

ORIGINAL ARTICLE



Proton therapy for early breast cancer patients in the DBCG proton trial: planning, adaptation, and clinical experience from the first 43 patients

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ABSTRACT

Background: The Danish Breast Cancer Group (DBCG) Proton Trial randomizes breast cancer patients selected on high mean heart dose (MHD) or high lung dose (V20Gy/V17Gy) in the photon plan between photon and proton therapy. This study presents the proton plans and adaptation strategy for the first 43 breast cancer patients treated with protons in Denmark.

Material and methods: Forty-four proton plans (one patient with bilateral cancer) were included; 2 local and 42 loco-regional including internal mammary nodes (IMN). Nineteen patients had a mastectomy and 25 a lumpectomy. The prescribed dose was either 50 Gy in 25 fractions ($n = 30$) or 40 Gy in 15 fractions ($n = 14$) wherefrom five received simultaneous integrated boost to the tumor bed. Using 2–3 *en face* proton fields, single-field optimization, robust optimization and a 5 cm range shifter ensured robustness towards breathing motion, setup- and range uncertainties. An anatomical evaluation was performed by evaluating the dose after adding/removing 3 mm and 5 mm tissue to/from the body-outline and used to define treatment tolerances for anatomical changes.

Results: The nominal and robust criteria were met for all patients except two. The median MHD was 1.5 Gy (0.5–3.4 Gy, 50 Gy) and 1.1 Gy (0.0–1.5 Gy, 40 Gy). The anatomical evaluations showed how 5 mm shrinkage approximately doubled the MHD while 5 mm swelling reduced target coverage of the IMN below constraints. Ensuring 3–5 mm robustness toward swelling was prioritized but not always achieved by robust optimization alone emphasizing the need for a distal margin. Twenty-eight patients received plan adaptation, eight patients received two, and one received five.

Conclusion: This proton planning strategy ensured robust treatment plans within a pre-defined level of acceptable anatomical changes that fulfilled the planning criteria for most of the patients and ensured low MHD.

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KEYWORDS

Breast cancer; proton therapy; treatment planning; plan evaluation

Background

Radiation therapy (RT) of early breast cancer reduces the risk of local, regional and distant failure, and for selected patients it improves overall survival [1,2]. RT is the standard treatment following breast conserving surgery (BCS) and for all high-risk patients, which in most countries are defined by having minimum one regional node macro-metastasis or a tumor larger than 50 mm. The majority of these patients receives target coverage and low dose to organs at risk (OAR) with photon RT using conventional tangential field arrangements. This technique has many practical advantages such as high robustness toward shrinkage, swelling and other smaller day-to-day variations. However, for some anatomies, it can be challenging to provide adequate target coverage without a high dose to the heart, lung or contralateral breast despite treatment in deep inspiration breath-hold. This is especially seen when the internal mammary nodes (IMN) are a target

and for these patients, a coverage compromise is often made to achieve a lower dose to heart and lung [3]. These high-risk patients may be the best candidates for proton therapy and several comparative treatment planning studies have shown that protons can provide full target coverage and a low dose to the heart and lung for all anatomies [4–7]. Indeed, proton therapy has been introduced for selected breast cancer patients in several proton centers across the world [8–14] and randomized clinical trials are currently enrolling patients to clarify benefits and risks and refine selection criteria for future standard use of proton therapy for breast cancer patients [15,16].

The Danish Breast Cancer Group (DBCG) proton trial (NCT04291378) is a randomized trial selecting early breast cancer patients based on a high dose to the heart and the ipsilateral lung in a photon plan with full target coverage as defined per DBCG guidelines [16]. The primary endpoint is 10-year risk of ischemic heart disease. A set of criteria have

been established for the photon plan by the DBCG RT Committee, determining when a patient is eligible for the DBCG proton trial; mean heart dose (MHD) ≥ 4 Gy and/or V20 Gy/V17 Gy $\geq 37\%$ to the ipsilateral lung. This is based on an increased risk of cardiac event and secondary cancer with higher doses [3,17–21].

In this study, we present the treatment strategy at the Danish Centre for Particle Therapy (DCPT) for patients referred to proton therapy based on the DBCG proton trial selection criteria. The main focus is the planning strategy that aims at being robust toward breathing motion, setup- and range uncertainties, and a well-defined level of smaller anatomical changes. This includes how the level is determined and how an adaptive strategy evolved based on it. Furthermore, fixation, CT scanning, treatment setup, and quality assurance are discussed.

