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Original Article

Model-Based Selection for Proton Therapy in Breast Cancer: Development of the National Indication Protocol for Proton Therapy and First Clinical Experiences

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Abstract

Aims: Proton therapy is a radiation technique that yields less dose in normal tissues than photon therapy. In the Netherlands, proton therapy is reimbursed if the reduced dose to normal tissues is predicted to translate into a prespecified reduction in toxicity, based on nationally approved validated models. The aim of this paper is to present the development of a national indication protocol for proton therapy (NIPP) for model-based selection of breast cancer patients and to report on first clinical experiences.
Materials and methods: A national proton therapy working group for breast cancer (PWG-BC) screened the literature for prognostic models able to estimate the individual risk of specific radiation-induced side-effects. After critical appraisal and selection of suitable models, a NIPP for breast cancer was written and subjected to comments by all stakeholders. The approved NIPP was subsequently introduced to select breast cancer patients who would benefit most from proton therapy.
Results: The model of Darby *et al.* (N Engl J Med 2013; 368:987–82) was the only model fulfilling the criteria prespecified by the PWG-BC. The model estimates t*he relative* risk of an acute coronary event (ACE) based on the mean heart dose. The absolute lifetime risk of ACE <80 years was calculated by applying this model to the Dutch absolute incidence of ACE for female and male patients, between 40 and 70 years at breast cancer radiotherapy, with/without cardiovascular risk factors. The NIPP was approved for reimbursement in January 2019. Based on a threshold value of a 2% absolute lower risk on ACE for proton therapy compared with photons, 268 breast cancer patients have been treated in the Netherlands with proton therapy between February 2019 and January 2021.
Conclusion: The NIPP includes a model that allows the estimation of the absolute risk on ACE <80 years based on mean heart dose. In the first 2 years, 268 breast cancer patients have been treated with proton therapy in The Netherlands.

Key words: Acute coronary events; breast cancer; cardiac toxicity; model-based selection; prognostic models; proton therapy

Abbreviations: PT, Proton therapy; PWG-BC, Proton therapy working group Breast Cancer; BC, Breast Cancer; NIPP, National Indication Protocol Proton therapy; ACE, Acute Coronay Events; MHD, Mean Heart Dose; NTCP, Normal Tissue Complication Probability; OAR, Organ at Risk.

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Introduction

Proton therapy is a radiation technology that yields less dose to normal tissues without jeopardising the target dose compared with photon therapy. Despite the lower dose to the normal tissues, randomised clinical trials (RCT) showing the actual clinical benefit of proton therapy compared with photon therapy are scarce, whereas the costs of proton therapy are around two times higher than with photons [1]. In the Netherlands, few standard indications have been defined for which proton therapy is always reimbursed, i.e. paediatric tumours, eye tumours and chondromas/chondrosarcomas. For other indications, it has been postulated that proton therapy can be cost-effective, if the superior dose distribution indeed translates into a clinically relevant decrease in the risk of radiation-induced side-effects [2]. Consequently, for most adult patients, proton therapy is only reimbursed by the health insurance for selected patients. For each individual patient, the risk of a specific side-effect (i.e. the normal tissue complication probability; NTCP) has to be estimated for both the proton therapy plan and the photon plan, and proton therapy is reimbursed only if the difference (i.e. ΔNTCP) exceeds a predefined threshold [3]. The estimation of the NTCP has to be made based on nationally approved NTCP models, i.e. prediction models describing the relationship between dose distributions and the risk of a certain toxicity. The threshold of the required ΔNTCP decreases with an increase in severity of toxicity: for grade 2 toxicity (Common Terminology Criteria for Adverse Events; CTCAE) the ΔNTCP should be $\geq$10%, for grade 3 toxicity $\geq$5% and for grade 4 or 5 $\geq$2%. In the case of multiple grade 2 side-effects, the sum of the ΔNTCP should be $\geq$15%, with at least $\geq$5% per side-effect; for multiple grade 3 side-effects the sum of ΔNTCP has to be $\geq$7.5%, with at least 2.5% per side-effect [4]. To allow validation of the added value of proton therapy using model-based clinical evaluation as an alternative for RCTs and for the validation of the NTCP models when used among patients treated with proton therapy, side-effects have to be prospectively scored in the proton therapy centres [4]. Currently, three centres provide proton therapy in The Netherlands: UMC Groningen Proton Therapy Centre, Holland Proton Therapy Centre in Delft and Maastro Proton Therapy in Maastricht.

When irradiating patients for breast cancer, the most important organs at risk to spare are the heart, lungs and contralateral breast. With current modern photon radiation techniques, the dose to these organs at risk is low in most breast cancer patients [5–7], such that the risk of radiation-induced side-effects is relatively low [7,8]. Treatment planning comparative studies showed that proton therapy plans usually yield a lower dose to the heart, lungs and contralateral breast [6,9–11]. In a specific subset of patients, i.e. in patients with an adverse anatomy (e.g. like a pectus excavatum), patients not being able to hold their breath or patients to be irradiated to the (left-sided) internal mammary chain [12–15], it is sometimes difficult to adequately spare simultaneously heart, lungs and contralateral breast even with the most advanced photon techniques. In these patients, proton therapy may offer the opportunity to yield lower doses to multiple organs at risk, which are expected to translate into a clinical benefit.

However, RCTs showing clinical benefit of proton therapy over photon therapy in breast cancer patients, are not (yet) available. One of the reasons for this lack of evidence is the assumed long latency time of the most relevant end points (>10 years), such as acute coronary event (ACE) and secondary tumour induction. Several smaller cohort studies with proton therapy, mainly single institute studies, indicate good local control, with low normal tissue toxicity [16]. Several initiatives have been taken to set-up RCTs to provide evidence for the additional value of proton therapy. The RadComp trial [17] includes all breast cancer patients treated to the nodal regions, including the internal mammary chain, with curative intent (NCT02603341), without selecting on heart dose or estimated toxicity. The Danish Breast Cancer Group (DBCG) started the DBCG Proton Trial, an RCT (NCT04291378) including patients with a mean heart dose (MHD) $\geq$ 4 Gy in their photon plan and/or a V20 of the lung of $\geq$37% [18]. In the UK, a protocol for an RCT is currently under development.

In the Netherlands, a model-based approach is used in which selection of patients for proton therapy is based on a predicted clinically relevant predefined benefit in side-effects, according to a national indication protocol for proton therapy (NIPP). The aim of the current paper is to present the development of the NIPP for breast cancer patients, and to report on the first experiences with model-based selection.

