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Spot-scanning proton therapy for targets with adjacent cardiac implantable electronic devices – Strategies for breast and head & neck cancer

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ABSTRACT

Background and purpose: Cardiac implantable electronic device (CIED) malfunctions can be induced by secondary neutron dose from spot-scanning proton therapy. A recent in-vitro study investigating secondary neutron dose to CIEDs up to 7 mSv per fraction found that exposure of secondary neutrons in this range was clinically manageable. This study presents decision algorithms proposed by a national expert group for selection of patients with breast and head & neck (H&N) cancer with CIEDs adjacent to target for proton therapy based on the 7 mSv threshold.

Methods and materials: Ten patients with breast cancer and five with H&N cancer were included in the study. Five patients with breast cancer received photon therapy with CIED and proton plans were retrospectively created. The remaining patients received proton therapy without CIED and a worst-case position of a virtual CIED was retrospectively delineated. Secondary neutron dose was estimated as ambient dose equivalent H*(10) using Monte Carlo simulations.

Results: For patients with breast cancer and with contralateral CIED, the secondary neutron dose to the CIED was below 7 mSv per fraction for CTV < 1500 cm^3 in 2 Gy fractions and CTV < 1000 cm^3 in 2.67 Gy fractions. The secondary neutron dose to the CIED was below 7 mSv per fraction for all patients with H&N cancer.

Conclusions: Simulations of neutron exposure suggest that proton therapy is feasible for most patients with CIED adjacent to target. This forms the basis for decision algorithms for selection of patients with CIED for proton therapy.

1. Introduction

Scattered secondary neutrons from treatment with radiotherapy cause malfunctions in cardiac implantable electronic devices (CIEDs) such as pacemakers and implantable cardioverter defibrillators [1,2]. The primary mechanism behind is that neutrons stochastically may induce single-event upsets causing the device to reset to backup mode [3,4]. The use of proton therapy for selected patients is currently increasing [5], however, the reported experience with proton therapy for patients with CIEDs is limited [6–9]. The American Association of Physicists in Medicine Task Group 203 (AAPM-TG203) report on management of radiotherapy patients with implanted cardiac pacemakers and defibrillators from 2019 states that cumulative doses from proton therapy are not generally a concern as long as the device is located outside the proton beam [10]. Location within the proton beam may cause hardware errors in the device and artefacts from the device may interfere with the proton therapy dose calculation. The report, however, defines proton therapy for patients with CIEDs as a high-risk procedure due to secondary neutrons and recommends weekly monitoring and available cardiologist or CIED technologist if needed. The 2021 European Society of Cardiology (ESC) Guidelines [11] has no specific recommendations for proton therapy due to the limited experience.

Spot-scanning proton therapy, where magnets are used to direct the beam, produces fewer neutrons compared to passive scattering proton therapy, where the beam is collimated. Thus, for spot-scanning proton therapy, the majority of neutrons are generated within the patient

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[12–14]. However, the use of a range shifter to cover target near the patient's surface will cause an increased amount of scattered secondary neutrons. The number of secondary neutrons in the CIEDs depends on the number of protons (proportional to treatment dose and increasing with the size of CTV), the beam energy and the distance from the beam [15].

A recent in-vitro study at our institution investigated risk of CIED malfunctions with daily 2 Gy per fraction spot-scanning proton therapy in 62 explanted, fully functional devices from four different vendors [16]. A total of 61 reset malfunctions were detected in 14 devices during 1728 fractions of which 60 malfunctions occurred in devices from one vendor and were successfully reprogrammed and one device from a different vendor was locked permanently in safety mode. Three groups of devices were located at different lateral distances from the beam, 0.5, 5.0 and 10.0 cm respectively. Secondary neutron dose to CIEDs was up to 7 mSv per fraction in the group located closest to the beam, and the relative risk of CIED error increased by 55% per mSv. The study found no association between risk of errors and cumulative dose. Five CIEDs from a third vendor had significant loss of battery capacity. Thirteen devices were live monitored during irradiation with leads connected and no transient noise leading to pace inhibition or potential shock therapy due to over sensing was observed during 362 fractions. The study concluded that the frequency and severity of observed errors would be clinically manageable and that this risk level would be acceptable considering the general benefits of spot-scanning. Only malfunctions leading to hardware replacement of devices or leads would potentially increase the morbidity of patients significantly and therefore in most cases outweigh the benefit of spot-scanning proton therapy over standard photon therapy. As the neutron dose never superseded 7 mSv in the tested scenario, the risk of errors beyond this dose was considered unclear, prompting the authors to recommend limiting the neutron dose to CIEDs to below 7 mSv. These results lead to implementation of a clinical decision algorithm for the majority of patients with CIEDs receiving proton therapy at our institution, however special attention toward patients with CIED adjacent to the target is needed.