Material and methods

Patient selection

The initial consecutive 43 early breast cancer patients treated with proton therapy at DCPT between October 2019 and February 2021 were included. The patients were referred to proton therapy if the heart and lung constraints determined by DBCG [3] could not be met with a photon plan with full target coverage. The DBCG proton trial initiated accrual in June 2020 and 10/43 were randomized in the trial, while 33/43 were treated prior to the trial. Treatment prior to the trial was done in a pilot phase or if the patient despite high dose to heart/lung did not fulfill inclusion criteria (mostly previous cancers). Details about the 43 patients and 44 proton plans are shown in Table 1.

Patient positioning

The patients were immobilized in an Access™ Supine breast board from Qfix™ combined with individual VacQfix™

vacuum cushions. This created a comfortable and reproducible fixation with both arms above the head (Figure 1(a)). The breast board was pitched by either 5° or 7.5° to minimize skin folds in the neck area and to stabilize the breast position. The patient was asked to turn the head toward the healthy side to pull the chin and the esophagus away from the irradiation field.

Planning CT images were acquired during free breathing with the Siemens Somatom Definition Edge scanner, using 120 kVp and 15–30 mGy CTDIvol (32 cm). The images were reconstructed using a kernel including bone beam hardening correction. The entire breast was placed within 50 cm field of

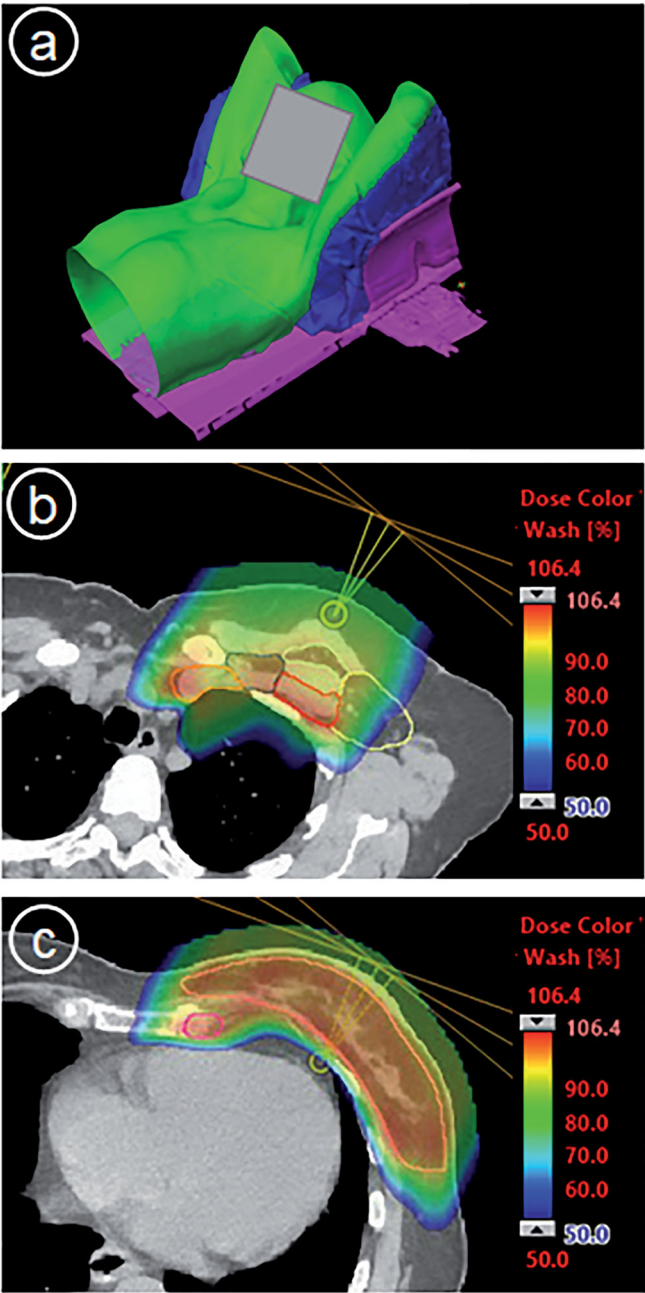


Figure 1. (a) The patient (green) in the vacuum cushion fixation (blue) in the breast board (pink). (b and c) Two CT slices from the same patient and treatment plan showing CTV delineations with dose color wash ranging from 50% to 106.4% of prescribed dose. Note that level 1 lymph nodes (yellow delineation) were not a target.