Materials and Methods

Procedure of Model Selection

In 2016, a national proton therapy working group for breast cancer (PWG-BC) was established to develop a NIPP for breast cancer patients. All members of the Dutch Platform for Radiation Therapy of Breast Cancer and of the Dutch Platform for Proton Therapy were invited to participate in the PWG-BC, to ascertain broad national input and support. The PWG-BC consisted of 10 radiation oncologists and three medical physicists; eight of the 13 members worked in a radiotherapy centre with a proton facility. In addition, an independent clinical epidemiologist (ES) (University Medical Centre Utrecht) was part of the PWG-BC, for methodological support. The PWG-BC applied the following steps:

(1) Assessment of the most relevant side-effects for patients who were expected to benefit from proton therapy (January to July 2017);
(2) Review of the literature on these side-effects, to identify whether NTCP models were available to predict the risk for the relevant side-effect, based on at least one dose-volume parameter. The quality of the models was assessed using the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) criteria [17] (July 2017 to May 2018);

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(3) One model was selected and adjusted to make it more applicable to the Dutch breast cancer population (May to September 2018);
(4) The indications for plan comparison and model-based selection were included in a NIPP, approved by the PWG-BC (January to October 2018);
(5) An invitational conference was organised, where all members of the Dutch Society of Radiation Oncology involved in breast cancer treatment were invited, as well as patient advocates, representatives of the national multidisciplinary breast cancer organ (NABON) and representative of health insurance companies. After final corrections were made in the NIPP, it was officially approved by the Dutch Society of Radiation Oncology (October 2018);
(6) The final NIPP was sent to the Dutch Health Care Institute for approval to ensure reimbursement (sent October 2018, approval January 2019).

First Clinical Experiences

The approved NIPP was used to select breast cancer patients for proton therapy, from January 2019 onwards. Radiation oncologists from all radiotherapy departments in the Netherlands can refer their patients for plan comparison (i.e. comparing the NTCP of the original photon plan with the NTCP of the corresponding proton plan), and for proton therapy if the ΔNTCP exceeds the threshold, to one of the three proton therapy centres. Requirements for target coverage of the proton and photon plans are identical: for photon plans >98% of the planning target volume has to receive >95% of the prescribed dose; the proton therapy plans are made using intensity-modulated proton therapy, and are robustly optimised and evaluated with corresponding requirements for target coverage of the clinical target volume in the voxelwise minimum dose distribution [19]. The proton therapy centres started treating breast cancer patients between February 2019 and May 2019.

Results

Assessment of the Most Relevant End Points

The PWG-BC considered cardiac injury, such as ACE, heart failure and valve disorders, radiation pneumonitis and induction of secondary tumours (mainly lung and contralateral breast cancer) as the most relevant end points, from which they could potentially expect a benefit of proton therapy over photon therapy.

Review of the Literature, Selection of a Model

Although a review of the literature showed that these end points are all related to the radiation dose [20–24], useful NTCP models for these end points fulfilling the TRIPOD criteria [25] could not be identified. As ACE were considered the most important, the PWG-BC further analysed the paper of Darby *et al.* [23], who found a relationship between MHD and the risk of developing an ACE <80 years in a case control study, where ACE were defined as a diagnosis of myocardial infarction (International Classification of Diseases, 10th Revision [ICD-10] codes I21–I24), coronary revascularisation or death from ischaemic heart disease (ICD-10 codes I20–I). Darby *et al.* [23] reported that the relative risk of ACE was increased by 7.4% per Gy MHD. As an example, Darby *et al.* [23] translated the relative estimates on ACE into absolute estimates, based on the incidence of ACE in general populations found in literature [26], and using a multiplication factor to estimate the absolute risk for patients with and without cardiovascular risk factors separately. The PWG-BC concluded that the Darby model was a good starting point for estimating the absolute risk of ACE based upon the MHD and pre-existing cardiovascular risk factors as defined by the same publication.

The PWG-BC subsequently considered external validation of this model in an independent dataset. Assessment of external validity of an existing model is important before applying such a model to new patients, especially when the original model is prone to over-fitting due to a combination of having limited data and multiple predictors [27–30]. Although the analysis of two Dutch datasets reported results in line with the Darby model [24,31], a proper dataset of breast cancer patients with data on their risk of ACE <80 years of age after breast cancer radiotherapy was lacking. Consequently, a formal external validation could not be carried out. Nevertheless, the PWG-BC group decided to use the original Darby model for model-based selection to determine the absolute risk of ACE after radiotherapy, before 80 years, based upon the following arguments:

- The quality of the study by Darby *et al.* [23] is high, as it is a large international population-based study with relevant long-term follow-up, and only one predictor (MHD). As the study population was already composed of breast cancer patients from different datasets from several countries, external validation was deemed less essential.
- The Darby model is generally accepted and currently being used worldwide in daily practice.
- The Darby model makes it possible to assess the ACE risk <80 years for individual patients.
- Research in the Dutch population [24] found a similar association between MHD and ACE in the first 9 years after treatment as Darby *et al.* [23].
- Research on irradiated Hodgkin patients found a similar association between MHD and ACE [31].

Further Development of the Model for the Dutch Population

A well-maintained registry of ACE is available in the Netherlands, including absolute risk per age category of 5 years, separately for men and women. The relative risk found by Darby *et al.* [23] was applied to the absolute risk of ACE in the general Dutch population based on this registry. In addition, we used mortality data of the Central Office of Statistics (CBS) to correct for deaths due to other causes, for

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men and women separately, to estimate the risk of ACE <80 years of age, for breast cancer radiotherapy at each life-year between 40 and 70 years (i.e. the age range in the Darby *et al.* publication). Subsequently, we applied the same multiplication factor to take into account the presence or absence of cardiovascular risk factors as used by Darby *et al.* [23]: previous ischemic cardiovascular disease (ICD-10 code I20-25); any previous 'circulatory disease' other than ischemic cardiovascular disease (ICD-10 code I00–I19 and ICD-10 code I26–I99); diabetes; chronic obstructive pulmonary disease; active smoker; body mass index ≥30 kg/m^2; chronic pain medication (opiates and/or non-steroidal anti-inflammatory drugs). In this way, we were able to calculate the absolute risk of ACE <80 years, without

