereotactic radiotherapy, the NART duration can be very short, not resulting in a significant treatment delay. This was confirmed in the POP-ART trial, which further established the safety of the treatment. Based on the current results, NART is not the standard of care. However, several trials are recruiting that could introduce the use of NART in the standard of care. The results are eagerly awaited.

4. Combining technological innovations

The release of ChatGPT, a generative artificial intelligence chatbot, in late November 2022 sparked renewed enthusiasm for artificial intelligence (AI), which persisted until the completion

of this dissertation. Advances in computational power and the refinement of existing algorithms have significantly expanded the capabilities of AI, enabling achievements in fields such as image recognition and generation, natural language processing, and protein folding. Given the already highly technological and computerized nature of radiotherapy departments, the initial steps toward implementing AI in this domain are well underway.

The increasing computational power and sophistication of AI are likely to enhance radiotherapy workflows by enabling faster planning, more precise treatment delivery, and reduced treatment-related toxicity. For instance, AI could synergize with the techniques discussed in this dissertation. Firstly, automatic delineation and automated planning (or dose estimation) could simulate the benefits of DIBH for each patient. Currently, comparing the MHD and MLD between free-breathing and DIBH techniques is resource-intensive due to the lengthy treatment planning process. AI could optimize resource allocation by rapidly evaluating the advantages and disadvantages of different techniques for breast cancer radiotherapy. Secondly, AI-driven adaptive radiotherapy could address breast swelling during treatment, improving dose homogeneity and reducing toxicity. Thirdly, SGRT combined with AI could reduce the radiation dose required for positional verification before each treatment session.

In the future, the extensive data accumulated from the numerous patients already treated with radiotherapy will serve as a foundation for further improving the risk-benefit ratio of breast cancer radiotherapy through AI. However, this advancement also raises ethical concerns, particularly regarding the control and use of structured data. Institutions or corporations that own these datasets could wield disproportionate influence for financial or other gains. Therefore, it is crucial for the academic and medical communities to act as vigilant custodians, ensuring the ethical and equitable use of the collected data for the benefit of the patient.

Summary - Samenvatting

A. Summary

The thesis begins in **Chapter 1** by outlining the indications for radiotherapy in treating breast cancer and the requirements for effective radiotherapy. It discusses both the benefits and risks of radiotherapy, along with the acute and long-term side effects of treatment.

Chapter 2 reviews existing methods aimed at reducing the side effects of breast cancer radiotherapy.

In **Chapter 3**, the thesis objectives are presented, which include: 1) enabling complex treatments during deep inspiration breath-hold (DIBH), 2) strengthening the evidence for the prone position, 3) exploring the feasibility of pre-operative radiotherapy in five fractions, and 4) assessing the availability of advanced radiotherapy techniques for breast cancer in Belgium.

Chapter 4 explores ways to extend DIBH to allow more complex treatments. The first article introduces a new protocol for prolonged DIBH, while the second article examines the possibility of repeating prolonged DIBH within a short time frame.

The second method for minimizing side effects is prone radiotherapy, discussed in **Chapter 5** through three articles. The third article presents a matched case-control study using data from a prospective multi-centre trial. The fourth article reports on the five-year update of the first randomized controlled trial comparing prone and supine positions. The fifth article details the findings of the PRO-SURF trial, which investigates differences between prone and supine positions, as well as treatments delivered in five or fifteen fractions for patients requiring whole breast and lymph node irradiation.

A third strategy for reducing side effects is delivering radiotherapy before surgery. **Chapter 6** explores neo-adjuvant radiotherapy through the results of a randomized trial that compares overall treatment times between pre-operative and post-operative radiotherapy.

Finally, the thesis concludes with a discussion in **Chapter 7**. Three main conclusions can be made: 1) long duration DIBHs are feasible with simple techniques, 2) prone radiotherapy lowers the risk of side effects and secondary lung cancer while remaining compatible with lymph node irradiation, and 3) neo-adjuvant radiotherapy is feasible.

B. Samenvatting

De thesis begint in **Hoofdstuk 1** met een overzicht van de indicaties voor radiotherapie bij de behandeling van borstkanker en de vereisten voor een effectieve radiotherapie. Zowel de voordelen als de risico's van radiotherapie worden besproken, samen met de acute en langdurige bijwerkingen van de behandeling.

Hoofdstuk 2 bespreekt bestaande methoden die gericht zijn op het verminderen van de bijwerkingen van radiotherapie bij borstkanker.

In **Hoofdstuk 3** worden de doelstellingen van de thesis gepresenteerd, waaronder: 1) het mogelijk maken van complexe behandelingen tijdens diepe inademingsvasthouding (DIBH), 2) het versterken van het bewijs voor de buikligging, 3) het onderzoeken van de haalbaarheid van preoperatieve radiotherapie in vijf fracties, en 4) het evalueren van de beschikbaarheid van geavanceerde radiotherapietechnieken voor borstkanker in België.