Table 1. Plan and patient details.

Number of breast plans	44
Laterality	
Left sided	36
Right sided	6
Bilateral	1
CTVp	
Chest wall	19
Whole breast	25
CTVn	
No lymph nodes	2
LN2, LN3, LN4, interpectoralis, IMN	14
LN1, LN2, LN3, LN4, interpectoralis, IMN	28
Skin irradiation	11
CTVp size (median and range)	565 cm ³ [71 cm ³ , 2826 cm ³]
Fractionation	
50 Gy (RBE) in 25 fractions	26
40 Gy (RBE) in 15 fractions	13
63 Gy (RBE) in 28 fractions	2
57 Gy (RBE) in 25 fractions	2
45.75 Gy (RBE) in 15 fractions	1
Age (median and range)	57 years [32 years;82 years]
Patient selection	
Pilot phase	33
Included in protocol	10

view ensuring a high Hounsfield Unit (HU) precision. The HU conversion to stopping power ratio (SPR) was done *via* a site-specific stoichiometric calibration curve. In addition to the planning CT, the patient received a low-dose CT scan extending beyond the elbows and with metal markings of the breast contour and scar to guide the target delineations and the position of the treatment snout. Furthermore, all patients received weekly surveillance CT scans.

Delineations

The target volumes were delineated according to ESTRO consensus guidelines [22,23]. The clinical target volume (CTV) consisted of the whole breast or chest wall (CTVp) and for most of the patients a selection of lymph nodes was included in the target (CTVn). Irradiated lymph nodes included levels 2–4, interpectoral nodes and IMN. Level 1 was included for patients with macro metastases in the axilla and less than 10 nodes removed, or if more than 6 macro-metastases were removed. The tumor bed was delineated if the patient was prescribed a simultaneous integrated boost (SIB) (BCS at age < 50 years or a resection margin < 2 mm). The CTVp was retracted 5 mm from the body outline except for patients with very narrow chest walls where 3 mm were used. If the skin around the scar following mastectomy was prescribed full dose (T3–4 tumors), it was included in the CTVp. The body structure was created using a –350 HU threshold and expanded 1 cm to include all surface pixels and forcing the dose calculation algorithm to calculate a surface dose. Delineated OARs were heart, ipsilateral lung, contralateral lung, esophagus, trachea, left anterior descending coronary artery (LADCA), thyroid gland, liver, contralateral breast and ipsilateral humeral head. The heart and LADCA were contoured according to the DBCG guidelines defined by Milo *et al.* [24]. The only delineation difference between patients referred to either photons or protons were the number of OARs.

Dose prescription

Patients without boost irradiation were prescribed 50 Gy (RBE) in 25 fractions or 40 Gy (RBE) in 15 fractions to the CTVp according to the DBCG Skagen 1 trial (NCT02384733) or clinical practice during the Covid-19 pandemic. The relative biological effectiveness (RBE) factor was fixed to 1.1 and omitted in the text hereafter. Patients receiving SIB irradiation were prescribed 63 Gy to the tumor bed and 51.52 Gy to CTVp_breast in 28 fractions or 57 Gy/50 Gy/25 fractions. The corresponding hypo-fractionated prescriptions for the SIB plans were 52.2 Gy/42.3 Gy/18 fractions or 45.75 Gy/40 Gy/15 fractions. In this study, the SIB plans are reported together with the corresponding non-SIB fractionation scheme. For non-SIB patients, the mean dose of the total CTV was normalized to the prescription dose. For boost plans, the mean dose to the tumor bed was normalized to the boost prescription dose. The dose prescriptions for the 43 patients are shown in Table 1. The DBCG planning objectives for both photon and proton plans were to cover at

least 98% of CTVp volume by 95% of the prescribed dose and at least 98% of the CTVn volume by 90% prescription dose while preferably keeping the maximum dose below 107%.

