



Original Research Article

Selection criteria for early breast cancer patients in the DBCG proton trial – The randomised phase III trial strategy



Line Bjerregaard Stick^{a,b,c,*}, Ebbe Laugaard Lorenzen^d, Esben Svitzer Yates^e, Carmel Anandadas^f, Karen Andersen^g, Cynthia Aristei^h, Orla Byrneⁱ, Sandra Hol^j, Ingelise Jensen^k, Anna M. Kirby^l, Youlia M. Kirova^m, Livia Marrazzoⁿ, Angela Matías-Pérez^o, Mette Marie Bruun Nielsen^p, Henrik Dahl Nissen^q, Sileida Oliveros^r, Karolien Verhoeven^s, Johan Vikström^t, Birgitte Vrou Offersen^{c,u}

^a Department of Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

^b Niels Bohr Institute, Faculty of Science, University of Copenhagen, Copenhagen, Denmark

^c Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

^d Laboratory of Radiation Physics, Odense University Hospital, Odense, Denmark

^e Department of Medical Physics, Aarhus University Hospital, Aarhus, Denmark

^f Department of Clinical Oncology, The Christie Hospital NHS Foundation Trust, Manchester, UK

^g Department of Radiotherapy, Herlev & Gentofte Hospital, Herlev, Denmark

^h Department of Medicine and Surgery, Radiation Oncology Section, University of Perugia & Perugia General Hospital, Perugia, Italy

ⁱ Department of Medical Physics, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK

^j Department of Radiation Oncology, Institute Verbeeten, Tilburg, the Netherlands

^k Department of Medical Physics, Aalborg University Hospital, Aalborg, Denmark

^l Department of Radiotherapy, The Royal Marsden Hospital NHS Foundation Trust & Institute of Cancer Research, London, UK

^m Department of Radiation Oncology, Institut Curie, Paris, France

ⁿ Department of Medical Physics, Careggi University Hospital, Florence, Italy

^o Département de Radiothérapie, Institut Gustave Roussy, Villejuif, France

^p Department of Oncology, Zealand University Hospital, Næstved, Denmark

^q Department of Oncology, Vejle Sygehus, Vejle, Denmark

^r Department of Oncology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

^s Department of Radiation Oncology (Maastrro), GROW School for Oncology, Maastricht University Medical Centre, Maastricht, the Netherlands

^t Department of Radiotherapy, Stavanger University Hospital, Stavanger, Norway

^u Department of Experimental Clinical Oncology & Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

ARTICLE INFO

Article history:

Received 3 December 2020

Revised 27 January 2021

Accepted 31 January 2021

Available online 4 February 2021

Keywords:

Patient selection

Breast cancer

Proton therapy

Heart and lung exposure

ABSTRACT

Background and purpose: Adjuvant radiotherapy of internal mammary nodes (IMN) improves survival in high-risk early breast cancer patients but inevitably leads to more dose to heart and lung. Target coverage is often compromised to meet heart/lung dose constraints. We estimate heart and lung dose when target coverage is not compromised in consecutive patients. These estimates are used to guide the choice of selection criteria for the randomised Danish Breast Cancer Group (DBCG) Proton Trial.

Materials and methods: 179 breast cancer patients already treated with loco-regional IMN radiotherapy from 18 European departments were included. If the clinically delivered treatment plan did not comply with defined target coverage requirements, the plan was modified retrospectively until sufficient coverage was reached. The choice of selection criteria was based on the estimated number of eligible patients for different heart and lung dose thresholds in combination with proton therapy capacity limitations and dose–response relationships for heart and lung.

Results: Median mean heart dose was 3.0 Gy (range, 1.1–8.2 Gy) for left-sided and 1.4 Gy (0.4–11.5 Gy) for right-sided treatment plans. Median V17Gy/V20Gy (hypofractionated/normofractionated plans) for ipsilateral lung was 31% (9–57%). The DBCG Radiotherapy Committee chose mean heart dose ≥ 4 Gy and/or lung V17Gy/V20Gy $\geq 37\%$ as thresholds for inclusion in the randomised trial. Using these

* Corresponding author at: Danish Centre for Particle Therapy, Aarhus University Hospital, Palle Juul-Jensens Blvd. 99, 8200 Aarhus N, Denmark.

E-mail address: linsti@rm.dk (L.B. Stick).

thresholds, we estimate that 22% of patients requiring loco-regional IMN radiotherapy will be eligible for the trial.

Conclusion: The patient selection criteria for the DBCG Proton Trial are mean heart dose ≥ 4 Gy and/or lung V17Gy/V20Gy $\geq 37\%$.

© 2021 The Author(s). Published by Elsevier B.V. on behalf of European Society for Radiotherapy and Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Irradiation of lymph nodes including the internal mammary nodes (IMN) improves overall and disease-free survival rates in high-risk breast cancer patients in a meta-analysis of the randomised EORTC 22922/10925 and NCIC-CTG MA.20 trials [1–4]. This is consistent with results from the population-based Danish Breast Cancer Group (DBCG) IMN trial demonstrating that IMN irradiation improves overall survival and reduces breast cancer mortality [5]. However, IMN irradiation can cause larger radiation exposure to the heart which in turn increases the risk of radiation-induced toxicity [6–10]. Likewise, lymph node irradiation increases the dose to the lung which can lead to second lung cancer [11,12]. Modern radiotherapy techniques can improve the balance between target coverage and exposure to heart and lung [13–15]. Still, it is sometimes necessary to compromise the IMN coverage to comply with dose constraints for heart and lung defined in treatment planning guidelines.