Hoofdstuk 4 onderzoekt manieren om DIBH te verlengen om meer complexe behandelingen mogelijk te maken. Het eerste artikel introduceert een nieuw protocol voor verlengde DIBH, terwijl het tweede artikel de mogelijkheid onderzoekt om verlengde DIBH binnen een korte tijdspanne te herhalen.

De tweede methode om bijwerkingen te minimaliseren is radiotherapie in buikligging, besproken in **Hoofdstuk 5** aan de hand van drie artikelen. Het derde artikel presenteert een gematchte case-control studie op basis van een prospectieve multicentrische studie. Het vierde artikel geeft een update van vijf jaar van de eerste gerandomiseerde gecontroleerde studie die buikligging en rugligging vergelijkt. Het vijfde artikel beschrijft de resultaten van de PRO-SURF studie, waarin het verschil tussen buikligging en rugligging wordt onderzocht, evenals behandelingen in vijf of vijftien fracties voor patiënten die bestraling van de hele borst en lymfeklieren nodig hebben.

Een derde strategie om bijwerkingen te verminderen is het toedienen van radiotherapie vóór de operatie. **Hoofdstuk 6** onderzoekt neo-adjuvante radiotherapie door de resultaten van een gerandomiseerde studie die de totale behandeltijd tussen preoperatieve en postoperatieve radiotherapie vergelijkt.

Tot slot wordt de thesis afgesloten met een discussie in **Hoofdstuk 7**. Er zijn drie hoofdconclusies: 1) langdurige DIBH is haalbaar met eenvoudige technieken, 2) bestraling in buikligging vermindert het risico op bijwerkingen en secundaire longkanker, terwijl het compatibel blijft met bestraling van de lymfeklieren, en 3) neo-adjuvante radiotherapie is haalbaar.

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Curriculum vitae

Vincent Vakaet

TRAINING

PhD — Ghent University
Department of human structure and repair — Expected beginning of 2025

Master in Radiation Oncology — Ghent University
Faculty of Medicine and Health Sciences — Expected beginning of 2025

Master in Medicine — Ghent University
Faculty of Medicine and Health Sciences — June 2018
Thesis "Chronic obstructive pulmonary disease and atrial fibrillation: the Rotterdam Study"

EXPERIENCE

AZ Sint-Lucas — Ghent, Belgium
Radiation oncology residency — October 2024 – January 2025

UZ Gent — Ghent, Belgium
Radiation oncology residency — October 2023 - Present
August 2022 – September 2022
August 2021 – January 2022

- Experience with LDR brachytherapy for prostate cancer

AZ Groeninge — Kortrijk, Belgium
Radiation oncology residency — October 2022 – September 2023

UZ Leuven — Leuven, Belgium
Radiation oncology residency — February 2022 – July 2022

- Experience in the only proton centre in Belgium : Particle
- Experience with brachytherapy for cervical cancer, keloid, skin cancer

Ghent University, Faculty of Medicine and Health Sciences — Ghent, Belgium
PhD student in the department of human structure and repair — August 2018- July 2021

- Development of a new breath-hold technique using high flow nasal oxygen and hyperventilation
- Participation in various clinical trials
- BeSTRO Ph.D. award (Belgian society for radiation oncology) for best presentation (2021)

Hospital Central de Maputo — Maputo, Mozambique
Overseas internship as a medical student — February 2018 – March 2018

LEADERSHIP

Resident Representation in the Medical Council — Ghent, Belgium
UZ Gent — October 2023 – September 2024

180 Degrees Consulting – Ghent Branch — Ghent, Belgium
Team leader – Cultureghem project — February 2016 – June 2016
Consultant – Stichting tegen kanker — October 2015 – January 2016

Sailing instructor — Ostend - Nieuwpoort, Belgium
WOS - KYCN — Summer 2012 – Summer 2015

SKILLS & INTERESTS

Languages: Dutch level C2, English level C1, French level B2, **ICT**: R, SPSS, REDCap, **Photography,** Sailing

PUBLICATIONS

1. **Vakaet V**, Van Hulle H, de Noyette R, Schoepen M, Deseyne P, Huybrechts V, et al. Minimizing preparation time for repeated prolonged deep-inspiration breath holds during breast cancer irradiation using pre-oxygenation with high-flow nasal oxygen and voluntary hyperventilation. British Journal of Radiology. 2025 Jan 1;98(1165):45–9.

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5. Aldraimli M, Osman S, Grishchuck D, Ingram S, Lyon R, Mistry A, … **Vakaet V**, … et al. Development and Optimization of a Machine-Learning Prediction Model for Acute Desquamation After Breast Radiation Therapy in the Multicenter REQUITE Cohort. Advances in Radiation Oncology. 2022;7(3):100890.

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11. **Vakaet V**, Van Hulle H, Vergotte M, Schoepen M, Deseyne P, van Greveling A, et al. 5-Year Outcomes of a Randomized Trial Comparing Prone and Supine Whole Breast Irradiation in Large-Breasted Women. International Journal of Radiation Oncology*Biology*Physics. 2021;110(3):766–71.

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Lay-out: Ingrid Vernemmen

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