Table 1
Cumulative risk of acute coronary events (ACE) for women (A, B) and men (C, D), without (A, C) and with (B, D) risk factors for ACE <80 years of age, per age (years) and per Gy mean heart dose (MHD). The last column indicates for which minimum MHD a planning comparison might be useful; this threshold dose is based upon the assumption that the MHD of the proton plan will be 0.0 Gy, which is rarely the case. This threshold dose indicates by how much the MHD with protons must decrease in order for the patient to be eligible for proton therapy. To illustrate how to use the tables we here present an example: for a 45-year-old woman without cardiovascular risk factors, the life time risk of an ACE is 6.9% in the case of an MHD of 0 Gy (A). If her photon plan has an MHD of 6 Gy, her risk of an ACE is increased to 9.9%. As the 6 Gy is above the threshold value of 3.92 Gy, a plan comparison can be carried out. If the proton plan results in an MHD of 1 Gy, her risk of an ACE is 7.4%. The proton plan then thus results in a reduction in the risk of an ACE from 9.9% to 7.4%, which is 2.5%. As this difference is >2%, we consider this a positive plan comparison, and her proton treatment will be reimbursed (Note: the row for patients aged 40 years should be used for patients <40 years of age; the row for patients aged 70 years should be used for patients >70 years of age).

Table 1A. Cumulative risk of acute coronary events (ACE) for WOMEN WITHOUT risk factors for ACE < 80 years of age.

Age in years	Mean Heart Dose (Gy)											Age in years	Threshold MHD (Gy) for a plan comparison
	0 Gy	1 Gy	2 Gy	3 Gy	4 Gy	5 Gy	6 Gy	7 Gy	8 Gy	9 Gy	10 Gy		
40	6,9%	7,4%	7,9%	8,5%	9,0%	9,5%	10,0%	10,5%	11,0%	11,5%	12,0%	40	3,90
41	6,9%	7,4%	7,9%	8,4%	9,0%	9,5%	10,0%	10,5%	11,0%	11,5%	12,0%	41	3,91
42	6,9%	7,4%	7,9%	8,4%	9,0%	9,5%	10,0%	10,5%	11,0%	11,5%	12,0%	42	3,91
43	6,9%	7,4%	7,9%	8,4%	8,9%	9,5%	10,0%	10,5%	11,0%	11,5%	12,0%	43	3,92
44	6,9%	7,4%	7,9%	8,4%	8,9%	9,4%	10,0%	10,5%	11,0%	11,5%	12,0%	44	3,92
45	6,9%	7,4%	7,9%	8,4%	8,9%	9,4%	9,9%	10,5%	11,0%	11,5%	12,0%	45	3,92
46	6,8%	7,3%	7,8%	8,3%	8,8%	9,3%	9,8%	10,3%	10,8%	11,3%	11,8%	46	3,97
47	6,7%	7,2%	7,7%	8,2%	8,7%	9,2%	9,7%	10,2%	10,7%	11,2%	11,7%	47	4,02
48	6,6%	7,1%	7,6%	8,1%	8,6%	9,1%	9,6%	10,1%	10,6%	11,1%	11,6%	48	4,07
49	6,6%	7,0%	7,5%	8,0%	8,5%	9,0%	9,5%	10,0%	10,4%	10,9%	11,4%	49	4,12
50	6,4%	6,9%	7,4%	7,8%	8,3%	8,8%	9,3%	9,7%	10,2%	10,7%	11,2%	50	4,21
51	6,3%	6,8%	7,3%	7,7%	8,2%	8,7%	9,1%	9,6%	10,1%	10,6%	11,0%	51	4,27
52	6,3%	6,7%	7,2%	7,6%	8,1%	8,6%	9,0%	9,5%	10,0%	10,4%	10,9%	52	4,32
53	6,2%	6,6%	7,1%	7,5%	8,0%	8,5%	8,9%	9,4%	9,8%	10,3%	10,7%	53	4,38
54	6,1%	6,5%	7,0%	7,4%	7,9%	8,4%	8,8%	9,3%	9,7%	10,2%	10,6%	54	4,43
55	6,0%	6,5%	6,9%	7,4%	7,8%	8,2%	8,7%	9,1%	9,6%	10,0%	10,5%	55	4,49
56	5,9%	6,3%	6,7%	7,2%	7,6%	8,1%	8,5%	8,9%	9,4%	9,8%	10,2%	56	4,60
57	5,7%	6,2%	6,6%	7,0%	7,4%	7,9%	8,3%	8,7%	9,1%	9,6%	10,0%	57	4,71
58	5,6%	6,0%	6,4%	6,9%	7,3%	7,7%	8,1%	8,5%	8,9%	9,3%	9,8%	58	4,82
59	5,5%	5,9%	6,3%	6,7%	7,1%	7,5%	7,9%	8,3%	8,7%	9,1%	9,5%	59	4,94
60	4,5%	4,8%	5,1%	5,5%	5,8%	6,1%	6,5%	6,8%	7,1%	7,5%	7,8%	60	6,03
61	4,4%	4,7%	5,0%	5,3%	5,7%	6,0%	6,3%	6,6%	7,0%	7,3%	7,6%	61	6,19
62	4,3%	4,6%	4,9%	5,2%	5,5%	5,8%	6,1%	6,5%	6,8%	7,1%	7,4%	62	6,35
63	4,1%	4,4%	4,8%	5,1%	5,4%	5,7%	6,0%	6,3%	6,6%	6,9%	7,2%	63	6,52
64	4,0%	4,3%	4,6%	4,9%	5,2%	5,5%	5,8%	6,1%	6,4%	6,7%	7,0%	64	6,70
65	3,9%	4,2%	4,5%	4,8%	5,1%	5,4%	5,7%	6,0%	6,2%	6,5%	6,8%	65	6,89
66	3,7%	4,0%	4,3%	4,5%	4,8%	5,1%	5,4%	5,6%	5,9%	6,2%	6,5%	66	7,28
67	3,5%	3,8%	4,0%	4,3%	4,5%	4,8%	5,1%	5,3%	5,6%	5,8%	6,1%	67	7,70
68	3,3%	3,6%	3,8%	4,0%	4,3%	4,5%	4,8%	5,0%	5,3%	5,5%	5,8%	68	8,17
69	3,1%	3,3%	3,6%	3,8%	4,0%	4,3%	4,5%	4,7%	4,9%	5,2%	5,4%	69	8,71
≥70	1,9%	2,0%	2,2%	2,3%	2,4%	2,6%	2,7%	2,9%	3,0%	3,1%	3,3%	70	14,37

NOTE 1: The row for women aged 40 years should be used for women < 40 years of age.