Proton therapy has not been widely used for adjuvant breast cancer radiotherapy, thus the evidence supporting its clinical use is limited [16–23]. The properties of spot-scanning proton therapy allow adequate target coverage and low dose to the heart and lung compared with photon radiotherapy, independently of patient anatomy as demonstrated in a comparative planning study with 41 consecutive high-risk breast cancer patients [24]. Hence, there is no need for immediate individual proton therapy comparison if a photon radiotherapy plan has a high heart or lung dose. Recent treatment planning studies show limited benefit of spot-scanning proton therapy in deep inspiration breath-hold (DIBH) versus free breathing for patients with breast cancer [25,26].

The majority of breast cancer patients receive exemplary treatment with state-of-the-art photon radiotherapy techniques [13–15], but a subgroup of patients may have an additional clinically relevant benefit from proton therapy [24–29]. The strategy in the DBCG Proton Trial is to randomise highly selected patients between photon radiotherapy and proton therapy (ClinicalTrials.gov number, NCT04291378) [30]. The DBCG Radiotherapy Committee decided that patients with treatment plans showing high dose to heart and/or lung to fulfil adequate target coverage should be offered participating in the trial. No treatment plan comparison will be needed before randomisation in the trial assuming that proton therapy provides low exposure of heart and lung [24]. Compromises in target coverage to reduce dose to heart or lung are allowed after randomisation in the photon therapy plan, because that reflects clinical practice according to the DBCG guidelines.

In this study, we estimate heart and lung dose when target coverage is not compromised in consecutive breast cancer patients receiving loco-regional irradiation to guide the choice of dose selection criteria for the DBCG Proton Trial. The choice of dose selection criteria was based on these heart and lung dose estimates in combination with capacity limitations for proton therapy and considerations of dose–response relationships for heart and lung. The trial is open for international participation, and the trial protocol is available here [30].

2. Materials and methods

2.1. Patients

Patient data were collected retrospectively from 18 radiotherapy departments in six European countries including all seven Danish departments (see list of departments in [Supplementary Materials](#)). Breast cancer patients who were treated with whole breast or chest wall loco-regional radiotherapy including IMN were included in the study. Tumour bed boosts were allowed. Each department identified in May/June 2018 the five most recently treated patients with left-sided breast cancer and the five most recently treated patients with right-sided breast cancer for the retrospective analysis. If patients were re-planned during the course, the plan used for most fractions was chosen. Target contour delineations were performed following the ESTRO consensus guidelines [31]. Planning target volumes (PTV) in 3DCRT were not used in all centres; a distance of 10 mm between CTV and multileaf collimator (MLC) was applied instead.

2.2. Treatment plan modification

If fully or partly field-based planning was used (i.e. planned without target contours), missing target contours were delineated retrospectively for the purpose of this study. Target contours were re-delineated if they had been delineated without following the ESTRO consensus guidelines.

Treatment plans were modified if they did not comply with the DBCG constraints below for the clinical target volumes (CTV):

- a) 95% of the IMN CTV covered by 90% dose
- b) 95% of the lymph node CTV covered by 90% dose
- c) 95% of the whole breast CTV or chest wall CTV covered by 95% dose

Treatment plan modifications were made at the treating department. Modifications for 3D conformal radiotherapy (3DCRT) technique was performed by re-fitting the MLC to cover the whole target if parts of the target had been shielded by the MLC to reduce dose to heart or lung (see [Fig. 1](#)). Extra segments were added if the modified treatment plan still did not comply with the defined target constraints. Treatment plan modifications for inverse planning techniques were made by re-optimising the plan such that it met the defined target constraints.

2.3. Data reporting

Dose-volume data were reported as DICOM files through the Danish treatment plan bank (seven departments), by text files with dose-volume histogram data (five departments) or by dose reporting scheme (six departments) during May and June 2018. See dose reporting schemes in [Table A1–A3 in Supplementary Materials](#). The following additional information about the treatment was reported: laterality, surgery, irradiated lymph node levels, number of intercostal spaces in the IMN CTV, dose-fractionation scheme, boost, treatment planning technique, use of breath-hold or gating,