Treatment planning

All 44 plans consisted of 2–3 *en face* single-field optimized (SFO) spot scanning proton fields (Figure 1) except for one patient with breast implants, where multi-field optimization (MFO) was used. The most frequently used field angle was 35° off-normal, however an angle span of –25° to 55° relative to the normal was used. Three fields were often used for patients with large or pointy breasts. All fields were planned with a range shifter of 57 mm water equivalent material with a median central axis air gap of 27.1 cm ranging between 16.6 and 37.1 cm and limited by the ipsilateral elbow. The proton spots were placed within a volume defined by the CTV plus a field-specific margin. For the SFO plans the margin was: proximal axial margin of 0.3–0.5 cm, distal axial margin of 1.5–2.0 cm, and lateral circular margin of 2.0–3.0 cm. The proton spots were arranged in hexagonal patterns with an inter-spot distance of 0.30–0.425 times the full width at half maximum (FWHM) of the proton spot in air at the planned energy. This corresponds to distances of ~10–15 mm at low energies and ~5–7 mm at the higher energies. The energy layer spacing was fixed to 3.3 MeV. The breast or chest wall and all lymph nodes were individually, robustly optimized using the Eclipse treatment planning system v13.7 (Varian Medical Systems, Palo Alto, CA) and the non-linear universal proton optimizer (NUPO). The robust optimization was performed with 14 scenarios defined by combining 0 mm and 5 mm setup uncertainty with 3.5% range uncertainty. In addition to the targets, the heart and sometimes the humeral head were optimized robustly. The outer 3 mm of the skin was defined in a structure, and the dose was reduced with a high weighted upper dose constraint. To improve the robustness toward anatomical changes a distal margin of 5 mm was added to all targets and optimized to the corresponding CTV dose with low priority.

Two patients had breast implants: one with a known and one with an unknown implant. The SPR of the known implant (CPG™ Gel Breast Implants, Cohesive III™) had been determined experimentally to 0.935 ± 0.03 and the patient with this implant could, therefore, be treated with the same technique as patients without an implant, however, using a range uncertainty of 5% and an overwritten SPR value for the implant. For the unknown implant type, proton beams were not allowed to pass through the implant, and hence to ensure homogeneous target coverage a MFO technique with field-specific targets was used.

Plan evaluations

Prior to plan approval the nominal dose, the robustness toward setup uncertainties, range uncertainties, and anatomical changes were evaluated. The robustness toward setup