This study aimed to establish decision algorithms for selection of patients with breast and head & neck (H&N) cancer and a CIED for spot-scanning proton therapy based on Monte Carlo simulations of secondary neutron dose using the tested threshold of 7 mSv.

2. Methods and materials

2.1. Patients

The study was approved as a quality development project by Aarhus University Hospital with permission to use image and treatment plan data from the patients. Ten patients receiving adjuvant treatment for breast cancer and five patients treated radically for H&N cancer were included in the study. Five patients with breast cancer and a CIED received photon therapy (two with ipsilateral position and three with contralateral position) between 2015 and 2020, and proton therapy plans were retrospectively created. Five patients with breast cancer and five patients with H&N cancer without CIED received proton therapy between 2019 and 2021 at Danish Centre for Particle Therapy (DCPT); the clinically delivered proton therapy plan was used, and a worst-case position of a virtual CIED (contralateral position for breast cancer and ipsilateral position for H&N cancer) was retrospectively delineated, and potential position confirmed by a cardiologist with experience in device implantations (see Fig. 1 for examples). The five patients with breast cancer were selected based on breast varying volume and five patients with H&N cancer were selected based on the caudal extent of target volume including lymph node level 4 (with or without pathological lymph nodes).

Two patients with breast cancer were planned with breast only irradiation with an ipsilateral CIED (real), and the remaining eight patients with breast cancer were planned with loco-regional irradiation with a contralateral CIED (virtual or real). Seven patients had left-sided and three patients had right-sided breast cancer. All patients were scanned and treated in supine position with arms above the head. The patients with breast cancer were treated with either 50 Gy relative biological effectiveness (RBE) in 25 fractions or 40 Gy RBE in 15 fractions, but for the purpose of this study, evaluated for both 50 Gy RBE in 25 fractions (2 Gy RBE per fraction), 40 Gy RBE in 15 fractions (2.67 Gy RBE per fraction) and 26 Gy RBE in 5 fractions (5.2 Gy RBE per fraction). Secondary neutron dose was simulated once per patient using the dose-fractionation scheme used for treatment. For the remaining schemes, secondary neutron dose was estimated from the simulation by linear