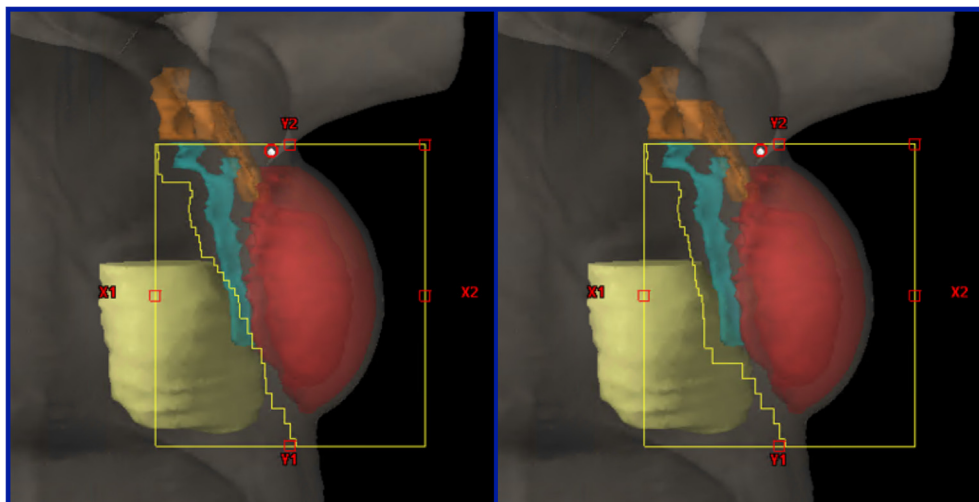


Fig. 1. Example of 3DCRT plan modification from beams eye view. Clinical treatment plan (left panel): The heart (yellow structure) is shielded by the multileaf collimators, and the IMN (cyan structure) are partially shielded. Modified treatment plan (right panel): the IMN are fully covered. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and whether the treatment plan had been modified to meet the defined target constraints. Dose-volume data from treatment plans prior to modification were not included. Mean doses to heart and lung were re-normalised to prescription dose of 40 Gy such that mean doses from 50 Gy plans were reduced to 80% in [Fig. A1 in Supplementary Material](#).

2.4. Choice of patient selection criteria

The DBCG Radiotherapy Committee chose to focus on heart and lung dose estimates from departments having 3DCRT and DIBH or enhanced inspiration gating (EIG) [15] as standard since these techniques by far are the most predominant in all Danish departments. To simplify the use of the selection criteria in daily clinical routine, the Committee decided that the dose thresholds should be the same for normofractionated and moderate hypofractionated dose-fractionation schemes and that the thresholds should be integer numbers. To guide the choice of patient selection criteria, the DBCG Radiotherapy Committee balanced the estimated number of eligible patients for different dose thresholds with limitations in capacity for proton therapy at the Danish Centre for Particle Therapy and the current knowledge of dose–response relationships for heart [6–10] and lung [11,12]. The assumptions regarding the number of eligible patients needed were as follows: We assumed that the majority of patients with excessive heart and lung exposure would be patients requiring loco-regional irradiation and additional patients with synchronous bilateral breast cancer or with complex anatomy, such as pectus excavatum [32]. The capacity limitation at Danish Centre for Particle Therapy was approximately 100 patients per year corresponding to 200 patients included in the trial each year when randomising patients 1:1. We assumed that roughly 75% of the eligible patients would willing to participate in the trial. More than 3500 breast cancer patients receive adjuvant radiotherapy in Denmark each year, and approximately 35% of the patients have indication for loco-regional irradiation. Following these assumptions, we should identify roughly 22% of the patients requiring loco-regional irradiation (corresponding to approximately 8% of all breast cancer patients referred to radiotherapy) as candidates for proton therapy.

3. Results

A total of 180 breast cancer patients treated with adjuvant loco-regional radiotherapy including the IMN were included in the study. One patient was excluded due to technical problems with data reporting. The prescription dose ranged from 39.9 Gy to 51.52 Gy in 15 to 28 fractions. Planning techniques included 3DCRT and several inversely optimised techniques: volumetric modulated arc therapy (VMAT), hybrid planning technique (combination of 3DCRT and VMAT), intensity modulated tomotherapy and step & shoot intensity modulated radiotherapy (IMRT) + static supraclavicular field. Sixty-three percent of the patients were treated in DIBH or EIG. Nine of the participating departments aimed at treating patients with 3DCRT using DIBH/EIG; 98% of the patients from these nine departments were treated with 3DCRT and 93% of them were treated using DIBH/EIG. Forty out of 90 plans were normofractionated and 50 were hypofractionated. The remaining nine departments treated mainly patients with inverse optimised techniques; 98% of these patients were treated with inverse optimised techniques, and 31% of the patients were treated using DIBH/EIG.

Target contours were (re-)delineated in 30 treatment plans from three departments, and these plans were all modified to fulfil the DBCG target coverage constraints. Additional 41 treatment plans needed modification to comply with the target coverage constraints. Treatment characteristics are provided in [Table 1](#).

It was not possible to achieve the required coverage of the whole breast or chest wall CTV (95% of the whole breast or chest wall CTV should be covered by 95% dose) for five patients in whom V95% (the volume percentage that received 95% of the prescription dose) ranged from 87% to 94% due to underdosage in superficial parts of the target.