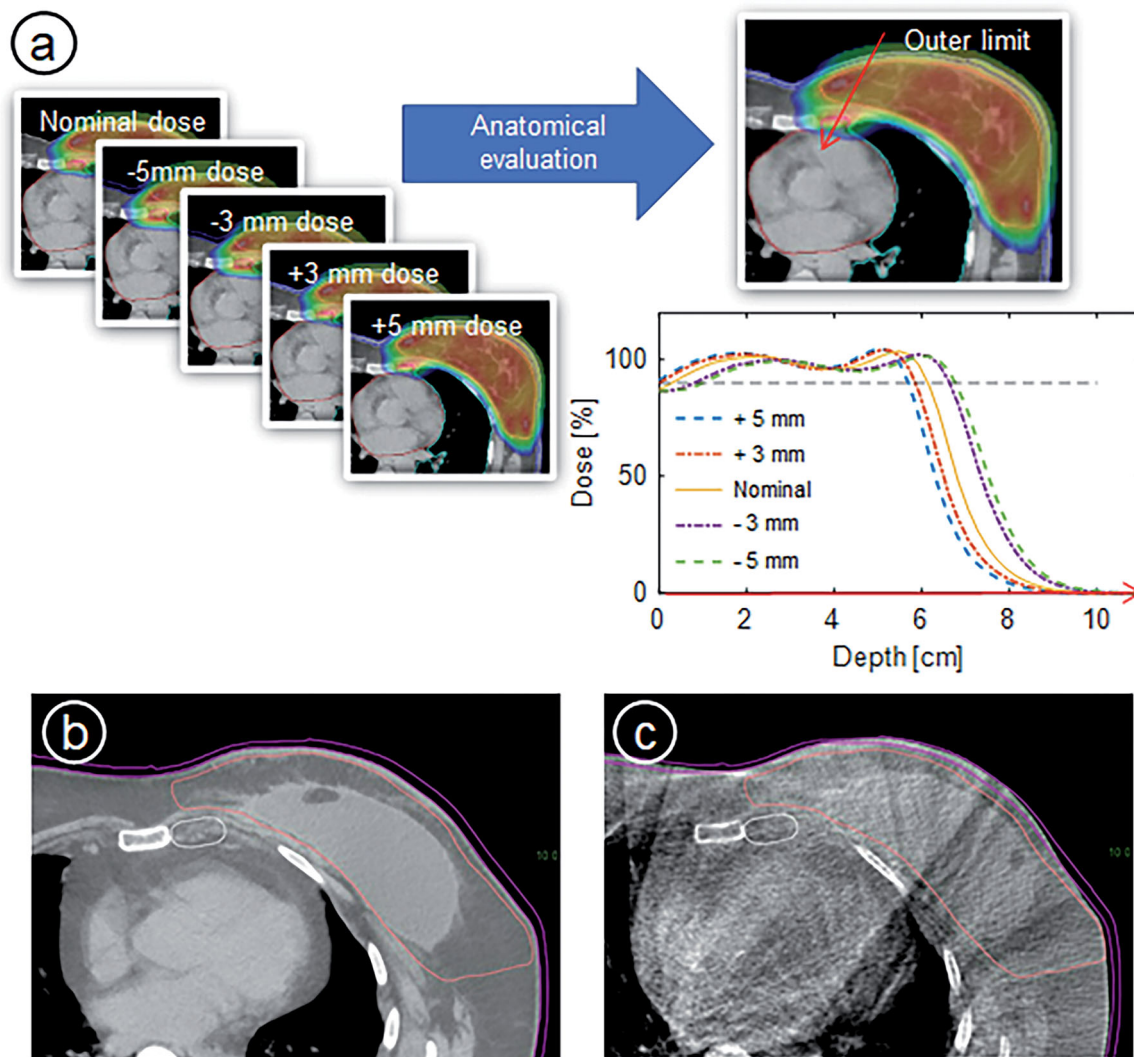


Figure 2. (a) Illustration of the four additional recalculations on artificial CTs and the construction of the structure defining the outer limit tolerance (blue). The dose profiles are extracted along the red arrow and shown in a graph. The black dashed line illustrates the 90% dose level which covers CTVn_IMN. (b and c) show CT and CBCT from a day where the patient was swollen by 5 mm reaching the outer limit structure (pink). The CTVp chest wall contour is red and the CTVn_IMN contour is white.

and range uncertainties was evaluated by calculating the dose-volume histograms (DVH) in all 14 robust scenarios for the CTVp, CTVp_tumour bed when included, CTVn_IMN, and the combined structure for all the remaining lymph nodes denoted CTVn_periclav. For the CTVp and the CTVp_tumour bed, the worst-case scenario was required to fulfill $V95\% \geq 95\%$, while for CTVn_IMN and CTVn_periclav the requirement was $V90\% \geq 95\%$. Furthermore, maximum two scenarios for the CTV_IMN were accepted being slightly below this constraint (Figure 2). The anatomical robustness evaluation was performed by creating four artificial CTs: two with 3 mm and 5 mm artificial tissue of $SPR = 1.0$ extending the outer contour of the patient and two with 3 and 5 mm removed tissue below the outer contour and overwritten by air. Hereafter, the nominal plan was recalculated and based on the achieved target dose coverage using the constraints for the nominal plan, a variable maximal tolerated outer contour (OC) was created and validated by creating a fifth artificial CT with an overwritten structure (Figure 3).

Treatment plan quality assurance

The quality control for all the treatment plans was based on measurements of dose-deposition using flat slabs of solid water and an absolute calibrated MatriXX PT (IBA Dosimetry, Schwarzenbruck, Germany). Two different depths (dose planes) were measured: 0.7 cm and an additional depth within the breast or chest wall target. The absolute dose was compared to the recalculated dose in the measurement geometry and a standard 2D global gamma analysis using 2 mm and 3% dose was performed with a passing criterion of 90%.

Treatment, image guidance and plan adaptation

The patient received a half-fan Cone Beam CT (CBCT) scan before each fraction, and a 4D match (translational and couch floor rotation) was performed and evaluated with a tolerance of 5 mm on the tissues and bones in the target area. Potential swelling or shrinkage was evaluated using