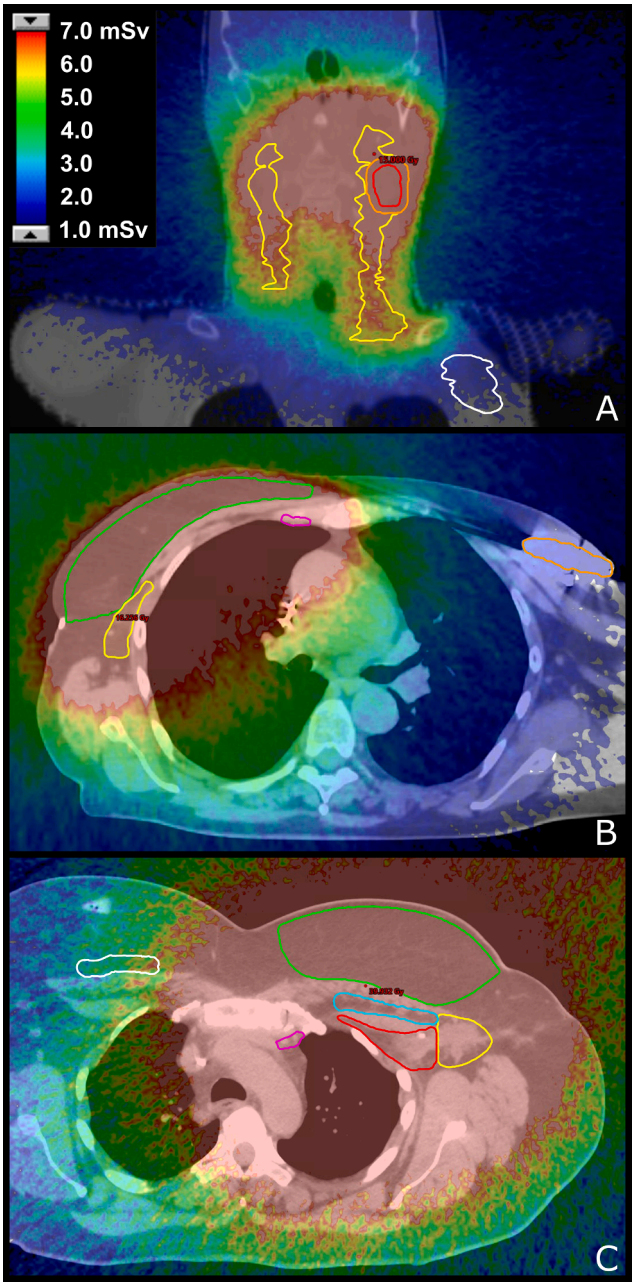

Fig. 1. Example of secondary neutron dose distribution for a patient with head and neck cancer (A) and for patients with breast cancer and a real CIED (B) and a virtual CIED (C). The dose colour wash ranges from 1 to 7 mSv per fraction and red areas represent regions with secondary neutron dose ≥7 mSv per fraction. The white structures are the virtual CIEDs (A + C), the orange structure is the real CIED (B) and the remaining structures are clinical target volumes.

scaling according to fraction dose.

All patients with H&N cancer had oropharynx cancer; four patients had bilateral disease and one patient had unilateral, left-sided disease. The prescription dose was 66 or 68 Gy RBE to CTV high risk, 60 Gy RBE to CTV intermediate risk and 50 Gy RBE to CTV low risk in 33 or 34 fractions.

2.2. Delineations and proton therapy planning

All CIEDs were isotropically expanded with 5 mm to define an area (CIED + 5 mm) that accounted for treatment uncertainties. All spot-scanning proton therapy plans were created in the Eclipse treatment planning system 13.7 (Varian Medical Systems) using robust optimisation (14 scenarios defined below) and a range shifter of 57 mm water equivalent thickness. The RBE was fixed to 1.1 for all proton therapy plans.

Clinical target volumes (CTVs) for breast cancer were delineated according to the European Society for Radiotherapy and Oncology (ESTRO) consensus guidelines [17]. Regional irradiation included internal mammary nodes, interpectoral nodes and nodes level 1–4 (level 1 was omitted in some cases). The clinical planning objectives were V95% (volume that received at least 95% of the prescribed dose) $\geq$98% for CTV breast or CTV chest wall, V90% $\geq$ 98% for lymph node CTVs and V107% $\leq$2% for all CTVs following the Danish Breast Cancer Group (DBCG) guidelines [18]. For the robust evaluation, all scenarios (14 scenarios defined by combining 0 mm and 5 mm setup uncertainty with 3.5% range uncertainty) should comply with V95% $\geq$ 95% for CTV breast or CTV chest wall and V90% $\geq$ 95% for lymph node CTVs. The plan was normalised with mean dose to the total CTV being equal to the prescription dose. The proton therapy plans consisted of two to three *en face* fields optimised using single-field optimisation with equal field weight. More details about the proton therapy planning for breast cancer can be found in Jensen et al [19]. The total volume of the CTV ranged from 281 cm^3 to 2977 cm^3 and the maximum beam energies used in the proton therapy plans ranged from 139 MeV to 193 MeV.

The CTVs were delineated according to the Danish Head and Neck Cancer Group (DAHANCA) radiotherapy guidelines [20]. The clinical planning objectives were to cover CTV high risk with 95% to 107% of the prescription dose and to cover CTV intermediate risk and CTV low risk with at least 95% of the prescription doses. A maximum volume of 1.8 cm^3 could receive more than 107% of the CTV high risk prescription dose. For the robust evaluation, all scenarios (14 scenarios defined by combining 0 mm and 4 mm setup uncertainty with 3.5% range uncertainty) should comply CTV high risk V95% $\geq$ 99% and CTV intermediate risk and CTV low risk V95% $\geq$ 98%. The plan was normalised with mean dose to the CTV high risk being equal to the prescription dose. The proton therapy plans consisted of four to six fields and were optimised using multi-field optimisation. The maximum beam energies ranged from 181 MeV to 199 MeV, and, if only considering the fields covering the caudal part of target, the maximum beam energies ranged from 144 MeV to 169 MeV.

2.3. Monte Carlo simulations

Ambient dose equivalent H*(10) from secondary neutrons was estimated using Monte Carlo simulations in Tool for Particle Simulation (TOPAS) v3.5 [21,22] for all 15 proton therapy plans. H*(10) was calculated using the same method as in [16]. After Monte Carlo simulations in TOPAS, the doses were imported to the Eclipse treatment planning system for evaluation (see Fig. 1).