NOTE 2: The row for women aged 70 years should be used for women > 70 years of age.

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Table 1B Cumulative risk of acute coronary events (ACE) for WOMEN WITH risk factors for ACE < 80 years of age.

NOTE 1: The row for women aged 40 years should be used for women < 40 years of age.

NOTE 2: The row for women aged 70 years should be used for women > 70 years of age.

Age in years	Mean Heart Dose (Gy)											Age in years	Threshold MHD (Gy) for a plan comparison
	0 Gy	1 Gy	2 Gy	3 Gy	4 Gy	5 Gy	6 Gy	7 Gy	8 Gy	9 Gy	10 Gy		
40	11,6%	12,5%	13,4%	14,2%	15,1%	15,9%	16,8%	17,7%	18,5%	19,4%	20,2%	40	2,32
41	11,6%	12,5%	13,3%	14,2%	15,1%	15,9%	16,8%	17,6%	18,5%	19,4%	20,2%	41	2,33
42	11,6%	12,5%	13,3%	14,2%	15,0%	15,9%	16,8%	17,6%	18,5%	19,3%	20,2%	42	2,33
43	11,6%	12,5%	13,3%	14,2%	15,0%	15,9%	16,7%	17,6%	18,5%	19,3%	20,2%	43	2,33
44	11,6%	12,4%	13,3%	14,2%	15,0%	15,9%	16,7%	17,6%	18,4%	19,3%	20,2%	44	2,33
45	11,6%	12,4%	13,3%	14,1%	15,0%	15,9%	16,7%	17,6%	18,4%	19,3%	20,1%	45	2,33
46	11,4%	12,3%	13,1%	14,0%	14,8%	15,7%	16,5%	17,4%	18,2%	19,1%	19,9%	46	2,36
47	11,3%	12,1%	13,0%	13,8%	14,6%	15,5%	16,3%	17,2%	18,0%	18,8%	19,7%	47	2,39
48	11,2%	12,0%	12,8%	13,6%	14,5%	15,3%	16,1%	16,9%	17,8%	18,6%	19,4%	48	2,42
49	11,0%	11,8%	12,7%	13,5%	14,3%	15,1%	15,9%	16,7%	17,6%	18,4%	19,2%	49	2,45
50	11,4%	12,2%	13,1%	13,9%	14,8%	15,6%	16,5%	17,3%	18,2%	19,0%	19,8%	50	2,37
51	11,3%	12,1%	12,9%	13,8%	14,6%	15,4%	16,3%	17,1%	17,9%	18,8%	19,6%	51	2,40
52	11,1%	11,9%	12,8%	13,6%	14,4%	15,2%	16,1%	16,9%	17,7%	18,5%	19,4%	52	2,43
53	11,0%	11,8%	12,6%	13,4%	14,2%	15,0%	15,9%	16,7%	17,5%	18,3%	19,1%	53	2,46
54	10,8%	11,6%	12,4%	13,2%	14,0%	14,8%	15,6%	16,5%	17,3%	18,1%	18,9%	54	2,49
55	10,7%	11,5%	12,3%	13,1%	13,9%	14,7%	15,4%	16,2%	17,0%	17,8%	18,6%	55	2,53
56	10,5%	11,2%	12,0%	12,8%	13,5%	14,3%	15,1%	15,9%	16,6%	17,4%	18,2%	56	2,59
57	10,2%	11,0%	11,7%	12,5%	13,2%	14,0%	14,7%	15,5%	16,3%	17,0%	17,8%	57	2,65
58	10,0%	10,7%	11,4%	12,2%	12,9%	13,7%	14,4%	15,1%	15,9%	16,6%	17,3%	58	2,71
59	9,7%	10,4%	11,2%	11,9%	12,6%	13,3%	14,0%	14,8%	15,5%	16,2%	16,9%	59	2,78
60	8,7%	9,3%	10,0%	10,6%	11,3%	11,9%	12,6%	13,2%	13,8%	14,5%	15,1%	60	3,11
61	8,5%	9,1%	9,7%	10,4%	11,0%	11,6%	12,2%	12,9%	13,5%	14,1%	14,8%	61	3,19
62	8,3%	8,9%	9,5%	10,1%	10,7%	11,3%	11,9%	12,5%	13,1%	13,8%	14,4%	62	3,27
63	8,0%	8,6%	9,2%	9,8%	10,4%	11,0%	11,6%	12,2%	12,8%	13,4%	14,0%	63	3,36
64	7,8%	8,4%	9,0%	9,6%	10,1%	10,7%	11,3%	11,9%	12,5%	13,0%	13,6%	64	3,45
65	7,6%	8,2%	8,7%	9,3%	9,9%	10,4%	11,0%	11,6%	12,1%	12,7%	13,2%	65	3,55
66	7,2%	7,7%	8,3%	8,8%	9,3%	9,9%	10,4%	10,9%	11,5%	12,0%	12,5%	66	3,75
67	6,8%	7,3%	7,8%	8,3%	8,8%	9,3%	9,8%	10,3%	10,8%	11,4%	11,9%	67	3,97
68	6,4%	6,9%	7,4%	7,8%	8,3%	8,8%	9,3%	9,7%	10,2%	10,7%	11,2%	68	4,21
69	6,0%	6,5%	6,9%	7,4%	7,8%	8,3%	8,7%	9,1%	9,6%	10,0%	10,5%	69	4,48
≥70	6,0%	6,4%	6,9%	7,3%	7,7%	8,2%	8,6%	9,1%	9,5%	10,0%	10,4%	70	4,52

radiotherapy, i.e. with an MHD of 0 Gy, for all ages between 40 and 70 years at the time of radiotherapy, for four categories of patients: female patients with and without cardiovascular risk factors, and male patients, although not included in the population from which the model was developed, with and without cardiovascular risk factors. Finally, we calculated the risk of ACE for each category and age, by applying the relative 7.4% increase in the risk of ACE for MHDs varying from 0–10 Gy. This resulted in four comparable tables (see Table 1).