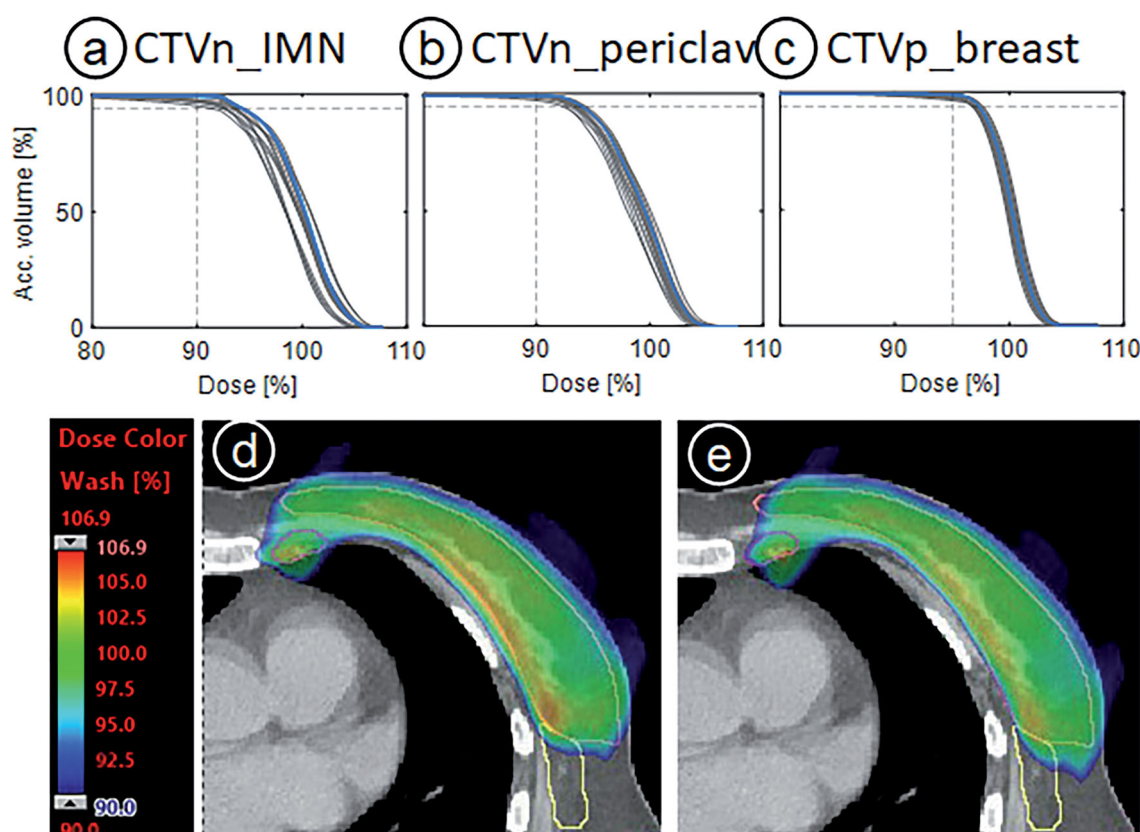


Figure 3. (a–c) Nominal DVH (blue) and DVHs for each of the 14 robust scenarios determined by 0 mm and 5 mm combined with 3.5% range uncertainty for CTVn_IMN, CTVn_periclav and CTVp_breast. The dashed lines indicate the constraint V90%=95% for the CTVn targets and V95%=95% for CTVp_breast. (d) shows the nominal dose coverage and (e) shows the worst-case scenario for the CTVn_IMN with the color wash starting at 90% dose. Note that level 1 lymph nodes (yellow delineation) were not a target.

Table 2. The median values and ranges for the target coverage, robust evaluation and anatomical evaluation.

All plans	CTVp_breast/chest wall	CTVn_IMN	CTVn_periclav
	V95%	V90%	V90%
Nominal	99.7% [96.4%; 100.0%]	100.0% [95.4%; 100.0%]	100.0% [98.9%; 100.0%]
Worst case	98.1% [94.4%; 99.5%]	95.8% [80.5%; 99.8%]	97.8% [95.3%; 99.5%]
+5 mm tissue	97.3% [86.1%; 99.5%]	89.1% [51.8%; 99.0%]	97.7% [95.2%; 99.9%]
+3 mm tissue	99.3% [96.8%; 100.0%]	96.9% [71.3%; 100%]	99.5% [89.0%; 100%]
50 Gy /25	Heart	Ipsilateral lung	
	Mean dose, Gy	Mean dose, Gy	V20Gy, %
Nominal	1.46 [0.5; 3.4]	9.6 [5.0; 13.4]	18.9 [9.2; 28.6]
Worst case	2.16 [0.97; 4.03]	13.5 [7.7; 19.4]	29.7 [16.8; 46.5]
+5 mm tissue	0.71 [0.16; 1.88]	5.7 [3.3; 8.0]	9.4 [5.4; 14.9]
+3 mm tissue	0.92 [0.26; 2.42]	7.0 [3.9; 9.6]	12.3 [6.8; 18.0]
–5 mm tissue	2.89 [0.84; 6.47]	15.3 [3.3; 24.3]	35.0 [5.4; 55.7]
–3 mm tissue	2.42 [1.13; 5.32]	13.5 [7.2; 20.4]	31.1 [15.5; 47.2]
40 Gy /15	Heart	Ipsilateral lung	
	Mean dose, Gy	Mean dose, Gy	V17Gy, %
Nominal	1.06 [0.04; 1.47]	7.9 [1.5; 10.5]	19.3 [2.2; 26.4]
Worst case	1.54 [0.08; 2.38]	11.3 [2.7; 14.8]	30.5 [6.4; 41.3]
+5 mm tissue	0.47 [0.01; 0.79]	4.7 [0.4; 6.2]	9.8 [0.1; 12.2]
+3 mm tissue	0.66 [0.01; 1.03]	6.0 [0.7; 7.2]	13.4 [0.4; 17.0]
–5 mm tissue	2.38 [0.16; 3.31]	12.9 [4.0; 19.6]	36.3 [10.5; 55.2]
–3 mm tissue	1.88 [0.011; 2.72]	11.2 [3.0; 16.2]	30.9 [7.7; 45.5]