2.4. Establishment of decision algorithms

Decision algorithms for selecting patients with breast or H&N cancer and a CIED for proton therapy were established by clinical oncologists and cardiologists based on results for maximum secondary neutron dose to the CIED, the beam energy, the distance between the CTV and the CIED, the distance between the CIED and the 5% and the 25% physical (RBE corrected) isodoses, the size of CTV, dose-fractionation schedule (only for breast cancer), and CTV risk, intermediate or low (only for H&N cancer). The aim was to establish decision algorithms for daily clinical use, without the need for performing Monte Carlo simulations of secondary neutron dose.

3. Results

3.1. Breast cancer

For the eight patients with breast cancer with contralateral CIED, the CTV to CIED distance ranged from 8.4 cm to 13.0 cm (see Table 1 for additional results). Maximum secondary neutron dose per fraction to the CIED and the CIED + 5 mm for the three different dose-fractionation schemes as function of CTV size can be seen in Fig. 2.

For the two patients with breast cancer and an ipsilateral CIED, the volumes of the CTV were 412 cm^3 and 955 cm^3 with the CTV to the CIED distance of 2.0 cm and 3.1 cm, respectively. The 25% physical (RBE corrected) isodose did overlap with CIED for both proton therapy plans. Maximum secondary neutron doses to the CIED + 5 mm were 5.6 mSv and 7.2 mSv for 2 Gy RBE fractions, 7.4 mSv and 9.6 mSv for 2.67 Gy RBE fractions and 14.5 mSv and 18.6 mSv for 5.2 Gy RBE fractions.

3.2. Head & neck cancer

The CTV to the CIED distance ranged from 2.7 cm to 5.5 cm. Maximum secondary neutron dose to the CIED + 5 mm was below 7 mSv per fraction for all patients with H&N cancer (see Table 2 for additional results).

3.3. Decision algorithms

A decision algorithm for evaluating whether patients with breast cancer and a contralateral CIED are eligible or not for spot-scanning proton therapy can be seen in Fig. 3. For patients with breast cancer and a contralateral CIED, we found that the evaluation of patients should depend on dose per fraction and size of the CTV since these were the most significant contributors to secondary neutron dose at the device position. The maximum secondary neutron dose to the CIED + 5 mm was below 7 mSv per fraction for CTV < 1500 cm^3 in 2 Gy RBE fractions and CTV < 1000 cm^3 in 2.67 Gy RBE fractions. Patients with CTV sizes below these thresholds were considered eligible for proton therapy. The 26 Gy RBE in 5 fractions scheme was not included in the decision algorithms since it is currently not a standard dose-fractionation scheme used in Denmark. Patients treated with simultaneous integrated boost follow the dose-fractionation scheme for non-boost target.

For patients with breast cancer and an ipsilateral CIED, we found that proton therapy is not feasible for patients requiring regional irradiation, as the device then will be located within the proton beam. Breast only irradiation with protons may be possible if the distance between the CTV and the CIED is at least 2 cm. Artefacts on the CT scan from the device may interfere with the proton therapy dose calculation for a distance less than 2 cm.

A decision algorithm for evaluating whether patients with H&N and a CIED are eligible or not for spot-scanning proton therapy can be seen in Fig. 4. For the patients with H&N cancer, we found that the evaluation should depend on the distance between the CTV and the CIED because it was the most significant contributor to secondary neutron dose in the device. Patients with a distance less than 2 cm will not be eligible for proton therapy due to artefacts on the CT scan from the device may interfere with the proton therapy dose calculation. Patients with a distance between 2 and 4 cm relies on individual evaluation and patients with a distance of more than 4 cm will be eligible for proton therapy. The selection of patients is independent of distance between the CIED and a

Table 1
Results for the eight patients with breast cancer and a contralateral CIED. The CTV is the total volume of all CTVs. are physical (RBE corrected) doses. Maximum secondary neutron dose is reported per fraction. Secondary neutron dose has been simulated once for each patient and scaled linearly according to fraction dose. Abbreviations: CTV, clinical target volume; CIED, cardiac implantable electronic device.