Implications for Plan Comparison and Model-based Selection

The PWG-BC classified ACE according to the CTCAE criteria as the ΔNTCP required for reimbursement is dependent on the CTCAE grade of the complication. ACE varied between grade 3 CTCAE (e.g. relatively small myocardial infarction) to grade 5 CTCAE (myocardial infarction leading to death). By consensus from the Dutch Platform for Radiation Therapy of Breast Cancer, the PWG-BC decided to consider ACE as a grade 4 toxicity, such that the ΔNTCP between a proton plan and a photon plan had to be ≥2% to be eligible for proton therapy.

To further improve practical implementation, we used the formula to calculate the risk of ACE in an Excel spreadsheet, which allowed calculation of the risk on ACE, based on age (between 40 and 70 years), gender, presence or absence of a cardiac risk factor and a continuous range of MHD with a maximum of 10 Gy. Patients younger than 40 years were assigned to an age of 40 and patients older than 70 years were assigned to 70 years. This spreadsheet was used to calculate the difference in risk of ACE for the MHD of a proton plan and the corresponding photon plan (Figure 1).

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Table 1C. Cumulative risk of acute coronary events (ACE) for MEN WITHOUT risk factors for ACE < 80 years of age.

Age in years	Mean Heart Dose (Gy)											Age in years	Threshold MHD (Gy) for a plan comparison
	0 Gy	1 Gy	2 Gy	3 Gy	4 Gy	5 Gy	6 Gy	7 Gy	8 Gy	9 Gy	10 Gy		
40	15,7%	16,9%	18,0%	19,2%	20,4%	21,5%	22,7%	23,9%	25,0%	26,2%	27,4%	40	1,72
41	15,7%	16,9%	18,0%	19,2%	20,3%	21,5%	22,7%	23,8%	25,0%	26,2%	27,3%	41	1,72
42	15,7%	16,8%	18,0%	19,2%	20,3%	21,5%	22,6%	23,8%	25,0%	26,1%	27,3%	42	1,72
43	15,7%	16,8%	18,0%	19,1%	20,3%	21,5%	22,6%	23,8%	24,9%	26,1%	27,3%	43	1,73
44	15,6%	16,8%	18,0%	19,1%	20,3%	21,4%	22,6%	23,8%	24,9%	26,1%	27,2%	44	1,73
45	15,6%	16,8%	17,9%	19,1%	20,3%	21,4%	22,6%	23,7%	24,9%	26,0%	27,2%	45	1,73
46	15,4%	16,5%	17,7%	18,8%	19,9%	21,1%	22,2%	23,3%	24,5%	25,6%	26,8%	46	1,76
47	15,1%	16,2%	17,4%	18,5%	19,6%	20,7%	21,8%	23,0%	24,1%	25,2%	26,3%	47	1,79
48	14,9%	16,0%	17,1%	18,2%	19,3%	20,4%	21,5%	22,6%	23,7%	24,8%	25,9%	48	1,82
49	14,6%	15,7%	16,8%	17,9%	19,0%	20,0%	21,1%	22,2%	23,3%	24,4%	25,5%	49	1,85
50	14,2%	15,3%	16,3%	17,4%	18,5%	19,5%	20,6%	21,6%	22,7%	23,7%	24,8%	50	1,90
51	14,0%	15,0%	16,1%	17,1%	18,1%	19,2%	20,2%	21,2%	22,3%	23,3%	24,4%	51	1,93
52	13,8%	14,8%	15,8%	16,8%	17,8%	18,8%	19,9%	20,9%	21,9%	22,9%	23,9%	52	1,97
53	13,5%	14,5%	15,5%	16,5%	17,5%	18,5%	19,5%	20,5%	21,5%	22,5%	23,5%	53	2,00
54	13,3%	14,2%	15,2%	16,2%	17,2%	18,2%	19,2%	20,1%	21,1%	22,1%	23,1%	54	2,04
55	13,0%	14,0%	15,0%	15,9%	16,9%	17,8%	18,8%	19,8%	20,7%	21,7%	22,7%	55	2,08
56	12,6%	13,5%	14,5%	15,4%	16,3%	17,3%	18,2%	19,1%	20,1%	21,0%	21,9%	56	2,15
57	12,2%	13,1%	14,0%	14,9%	15,8%	16,7%	17,6%	18,5%	19,4%	20,3%	21,2%	57	2,22
58	11,7%	12,6%	13,5%	14,4%	15,2%	16,1%	17,0%	17,8%	18,7%	19,6%	20,4%	58	2,30
59	11,3%	12,2%	13,0%	13,8%	14,7%	15,5%	16,3%	17,2%	18,0%	18,9%	19,7%	59	2,39
60	9,2%	9,8%	10,5%	11,2%	11,9%	12,5%	13,2%	13,9%	14,6%	15,3%	15,9%	60	2,95
61	8,8%	9,5%	10,1%	10,8%	11,4%	12,1%	12,7%	13,4%	14,0%	14,7%	15,3%	61	3,07
62	8,5%	9,1%	9,7%	10,3%	11,0%	11,6%	12,2%	12,8%	13,5%	14,1%	14,7%	62	3,20
63	8,1%	8,7%	9,3%	9,9%	10,5%	11,1%	11,7%	12,3%	12,9%	13,5%	14,1%	63	3,33
64	7,8%	8,3%	8,9%	9,5%	10,1%	10,6%	11,2%	11,8%	12,4%	12,9%	13,5%	64	3,48
65	7,4%	8,0%	8,5%	9,1%	9,6%	10,2%	10,7%	11,3%	11,8%	12,4%	12,9%	65	3,64
66	7,0%	7,5%	8,0%	8,5%	9,0%	9,5%	10,1%	10,6%	11,1%	11,6%	12,1%	66	3,88
67	6,5%	7,0%	7,5%	7,9%	8,4%	8,9%	9,4%	9,9%	10,4%	10,8%	11,3%	67	4,16
68	6,0%	6,5%	6,9%	7,4%	7,8%	8,3%	8,7%	9,2%	9,6%	10,1%	10,5%	68	4,47
69	5,6%	6,0%	6,4%	6,8%	7,3%	7,7%	8,1%	8,5%	8,9%	9,3%	9,7%	69	4,83
≥70	3,3%	3,6%	3,8%	4,1%	4,3%	4,6%	4,8%	5,1%	5,3%	5,6%	5,8%	70	8,09

NOTE 1: The row for men aged 40 years should be used for men < 40 years of age.

NOTE 2: The row for men aged 70 years should be used for men > 70 years of age.