The median values for the normal tissue doses to the heart and the ipsilateral lung split up between plans to 50 Gy (RBE) in 25 fractions and plans to 40 Gy (RBE) in 15 fractions. Relative biological effectiveness (RBE) is fixed to 1.1 and omitted in the notation within the table.

the OC structure. If the patient's OC was above the OC structure or substantially below the original body-outline, a dose recalculation was performed on an artificial CT based on overwrites using the outer contour of the day. If the target coverage or OAR doses were unsatisfying, the weekly CT scan was performed earlier.

Results

The nominal constraints were met for all plans except two. The robust plan criteria were met for all plans and targets, and the allowed 1–2 scenarios below the V90% ≥ 95% constraint for CTVn_IMN was used in 13 plans. Details on dose coverage of targets and OARs are provided in Table 2.

The robust evaluation showed that the worst-case heart and lung doses were substantially higher than the nominal. This occurred as the dose gradient at the distal edge was very steep, and the two OARs were located at the distal edge.

In the anatomical evaluation (Figure 3), the nominal coverage criteria were used to determine if 3 mm or 5 mm swelling was acceptable for the target structure. For most patients, a 5 mm swelling was tolerated for the CTVp, while for the CTVn_IMN, the coverage was often only robust to 3 mm swelling of the pre-sternal subcutaneous tissue. While swelling was especially critical for the target coverage, shrinkage had a high impact on the dose to the OAR. The calculations showed that the MHD was increased by 100–120% and the mean ipsilateral lung dose by 60–70% for 5 mm shrinkage, and 65–75% and 40–50%, respectively, for 3 mm shrinkage (Table 2).

Two-third of the patients received a plan adaptation, hereof 29% two adaptations and one patient five adaptations. Most of the adaptations were due to swellings caused by either physiological changes or systematic changes in the immobilization of the ipsilateral arm leading to an increased breast size. A total of 40 plan adaptations were made: 12 due to shrinkage, 24 due to swelling, and 4 for other reasons, such as a high maximum dose or other smaller adjustments. For most patients, the anatomical changes evolved over 5–6 days or more, while for patients with seroma the change could be on daily basis. There was no trend when the changes occurred during the course of treatment. Two patients referred to irradiation shortly after surgery, had their seroma drained several times weekly, leading to plan adaptations that swapped back and forth between plans on CT scans with either high or low filling.

All treatment plans passed the gamma evaluation criterion in the 7 mm depth. For some patients with large fields, an over-dosage was seen in a limited area in the center of the field of up to 4–5%. The measurements here were challenged by being close to the steep dose gradient and, therefore, sensitive to the daily variations of the machine output. Furthermore, large fields with a large air gap to the range shifter were seen during commissioning to deliver up to 3% higher doses, however, showing a very precise dose at the surface. This was all acceptable as the areas with hot spots (103–106%) in the treatment plans were in the lateral parts of the breast.

Discussion

The DBCG proton trial planning strategy follows the strategy from prior planning studies, showing that *en face* beams delivered during free breathing are robust towards the breathing motion [5,7,25–27]. The amount of tissue the proton penetrates will not change substantially within the breathing cycle. Combined with robustly optimized SFO and a range shifter the robustness is improved further [28]. This was confirmed on dose recalculation on 4DCT scans on the first 26 of the 43 patients in this study (manuscript in preparation).