In the revised treatment plans, median mean heart dose was 3.0 Gy (range, 1.1 to 8.2 Gy) for left-sided breast cancer and 1.4 Gy (0.4 to 11.5 Gy) for right-sided breast cancer (see [Fig. 2](#)). Median mean heart dose was 2.8 Gy (1.1 to 7.4 Gy) for left-sided breast cancer using DIBH or EIG (35% of all patients) and 5.2 Gy (2.2 to 8.2 Gy) for left-sided breast cancer not using DIBH or EIG (15% of all patients). Median mean dose to ipsilateral lung was 13.4 Gy (5.1 to 24.9 Gy). Median V17Gy/V20Gy (V17Gy for hypofractionated plans and V20Gy for normofractionated plans) for ipsilateral lung was 31% (9 to 57%). [Fig. A1 in Supplementary](#)

Table 1

Treatment characteristics. *50 Gy in 25 fractions included patients receiving 51.52 Gy in 28 fractions (n = 3), 40 Gy in 15 fractions included patients receiving 42.3 Gy in 18 fractions (n = 2) and other dose-fractionation schemes included 42.56 Gy in 16 fractions (n = 3), 45.57 Gy in 21 fractions (n = 4), 44.6 Gy in 22 fractions (n = 1) and 50.4 Gy in 28 fractions (n = 1). †All boosts were simultaneous integrated boosts. ‡DIBH (n = 102) and EIG (n = 10). §Partly field-based planning used i.e. lymph node target was not delineated (n = 20), and initial target delineations did not follow the ESTRO consensus guidelines (n = 10). ¶30 out of 71 treatment plans had modified target delineations. Abbreviations: n, number of patients; 3DCRT, 3D conformal radiotherapy; VMAT, volumetric modulated arc therapy; IMRT, intensity modulated radiotherapy; SCF, supraclavicular field; DIBH, deep inspiration breath-hold; EIG, enhanced inspiration gating; IMN, internal mammary nodes.

| | n (%) |
|-------------------------------------|------------|
| Laterality | |
| Left-sided breast cancer | 89 (50%) |
| Right-sided breast cancer | 90 (50%) |
| Dose-fractionation scheme* | |
| 50 Gy in 25 fractions | 69 (39%) |
| 40 Gy in 15 fractions | 101 (56%) |
| Other dose-fractionation schemes | 9 (5%) |
| Tumour bed boost | |
| Yes† | 12 (7%) |
| No | 167 (93%) |
| Treatment technique | |
| 3DCRT | 90 (50%) |
| VMAT | 26 (15%) |
| Hybrid | 17 (9%) |
| Intensity modulated tomotherapy | 35 (20%) |
| Step & shoot IMRT + static SCF | 11 (6%) |
| DIBH or EIG | |
| Yes‡ | 112 (63%) |
| No | 67 (37%) |
| Surgery | |
| Lumpectomy | 65 (36%) |
| Mastectomy | 95 (53%) |
| Mastectomy + reconstruction | 19 (11%) |
| Treated lymph node levels | |
| IMN | 179 (100%) |
| Axilla level 1 | 60 (34%) |
| Axilla level 2 | 131 (73%) |
| Axilla level 3 | 177 (99%) |
| Lymph node level 4 | 177 (99%) |
| Interpectoral nodes | 83 (46%) |
| Modified target delineations | |
| Yes§ | 30 (17%) |
| No | 149 (83%) |
| Modified treatment plan | |
| Yes¶ | 71 (40%) |
| No | 108 (60%) |

Material shows mean doses for heart and ipsilateral lung re-normalised to a prescription dose of 40 Gy in 15 fractions.

The percentage of plans exceeding several heart and lung dose thresholds in departments having 3DCRT and DIBH/EIG as standard can be seen [Table 2](#). The DBCG Radiotherapy Committee decided that the patient selection criteria for the DBCG Proton Trial were mean heart dose ≥ 4 Gy and/or ipsilateral lung V17Gy/V20Gy $\geq 37\%$ corresponding to 22% of the patients (20 out of 90 patients) being eligible for the trial. Twelve of these 20 patients had left-sided breast cancer, 11 had a mean heart dose ≥ 4 Gy (9 out of 11 had left-sided breast cancer) and 12 had lung V17Gy/V20Gy $\geq 37\%$. For the nine departments using inversely optimised treatment techniques as standard, 54% of the patients had mean heart dose ≥ 4 Gy and/or lung V17Gy/V20Gy $\geq 37\%$. In total, 68 of out of 179 patients exceeded the dose thresholds for heart and lung defined in patient selection criteria for the DBCG Proton Trial.

4. Discussion

This retrospective study estimates heart and lung doses when target coverage is not compromised in 179 high-risk breast cancer patients receiving loco-regional IMN radiotherapy. Sixty percent of the treatment plans did already comply with the delineation requirements and the DBCG target coverage constraints, and, thus, 60% of the reported heart and lung doses were from clinically delivered treatment plans. The need for treatment plan modification was seen among most participating departments implying that compromises on target coverage to lower the dose to the organs at risk were routinely performed in daily clinic despite of reduced probability of disease control [2–5,33]. For the purpose of this study, these treatment plans were modified to meet target coverage constraints according to DBCG guidelines and the quality of these plans is therefore variable. Still, we believe that this method was the best way to provide the dose estimates needed to guide the choice of selection criteria for the DBCG Proton Trial.