Approval of the National Indication Protocol for Proton Therapy

A NIPP was drafted, containing all relevant information and also referring to the ProTRAIT dataset, i.e. a dataset including variables to be prospectively registered, to allow prospective model validation. The NIPP was sent to all stakeholders, who were invited to an invitational conference where comments were collected and discussed. This led to minor adjustments, such as (1) clarification of the cardiovascular risk factors, (2) inclusion of radiation pneumonitis as a relevant outcome by referring to the prediction model to be included in the NIPP for lung cancer, which at that moment was still under development, and (3) inclusion of patients referred for re-irradiation for breast cancer. The final NIPP was approved for reimbursement from January 2019. An amendment was made and approved in July 2020, that also allowed inclusion of patients with oligometastatic disease treated with curative intent, and where the following factors were added as cardiovascular risk factors: previous mediastinal or internal mammary chain irradiation; left-sided breast radiation, e.g. without breath-hold or pectus excavatum, or other radiation with a substantial dose to the heart (see supplementary material for full NIPP).

First Clinical Experiences

From January 2019 to January 2021, a plan comparison was made for 311 breast cancer patients in whom the MHD with a photon treatment plan exceeded the threshold (i.e. ACE risk >2%) for plan comparison, resulting in 268 (86%) patients treated with proton therapy in the Netherlands. Reasons for not administering proton therapy were a negative plan comparison or patient's wish not to be referred. One hundred and eighty-four patients (69%) were

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Table 1D. Cumulative risk of acute coronary events (ACE) for MEN WITH risk factors for ACE < 80 years of age.

Age in years	Mean Heart Dose (Gy)											Age in years	Threshold MHD (Gy) for a plan comparison
	0 Gy	1 Gy	2 Gy	3 Gy	4 Gy	5 Gy	6 Gy	7 Gy	8 Gy	9 Gy	10 Gy		
40	26,4%	28,4%	30,3%	32,3%	34,2%	36,2%	38,2%	40,1%	42,1%	44,0%	46,0%	40	1,02
41	26,4%	28,3%	30,3%	32,2%	34,2%	36,2%	38,1%	40,1%	42,0%	44,0%	45,9%	41	1,02
42	26,4%	28,3%	30,3%	32,2%	34,2%	36,1%	38,1%	40,0%	42,0%	43,9%	45,9%	42	1,03
43	26,3%	28,3%	30,2%	32,2%	34,1%	36,1%	38,0%	40,0%	41,9%	43,9%	45,8%	43	1,03
44	26,3%	28,2%	30,2%	32,1%	34,1%	36,0%	38,0%	39,9%	41,9%	43,8%	45,8%	44	1,03
45	26,3%	28,2%	30,2%	32,1%	34,0%	36,0%	37,9%	39,9%	41,8%	43,8%	45,7%	45	1,03
46	25,8%	27,8%	29,7%	31,6%	33,5%	35,4%	37,3%	39,2%	41,1%	43,1%	45,0%	46	1,05
47	25,4%	27,3%	29,2%	31,1%	33,0%	34,8%	36,7%	38,6%	40,5%	42,4%	44,2%	47	1,06
48	25,0%	26,9%	28,7%	30,6%	32,4%	34,3%	36,1%	38,0%	39,8%	41,7%	43,5%	48	1,08
49	24,6%	26,4%	28,2%	30,1%	31,9%	33,7%	35,5%	37,3%	39,2%	41,0%	42,8%	49	1,10
50	25,3%	27,2%	29,1%	30,9%	32,8%	34,7%	36,6%	38,4%	40,3%	42,2%	44,0%	50	1,07
51	24,9%	26,7%	28,6%	30,4%	32,2%	34,1%	35,9%	37,8%	39,6%	41,5%	43,3%	51	1,09
52	24,4%	26,3%	28,1%	29,9%	31,7%	33,5%	35,3%	37,1%	38,9%	40,7%	42,5%	52	1,11
53	24,0%	25,8%	27,6%	29,3%	31,1%	32,9%	34,7%	36,5%	38,2%	40,0%	41,8%	53	1,13
54	23,6%	25,3%	27,1%	28,8%	30,6%	32,3%	34,1%	35,8%	37,5%	39,3%	41,0%	54	1,15
55	23,2%	24,9%	26,6%	28,3%	30,0%	31,7%	33,4%	35,1%	36,9%	38,6%	40,3%	55	1,17
56	22,4%	24,0%	25,7%	27,4%	29,0%	30,7%	32,3%	34,0%	35,6%	37,3%	39,0%	56	1,21
57	21,6%	23,2%	24,8%	26,4%	28,0%	29,6%	31,2%	32,8%	34,4%	36,0%	37,6%	57	1,25
58	20,9%	22,4%	24,0%	25,5%	27,1%	28,6%	30,1%	31,7%	33,2%	34,8%	36,3%	58	1,29
59	20,1%	21,6%	23,1%	24,6%	26,1%	27,6%	29,1%	30,6%	32,0%	33,5%	35,0%	59	1,34
60	17,8%	19,1%	20,4%	21,7%	23,0%	24,3%	25,7%	27,0%	28,3%	29,6%	30,9%	60	1,52
61	17,1%	18,4%	19,6%	20,9%	22,2%	23,4%	24,7%	25,9%	27,2%	28,5%	29,7%	61	1,58
62	16,4%	17,6%	18,8%	20,1%	21,3%	22,5%	23,7%	24,9%	26,1%	27,4%	28,6%	62	1,65
63	15,7%	16,9%	18,1%	19,2%	20,4%	21,6%	22,7%	23,9%	25,1%	26,2%	27,4%	63	1,72
64	15,1%	16,2%	17,3%	18,4%	19,5%	20,7%	21,8%	22,9%	24,0%	25,1%	26,2%	64	1,79
65	14,4%	15,5%	16,6%	17,6%	18,7%	19,8%	20,8%	21,9%	23,0%	24,0%	25,1%	65	1,87
66	13,5%	14,5%	15,5%	16,5%	17,5%	18,5%	19,5%	20,5%	21,5%	22,5%	23,5%	66	2,00
67	12,6%	13,6%	14,5%	15,4%	16,4%	17,3%	18,2%	19,2%	20,1%	21,0%	22,0%	67	2,14
68	11,7%	12,6%	13,5%	14,3%	15,2%	16,1%	17,0%	17,8%	18,7%	19,6%	20,4%	68	2,30
69	10,9%	11,7%	12,5%	13,3%	14,1%	14,9%	15,7%	16,5%	17,3%	18,1%	18,9%	69	2,49
≥70	10,6%	11,4%	12,2%	13,0%	13,7%	14,5%	15,3%	16,1%	16,9%	17,7%	18,5%	70	2,55

NOTE 1: The row for men aged 40 years should be used for men < 40 years of age.