The Achilles heel of proton therapy is the sensitivity to anatomical changes. We have shown that it is not possible to use the 5 mm setup uncertainty or the 3.5% range uncertainty to explicitly define the numerical value for the treatment tolerances for anatomical changes to the patient contour. The robust optimizer adds coverage in the depth based on the increased water equivalent distance (WED) to target with the range uncertainty and potentially increased WED from the isocenter shifts. This amount depends strongly on the target size and shape. For example, the distal target coverage will increase by 2 mm using 3.5% uncertainty for a 6 cm thick breast and using this margin for anatomical changes will leave no margin for the systematic errors propagated from the conversion from HU to SPR and finally to a range. The robustness toward anatomical changes must, therefore, be included in the planning *via* a margin and an extra evaluation must be performed to determine the individual tolerances. While swelling has a clear influence on the target coverage, shrinking will cause the end of range spots to reach the normal tissue, and place a potential high RBE dose in the heart and/or lung. Although clinical evidence is sparse, this could have adverse effects for the patients thus shrinkage must be monitored and reacted upon. This is one of the reasons why the expected advantage of protons in terms of reduction in cardiac morbidity needs validation in clinical trials [29,30]. These types of anatomical changes are usually not an issue for the photon RT. If the hypo-fractionation scheme with 26 Gy in 5 fractions is brought into the proton clinic, CBCT and adaptive planning would become even more important for breast cancer patients [31]. Furthermore, the use of neo-adjuvant chemotherapy instead of 24 weeks of adjuvant treatments will add further challenges with seroma changes at the time for RT, because the neo-adjuvant patients are operated shortly before RT.

When defining the robust evaluation objectives at DCPT, the volume percentage was chosen to be 95% and not 98% as for the nominal plan. The robustness was often 98% for the CTVp and the CTVn_periclav, however, increasing the robustness to 98% for the CTVn_IMN had major consequences for the heart dose. It could also be challenging to increase the robustness for the patients with a large or pointy CTVp in the areas where the breast contour was parallel to the proton trajectory.

The median MHD for the patients in this study was higher than the anticipated 0.5 Gy, as estimated in the DBCG proton trial based on results from a Danish treatment planning study [6]. Several planning and clinical studies report heart doses in this low range even for patients where the IMNs are included [4,5,7,8]. It was challenging to compare this study to studies performed without constraints for the robust evaluation, as our experience was that robust evaluations were responsible for the higher dose in the heart. Furthermore, the patients in the DBCG Proton trial were selected and, in some cases, the conventional photon plan MHD was well above 10 Gy for full target coverage. Optimizing robustly and reporting the robust coverage to a combined lymph node structure, may disguise a poor robust coverage of especially the IMN. The IMN is a small, elongated

structure, and often the hardest for the optimizer to cover robustly without increasing the dose of the heart, which often will be given a high penalty due to the constraints.

It became evident during planning that the spot size had a large impact on how challenging a plan was to make. This was due to the definition of the inter-spot distance which would result in an exceptionally large distance between the low energy spots resulting in too few spots and, therefore, causing hot and cold spots at the lateral edges of the CTVp. This was named “shark bites” due to the resemblance. Reducing the spot-distance could for some patients solve the problem, however, it could result in an excess of spots at high energy. Consequently, for a few patients, we chose to use 8 mm fixed distance between the spots.

Weekly CT scans were acquired for the first 43 patients, but hereafter replaced by daily assessments of CBCT scans using the OC structure and subsequently documentation in a dedicated electronic chart. All changes causing the patient contour to intersect the OC structure in more than three CBCT slices or retract below the original body-outline by more than 3 mm in more than three CBCT slices are documented. When three similar, consecutive changes are registered, a physicist performs an evaluation to determine if the observed changes are real, systematic, due to anatomical changes or if they are due to reversible deformations from, for example, the immobilization of the arm. This leads to a new immobilization strategy, an increased tolerance for swelling/shrinkage or a referral to a CT scan and plan adaptation.

Delivering proton therapy to early breast cancer patients can be challenging for a proton clinic due to the dosimetric consequences from anatomical changes. It is, however, possible to create treatment plans that are robust toward a certain level of changes and determine this level upfront in order to keep the clinical workflow efficient. Adaptations must, however, be performed if anatomical changes are detected, as the consequence for the target coverage or the OAR doses are substantial.

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Disclosure statement

The authors report no conflicts of interest.

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