Various treatment planning techniques were used for the patients in the participating departments. As a result, after recognising the heterogeneity among the treatment plans, we decided to guide our selection criteria based on departments aiming for treatment with 3DCRT in DIBH/EIG. In this work we have presented the full range of data analyzed in the process of setting up the inclusion criteria. This is done to illustrate the wide range of OAR doses seen in actual clinical use in the participating centers, which both informed our process and may be of interest to the community in general. For setting up the actual inclusion criteria we chose to focus on 3DCRT plans, as this is by far the dominant technique used in the Danish sites, which will include patients in the study. The reason for not simply use all patients treated with 3DCRT in DIBH was that difficult patient anatomies were usually handled with VMAT or hybrid planning technique in these departments and not all patients can comply with DIBH. Tumour bed boosts might come with increased exposure of heart and lung. However, we chose not to exclude patients receiving tumour bed boosts in this study since these patients reflected the variation in heart and lung irradiation seen across patients in the clinic. It was not possible to obtain the required target coverage for five patients, but we decided not to exclude these patients to resemble the heterogeneity among patient anatomies in daily clinical routine.

To ease the use of the patient selection criteria in daily clinical practice, the DBCG Radiotherapy Committee decided to choose integer numbers as dose thresholds that were independent of 40 Gy in 15 fractions or 50 Gy in 25 fractions [34]. This implies that the 4 Gy mean heart dose threshold is 10% of prescription dose for 40 Gy treatments and 8% of prescription dose for 50 Gy treatments. Thus, it can be argued that it is more unbiased to use a relative heart dose threshold or even an equivalent dose in 2 Gy fractions (EQD2) threshold. On the other hand, from an EQD2 point of view, the 4 Gy mean heart dose threshold is, within reasonable uncertainties, about equivalent between the two dose-fractionation schemes, even though it is not the actual EQD2 dose but rather the physical dose. A V17Gy threshold for 40 Gy treatments and a V20Gy for 50 Gy treatment were used following DBCG lung constraints. Breast only radiotherapy data from DBCG HYPO Trial have recently shown similar values when using V17Gy in 40 Gy plans and V20Gy in 50 Gy plans [35] suggesting that a shared dose metric can be used for both fractionation schemes. The DIBH technique has the potential to reduce dose to heart and lung [13,14] and should be examined before considering proton therapy for the patient.

Modern loco-regional radiotherapy for breast cancer is associated with high survival rates and most patients become long-

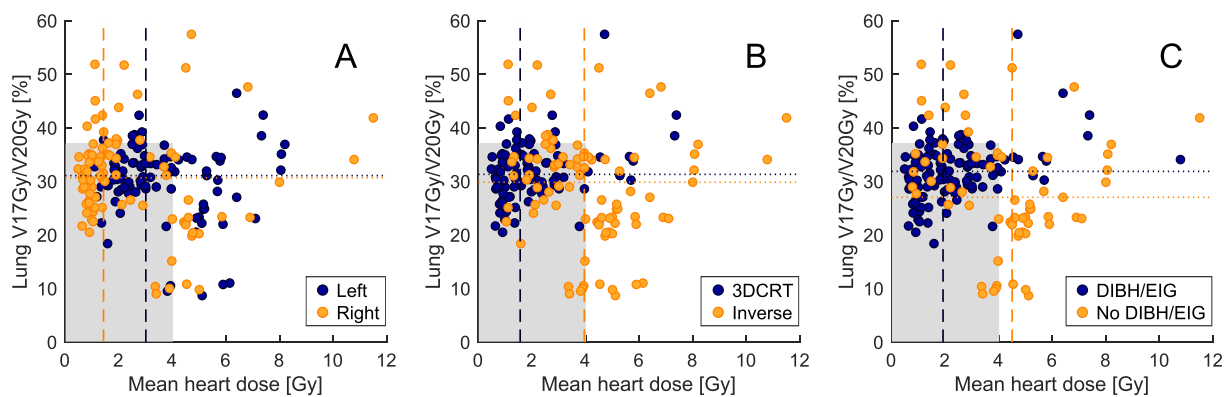


Fig. 2. Each panel shows mean heart dose versus V17Gy/V20Gy for ipsilateral lung for the 179 revised treatment plans fulfilling the DBCG target coverage constraints. The patients are divided in categories: A) left- versus right-sided breast cancer, B) 3DCRT versus inverse treatment techniques and DIBH and EIG versus no DIBH or EIG (right panel). The dashed lines represent the median mean heart dose for each category, and the dotted lines represent the median ipsilateral lung V17Gy/V20Gy for each category. The grey areas show patients with doses lower than the mean heart dose = 4 Gy and lung V17Gy/V20Gy = 37% thresholds.