NOTE 2: The row for men aged 70 years should be used for men > 70 years of age.

referred from the radiotherapy departments with a proton therapy facility, whereas 84 patients (31%) were referred from radiotherapy departments without a proton therapy facility.

Patient and radiation characteristics of the patients actually receiving proton therapy show that most of the selected patients had baseline cardiovascular risk factors (76%) and left-sided breast cancer (219/268 = 82%) (Table 2). Dose-volume histogram parameters of photon and proton plans of the plan comparison are given in Table 2. The ΔNTCP for ACE between proton and photon plans was on average 2.9%, with a range of 2–11.7%.

Discussion

We developed a nationally approved indication protocol to select breast cancer patients for proton therapy based on their predicted reduction in risk of ACE <80 years of age. Based upon this protocol, about 3.4% of breast cancer patients were selected for proton therapy in the radiotherapy departments with a proton facility.

The Dutch model-based approach to select patients for proton therapy is unique in the world. In combination with prospective monitoring of side-effects, it allows for the external validation of the selected model. In addition, it

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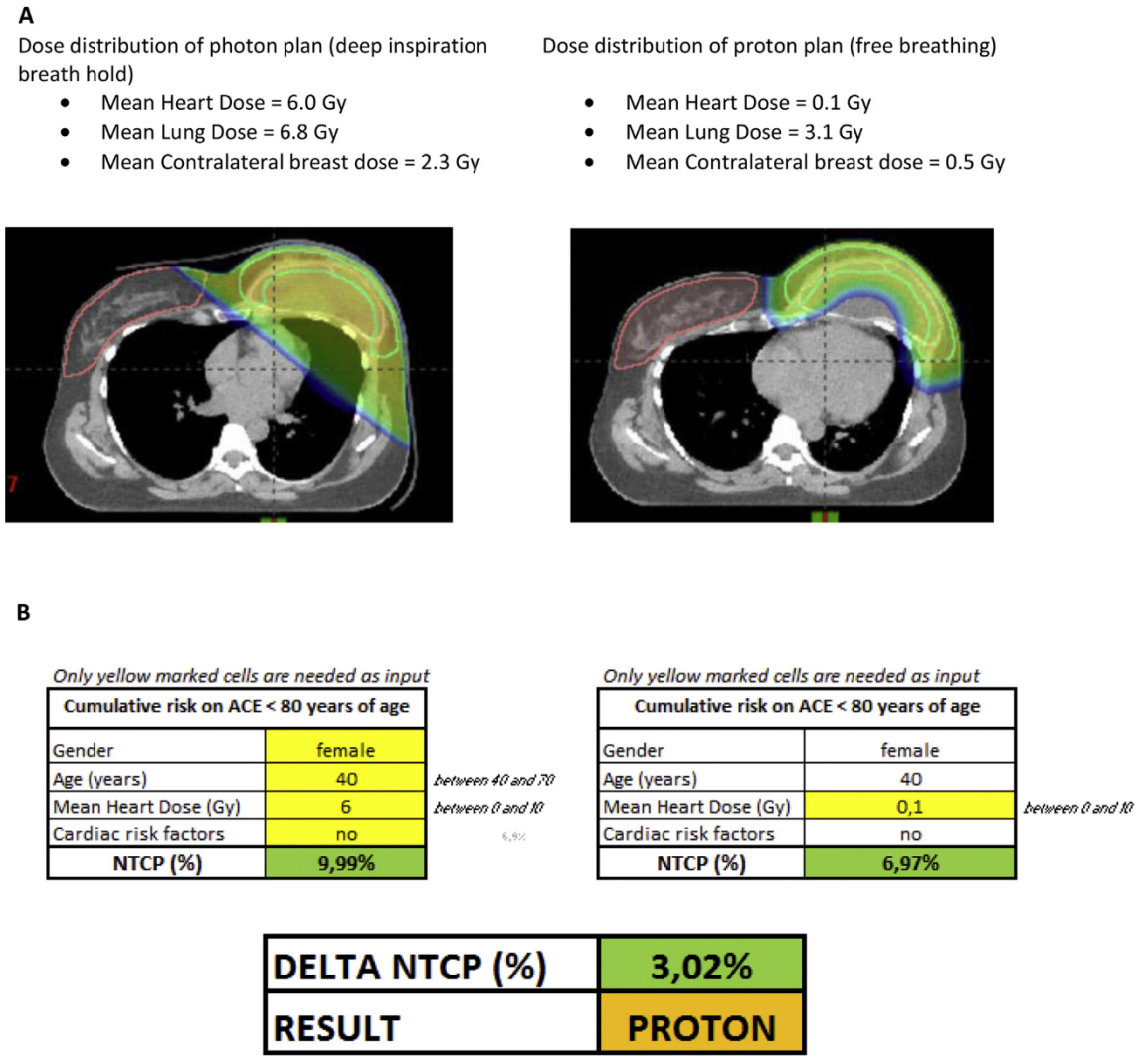

Fig 1. Example of a plan comparison for a female patient of 40 years of age, with an indication for radiotherapy of the chest wall, and axilla level 1–4, with a dose of 20 × 2.18 Gy to the elective regions and 20 × 2.67 Gy to the tumour bed because of involved margins. (A) Dose distributions, left photons, right protons. The mean heart dose in the photon plan of 6 Gy exceeds the threshold dose (see Table 1A: threshold dose for a 40-year-old female without cardiovascular risk factors = 3.9 Gy), such that a plan comparison is indicated. (B) The completed Excel spreadsheet to calculate the difference in risk on an acute coronary event <80 years of age between the proton and the photon plan.

allows comparison of the observed incidence of complications after proton therapy, with the expected incidence of those complications when patients would have been treated with photons, based on the back up photon plan from the plan comparison (i.e. model-based clinical evaluation [4]). In this way, each patient serves as his/her own control in silico. The advantages of this approach are: (1) only the patients expected to benefit the most are selected for proton therapy; (2) it corrects for practice variation in treatment planning as it compares the clinically applicable photon plan from the referring centres with the proton therapy plan, and (3) it considers technological improvements of both modalities over time.