Table 2

Percentage of patients exceeding heart and/or lung dose thresholds in departments having 3DCRT and DIBH/EIG as standard. Note that only one of the two thresholds needs to be exceeded. Based on the defined dose thresholds for the DBCG Proton Trial (mean heart dose ≥ 4 Gy and/or lung V17Gy/V20Gy $\geq 37\%$), 22% of the breast cancer patients treated with loco-regional RT including the IMN are eligible for participation in the trial.

| MHD Ipsilateral lung V20Gy/V17Gy | >1 Gy | >2 Gy | >3 Gy | >4 Gy | >5 Gy | >6 Gy |
|----------------------------------|-------|-------|-------|-------|-------|-------|
| >25% | 94% | 92% | 92% | 91% | 91% | 91% |
| >30% | 84% | 72% | 67% | 63% | 63% | 63% |
| >35% | 73% | 49% | 34% | 28% | 24% | 20% |
| >36% | 72% | 48% | 32% | 26% | 22% | 18% |
| >37% | 72% | 46% | 29% | 22% | 19% | 14% |
| >38% | 72% | 41% | 24% | 18% | 14% | 10% |
| >39% | 72% | 41% | 24% | 18% | 14% | 10% |
| >40% | 72% | 40% | 22% | 16% | 12% | 8% |
| >45% | 71% | 38% | 19% | 12% | 9% | 4% |

term cancer survivors [2,4,5]. This means that even small excess absolute risks for late radiation-induced toxicity should be considered. The study by Darby et al. estimates that a mean heart dose of 4 Gy in a 50-year-old breast cancer patient with cardiac risk factor would increase her risk of experiencing an acute coronary event before the age of 80 years from 8.0% to 10.2% and increase her risk of death from ischemic heart disease before the age of 80 years from 3.4% to 4.3% [6]. Likewise, the study by Taylor et al. estimates that a mean lung dose of 5 Gy to the whole lung in a 50-year-old ever-smoker breast cancer patient would increase her risk of death from lung cancer before age of 80 years from 9.4% to 13.8% [12].

The DBCG Radiotherapy Committee did consider using predicted benefit in normal tissue complication probability (NTCP) for patient selection in the DBCG Proton Trial following the Dutch model-based proton selection strategy [36,37] of radiation-induced ischemic heart disease as criteria. In the Netherlands breast cancer patients can be referred to proton therapy if they have a predicted Δ NTCP $\geq 2\%$ of acute coronary event at age 80 as defined in the study by Darby et al. [6]. Model-based selection allows the inclusion of patient-specific factors, such as age and cardiac risk factors. However, it was decided to use only dosimetric parameters due to large uncertainties in the risk modelling (especially, if including cardiac risk factors). Hopefully, the extensive data collection of baseline information about lifestyle and comorbidities in the DBCG Proton Trial will provide data for establishing NCTP models in the future. The UK Breast Proton Beam Therapy Group will use internationally harmonised dose thresholds (mean heart dose of ≥ 4 Gy and/or ipsilateral lung V17Gy $\geq 35\%$) in the trial PARABLE (Proton beAm theRApy in patients with Breast cancer: Evaluating early and Late-Effects). The committee acknowledges that there is currently no optimal objective answer to the

best patient selection criteria for proton therapy. The DBCG Proton Trial has recruited patients since June 2020.

In conclusion, breast cancer patients (including patients referred to breast only radiotherapy or with bilateral breast cancer) with a mean heart dose of ≥ 4 Gy and/or ipsilateral lung V17Gy/V20Gy $\geq 37\%$ are candidates for the randomised DBCG Proton Trial. We estimate that 22% of all patients requiring loco-regional IMN radiotherapy will be eligible for the trial in departments treating with 3DCRT in breath-hold.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2021.01.012>.

References

- [1] Budach W, Bölke E, Kammers K, Gerber PA, Nestle-Krämling C, Matuschek C. Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update. *Radiat Oncol* 2015;10:1–7. <https://doi.org/10.1186/s13014-015-0568-4>.
- [2] Poortmans PM, Collette S, Kirkove C, Van Limbergen E, Budach V, Struikmans H, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. *N Engl J Med* 2015;373:317–27. <https://doi.org/10.1056/NEJMoa1415369>.
- [3] Poortmans P, Collette S, Struikmans H, De Winter K, Van Limbergen E, Kirkove C, et al. Fifteen-year results of the randomised EORTC trial 22922/10925

- investigating internal mammary and medial supraclavicular (IM-MS) lymph node irradiation in stage I-III breast cancer. *J Clin Oncol* 2018;36:504–504. DOI:10.1200/JCO.2018.36.15_suppl.504.
- [4] Whelan TJ, Olivetto IA, Parulekar WR, Ackerman I, Chua BH, Nabid A, et al. Regional nodal irradiation in early-stage breast cancer. *N Engl J Med* 2015;373:307–16. <https://doi.org/10.1056/NEJMoa1415340>.
- [5] Thorsen LBJ, Offersen BV, Danø H, Berg M, Jensen I, Pedersen AN, et al. DBCG-IMN: a population-based cohort study on the effect of internal mammary node irradiation in early node-positive breast cancer. *J Clin Oncol* 2016;34:314–20. <https://doi.org/10.1200/JCO.2015.63.6456>.
- [6] Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–98. <https://doi.org/10.1056/NEJMoa1209825>.
- [7] van den Bogaard VAB, Ta BDP, van der Schaaf A, Bouma AB, Middag AMH, Bantema-Joppe EJ, et al. Validation and modification of a prediction model for acute cardiac events in patients with breast cancer treated with radiotherapy based on three-dimensional dose distributions to cardiac substructures. *J Clin Oncol* 2017;35:1171–8. <https://doi.org/10.1200/JCO.2016.69.8480>.
- [8] Laugaard Lorenzen E, Christian Rehammar J, Jensen M-B, Ewertz M, Brink C. Radiation-induced risk of ischemic heart disease following breast cancer radiotherapy in Denmark, 1977–2005. *Radiother Oncol* 2020;152:103–10. <https://doi.org/10.1016/j.radonc.2020.08.007>.
- [9] Taylor CW, Wang Z, Macaulay E, Jaggi 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;93:845–53. <https://doi.org/10.1016/j.ijrobp.2015.07.2292>.
- [10] Milo MLH, Thorsen LBJ, Johnsen SP, Nielsen KM, Valentim JB, Alsner J, et al. Risk of coronary artery disease after adjuvant radiotherapy in 29,662 early breast cancer patients: a population-based Danish Breast Cancer Group study. *Radiother Oncol* 2021. In press.
- [11] Grantzau T, Thomsen MS, Væth M, Overgaard J. Risk of second primary lung cancer in women after radiotherapy for breast cancer. *Radiother Oncol* 2014;111:366–73. <https://doi.org/10.1016/j.radonc.2014.05.004>.
- [12] Taylor C, Correa C, Duane FK, Aznar MC, Anderson SJ, Bergh J, et al. Estimating the Risks of Breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol* 2017;35:1641–9. <https://doi.org/10.1200/JCO.2016.72.0722>.
- [13] Nissen HD, Appelt AL. Improved heart, lung and target dose with deep inspiration breath hold in a large clinical series of breast cancer patients. *Radiother Oncol* 2013;106:28–32. <https://doi.org/10.1016/j.radonc.2012.10.016>.
- [14] Vikström J, Hjelstuen MHB, Mjaaland I, Dybvik KI. Cardiac and pulmonary dose reduction for tangentially irradiated breast cancer, utilizing deep inspiration breath-hold with audio-visual guidance, without compromising target coverage. *Acta Oncol (Madr)* 2011;50:42–50. <https://doi.org/10.3109/0284186X.2010.512923>.
- [15] Damkjær SMS, Aznar MC, Pedersen AN, Vogelius IR, Bangsgaard JP, Josipovic M. Reduced lung dose and improved inspiration level reproducibility in visually guided DIBH compared to audio coached EIG radiotherapy for breast cancer patients. *Acta Oncol (Madr)* 2013;52:1458–63. <https://doi.org/10.3109/0284186X.2013.813073>.
- [16] MacDonald SM, Patel SA, Hickey S, Specht M, Isakoff SJ, Gadd M, et al. Proton therapy for breast cancer after mastectomy: early outcomes of a prospective clinical trial. *Int J Radiat Oncol Biol Phys* 2013;86:484–90. <https://doi.org/10.1016/j.ijrobp.2013.01.038>.
- [17] Bradley JA, Dagan R, Ho MW, Rutenberg M, Morris CG, Li Z, et al. Initial report of a prospective dosimetric and clinical feasibility trial demonstrates the potential of protons to increase the therapeutic ratio in breast cancer compared with photons. *Int J Radiat Oncol Biol Phys* 2016;95:411–21. <https://doi.org/10.1016/j.ijrobp.2015.09.018>.
- [18] Verma V, Iftekaruddin Z, Badar N, Hartsell W, Han-Chih Chang J, Gondi V, et al. Proton beam radiotherapy as part of comprehensive regional nodal irradiation for locally advanced breast cancer. *Radiother Oncol* 2017;123:294–8. <https://doi.org/10.1016/j.radonc.2017.04.007>.
- [19] Luo L, Cuaron J, Braunstein L, Gillespie E, Kahn A, McCormick B, et al. Early outcomes of breast cancer patients treated with post-mastectomy uniform scanning proton therapy. *Radiother Oncol* 2019;132:250–6. <https://doi.org/10.1016/j.radonc.2018.10.002>.
- [20] Smith NL, Jethwa KR, Viehman JK, Harmsen WS, Gonuguntla K, Elswick SM, et al. Post-mastectomy intensity modulated proton therapy after immediate breast reconstruction: initial report of reconstruction outcomes and predictors of complications. *Radiother Oncol* 2019;140:76–83. <https://doi.org/10.1016/j.radonc.2019.05.022>.