However, for breast cancer, the prospective validation of the model is hampered by the fact that the primary end point is the risk of ACE before the age of 80 years. Consequently, if we want to reach that end point, 30–40 years of follow-up is required. In addition, if we want to investigate whether the observed incidence of ACE is at least 2% lower than the estimated incidence of the photon plan, a large number of patients are required to have sufficient power. Nevertheless, we are currently exploring two options to enable such a comparison. First, we explore the possibilities of collaboration with the DBCG and UK groups, to increase the available breast cancer patients treated with proton therapy. Second, Lorenzen *et al.* [32] analysed the Danish data and found a 19% increase per Gy MHD for ACE, for patients with a follow-up varying from 8 to 36 years, whereas Darby *et al.* [23] only found a 7.4% increase per Gy MHD. If the data of Lorenzen prove to be true, the observed reduction in NTCP will be much larger than predicted based upon the Darby model. This might enable an earlier analysis, i.e. an analysis after for example 10 years instead of an analysis after 30–40

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Table 2
Overview of breast cancer patients referred to Dutch proton centres from February 2019 until 1 January 2021 (A). Dose-volume parameters are averaged over the 268 patients actually receiving proton therapy. The values are based on the photon and proton plans made for plan comparison (B)

(A)	
Total number of patients irradiated with curative intent in the radiotherapy departments with a proton therapy facility*	5382
Number of patients with a plan comparison	311
Number of patients treated with proton therapy (referred from centre with proton therapy/centre without proton therapy)*	268 (184/84)
Percentage of patients treated with proton therapy of the total number of curatively treated patients in radiotherapy centre with a proton therapy facility	(184/5382) × 100 = 3.4%
Number IMC left/right treated with proton therapy	118/25
Number patients treated with proton therapy with cardiovascular risk factors	204
Mean age of patients treated with proton therapy in years (range)	49 (19–80)
Number of left-/right-sided patients treated with proton therapy	219/31
Number of bilateral proton therapy	18
Number of proton therapy without a boost	139

(B)		
Average DVH parameters for the 268 patients treated with proton therapy	Photons	Protons
Mean MHD in Gy (range)	5.1 (2.5–18.9)	0.74 (0.0–6.2)
Mean MLD in Gy (range)	7.2 (1.3–17.3)	3.7 (0.0–15.4)
Mean contralateral breast dose photons in Gy (range)	2.7 (0.1–15.1)	0.4 (0.0–5.3)
Mean NTCP in % (range)	13.0 (6.5–23.0)	10.0 (4.3–15.6)
Mean ΔNTCP in % (range) photons minus proton therapy	2.9 (2.0–11.7)	

DVH, dose-volume histogram; IMC, internal mammary chain; MHD, mean heart dose; MLD, mean lung dose; NTCP, normal tissue complication probability, i.e. risk of developing an acute coronary event before the age of 80 years.

* Holland Proton Therapy Centre is a proton therapy-only centre, parented by Leiden University Medical Centre and Erasmus University Medical Centre. In this table, Leiden University Medical Centre and Erasmus University Medical Centre are considered as belonging to Holland Proton Therapy Centre.

years. To test the underlying hypothesis that model-based selection for breast cancer patients is cost-effective, cost-effectiveness analyses will be carried out in the future, using the data on prospectively recorded side-effects, in combination with the applied EQ-5D questionnaires and estimated hospital-based costs.

The selection criteria in the current breast cancer NIPP do have their limitations. First, cardiovascular risk factors applied in the Darby model are defined very broadly: almost all ICD codes involving the word heart or vessel are considered a risk factor, whereas it is hard to believe that venous thrombosis of the calf really is a risk factor for ACE due to radiotherapy. On the other hand, known risk factors such as anthracycline containing chemotherapy [13] are not considered. Second, due to lack of data on the absolute incidence of ACE in the Netherlands <40 years of age, and to the fact that the model of Darby *et al.* was only based on a very limited number of patients <40 years of age, we decided to use the same lifetime risk for a patient <40 years as for a patient of 40 years of age. This probably leads to some underestimation of the lifetime risk for these young patients, especially if higher sensitivity to radiation exposure to the heart at younger ages is not considered. Third, in the current NIPP we only select patients based on an estimated difference in risk of ACE <80 years of age, whereas other toxicities, such as other cardiac injuries and induction of secondary tumours, may also be reduced with proton therapy [13,33,34].

Despite these shortcomings, we consider the chosen model as a good first step to select patients that will benefit the most. Future work will consist of improving the model, e.g., by adding new risk factors of ACE and or other dose-volume histogram parameters that are more predictive for the risk of ACE (MEDIRAD-BRACE clinicaltrials.gov: NCT03211442).

The clinical implementation in the proton centres showed that 3.4% of their breast cancer patients were selected for proton therapy. For radiotherapy departments without a proton facility this percentage was much lower. This can be explained by a variety of reasons: (1) when shared decision making is applied, some patients chose not to be referred for 'only >2%' reduction in risk on ACE; (2) centres without proton therapy and with proton therapy probably make different trade-offs when optimising the photon radiotherapy plan: in centres without proton therapy, probably more often a slight underdosage of the target is accepted, to allow better sparing of the heart, whereas in centres with proton therapy, no underdosage is accepted, resulting in a higher heart dose, such that in more patients a ΔNTCP >2% is reached. Similarly, in proton therapy centres the dose to the contralateral breast is probably minimised more often, resulting in a higher heart dose, whereas in non-proton therapy centres, some dose to the contralateral breast is accepted, to allow better sparing of the heart. Currently, several Dutch initiatives are underway to reduce practice variation in terms of the application of photon therapy [35].

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Conclusion

A nationally approved indication protocol for the selection of breast cancer patients for proton therapy has been composed, where selection is based on the predicted risk of ACE before the age of 80 years, according to the Darby model, applied to the Dutch incidence of ACE per age category. Based on this model-based selection, 268 breast cancer patients have been treated with proton therapy in the Netherlands in the past 2 years. Further studies are required to validate the applied model-based selection, and to add further models for other relevant toxicity end points.

Conflicts of interest

J.A. Langendijk has research collaborations with Mirada, IBA, Philips, Raysearch, Siemens, Elekta and Leonie. A consultancy fee is paid by IBA to UMCG Research B.V.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2021.12.007.

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