- [21] DeCesaris CM, Rice SR, Bentzen SM, Jatzczak J, Mishra MV, Nichols EM. Quantification of acute skin toxicities in patients with breast cancer undergoing adjuvant proton versus photon radiation therapy: a single institutional experience. *Int J Radiat Oncol Biol Phys* 2019;104:1084–90. <https://doi.org/10.1016/j.ijrobp.2019.04.015>.
- [22] Jimenez RB, Hickey S, DePauw N, Yeap BY, Batin E, Gadd MA, et al. Phase II study of proton beam radiation therapy for patients with breast cancer requiring regional nodal irradiation. *J Clin Oncol* 2019;37:2778–85. <https://doi.org/10.1200/JCO.18.02366>.
- [23] Mutter RW, Remmes NB, Kahila MM, Hoefl KA, Pafundi DH, Zhang Y, et al. Initial clinical experience of postmastectomy intensity modulated proton therapy in patients with breast expanders with metallic ports. *Pract Radiat Oncol* 2017;7:e243–52. <https://doi.org/10.1016/j.prrro.2016.12.002>.
- [24] Stick LB, Yu J, Maraldo MV, Aznar MC, Pedersen AN, Bentzen SM, et al. Joint estimation of cardiac toxicity and recurrence risks after comprehensive nodal proton versus proton therapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2017;97:754–61. <https://doi.org/10.1016/j.ijrobp.2016.12.008>.
- [25] Ranger A, Dunlop A, Hutchinson K, Convery H, MacLennan MK, Chantler H, et al. A dosimetric comparison of breast radiotherapy techniques to treat locoregional lymph nodes including the internal mammary chain. *Clin Oncol* 2018;30:346–53. <https://doi.org/10.1016/j.clon.2018.01.017>.
- [26] Flejmer AM, Edwardsson A, Dohlmair F, Josefsson D, Nilsson M, Witt Nyström P, et al. Respiratory gating for proton beam scanning versus photon 3D-CRT for breast cancer radiotherapy. *Acta Oncol (Madr)* 2016;55:577–83. <https://doi.org/10.3109/0284186X.2015.1120883>.
- [27] De Rose F, Cozzi L, Meattini I, Fogliata A, Franceschini D, Franzese C, et al. The potential role of intensity-modulated proton therapy in the regional nodal irradiation of breast cancer: a treatment planning study. *Clin Oncol* 2020;32:26–34. <https://doi.org/10.1016/j.clon.2019.07.016>.
- [28] Ares C, Khan S, MacArtain AM, Heuberger J, Goitein G, Gruber G, et al. Postoperative proton radiotherapy for localized and locoregional breast cancer: potential for clinically relevant improvements? *Int J Radiat Oncol Biol Phys* 2010;76:685–97. <https://doi.org/10.1016/j.ijrobp.2009.02.062>.
- [29] Fellin F, Iacco M, D'Avino V, Tommasino F, Farace P, Palma G, et al. Potential skin morbidity reduction with intensity-modulated proton therapy for breast cancer with nodal involvement. *Acta Oncol (Madr)* 2019;58:934–42. <https://doi.org/10.1080/0284186X.2019.1591638>.
- [30] Danish Breast Cancer Group (DBCG). The DBCG PROTON Trial. Adjuvant breast proton radiation therapy for early breast cancer patients: The Skagen Trial 2, a clinically controlled randomised phase III trial 2020. https://www.dbcg.dk/images/PDF/Protokoller/Proton/DBCG_Proton_trial_hovedprotokol_version_1.1_20220_VEK_godkendt.pdf.
- [31] Offersen BV, Boersma LJ, Kirkove C, Hol S, Aznar MC, Biete Sola A, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiother Oncol* 2015;114:3–10. <https://doi.org/10.1016/j.radonc.2014.11.030>.
- [32] Milo MLH, Spejlborg H, Thorsen LBJ, Offersen BV. Pectus excavatum and adjuvant radiotherapy for early stage breast cancer: balancing dose to target versus heart. *Acta Oncol (Madr)* 2017;56:1653–6. <https://doi.org/10.1080/0284186X.2017.1354132>.
- [33] Offersen BV, Alsner J, Nielsen HM, Jakobsen EH, Nielsen MH, Krause M, et al. Hypofractionated versus standard fractionated radiotherapy in patients with early breast cancer or ductal carcinoma in situ in a randomized phase III Trial: the DBCG HYPO trial. *J Clin Oncol* 2020;38:3615–25. <https://doi.org/10.1200/JCO.20.01363>.
- [34] Ratosa I, Chirilă ME, Steinacher M, Kozma E, Vojtišek R, Franco P, et al. Hypofractionated radiation therapy for breast cancer: preferences amongst radiation oncologists in Europe – results from an international survey. *Radiother Oncol* 2021;155:17–26. <https://doi.org/10.1016/j.radonc.2020.10.008>.
- [35] Thomsen MS, Berg M, Zimmermann S, Lutz CM, Makocki S, Jensen I, et al. Dose constraints for whole breast radiation therapy based on the quality assessment of treatment plans in the randomised Danish Breast Cancer Group (DBCG) HYPO trial. Submitted 2021.
- [36] Langendijk JA, Lambin P, De Ruyscher D, Widder J, Bos M, Verheij M. Selection of patients for radiotherapy with protons aiming at reduction of side effects: the model-based approach. *Radiother Oncol* 2013;107:267–73. <https://doi.org/10.1016/j.radonc.2013.05.007>.
- [37] Langendijk JA, Boersma LJ, Rasch CRN, van Vulpen M, Reitsma JB, van der Schaaf A, et al. Clinical trial strategies to compare protons with photons. *Semin Radiat Oncol* 2018;28:79–87. <https://doi.org/10.1016/j.semradonc.2017.11.008>.