Patient	CTV [cm^3]	CTV to CIED distance [cm]	5% isodose to CIED distance [cm]	25% isodose to CIED distance [cm]	Maximum secondary neutron dose to CIED [%]		
					2 Gy RBE fractions	2.67 Gy RBE fractions	5.2 Gy RBE fractions
1	281	10.8	6.2	7.8	2.4	3.2	6.2
2	592	13.0	6.6	9.9	1.3	1.7	3.4
3	678	11.4	5.0	7.9	2.5	3.3	6.5
4	1124	8.8	0.8	3.8	4.7	6.3	12.3
5	1405	8.6	3.6	5.3	5.0	6.6	12.9
6	1565	8.4	3.8	5.4	5.7	7.6	15.0
7	1753	8.5	2.2	3.8	8.0	10.6	20.8
8	2977	8.6	4.6	6.1	6.6	8.8	17.2

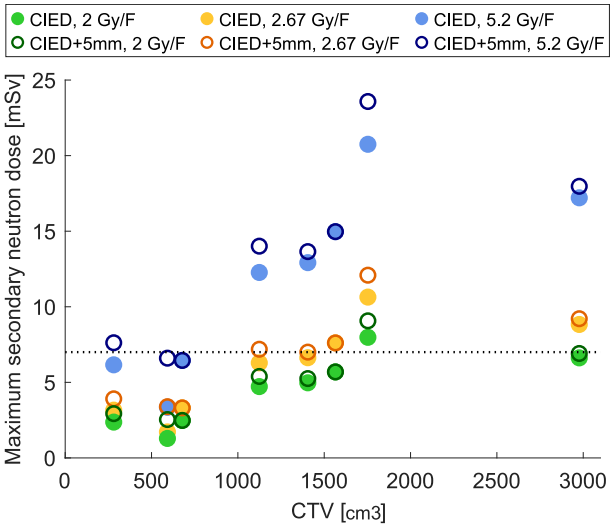

Fig. 2. Maximum secondary neutron dose per fraction in the cardiac implantable electronic device (CIED) and CIED + 5 mm as function of clinical target volume (CTV) for the eight patients with breast cancer and a contralateral CIED. Maximum secondary neutron dose is shown for three fractionation sizes: 2, 2.67 and 5.2 Gy RBE per fraction (F). Secondary neutron dose has been simulated once for each patient and scaled linearly according to fraction dose. The dotted line represents the 7 mSv per fraction threshold.

Table 2
Results for the five patients with head & neck cancer. The 5% and the 25% isodoses are physical (RBE corrected) doses. Maximum secondary neutron dose is reported per fraction. The CTV closest to the CIED was CTV intermediate risk for patient 3 and CTV low risk for the remaining patients. Abbreviations: CTV, clinical target volume; CIED, cardiac implantable electronic device.

Patient	CTV to CIED distance [cm]	5% isodose to CIED distance [cm]	25% isodose to CIED distance [cm]	Maximum secondary neutron dose [mSv]	
				CIED	CIED + 5 mm
1	2.7	0.0	0.0	4.9	6.3
2	3.0	0.0	0.7	2.5	3.4
3	5.0	1.4	2.4	2.7	2.7
4	5.2	0.5	1.2	2.4	2.9
5	5.5	1.3	2.0	3.4	3.6

low, intermediate or high risk CTV. An incoming beam through the CIED will not be allowed.

4. Discussion

We established decision algorithms formed by a national expert group of clinical oncologists and electrophysiology cardiologists for spot-scanning proton therapy for patients with CIED and breast cancer or H&N cancer. The decision algorithms can be used by the referring radiotherapy centres. Patients with eligibility depending on individual evaluation will be assessed using the CT scan by physicists and oncologists at the proton centre. We recommend that CIEDs from St. Jude Medical, Medtronic and Boston Scientific will be checked before and after the proton therapy course and weekly during the course, and that CIEDs from Biotronik will be checked before and after the proton therapy course and after each fraction due to the higher risk of reset to backup mode [16]. The expected gain from proton therapy compared with radiotherapy using photons should outweigh the risk of software errors that need to be reprogrammed and loss of battery longevity. Ongoing randomised studies will show if the benefit of proton therapy over photon therapy outweighs the risk of moving the device in a safe distance from the CTV (e.g. patients with breast cancer and an ipsilateral CIED requiring regional lymph irradiation).

Four retrospective studies report experience with proton therapy (both passive scattering and spot-scanning proton therapy) for 67 patients with CIEDs [6–9]. Eight patients with devices experienced 11 CIED resets to backup mode, and all devices were successfully reprogrammed. All CIEDs were located outside the proton beam, and malfunctions were independent of accumulated dose indicating that the malfunctions presumably have been induced by secondary neutrons.

In the in-vitro study, the estimation of secondary neutron dose to the CIEDs was 7 mSv for the devices located closest to the proton beam [16]. At 7 mSv, the risk of back-up mode errors for devices from one vendor was 19.4 % per fraction, and all errors were easily recoverable using standard programming equipment. No errors were recorded in devices from other vendors. The only unrecoverable error occurred in a device from another vendor at 3.7 mSv. As only 61 errors occurred in 1728 fractions, and only one of 61 errors were not recoverable, the frequency and severity of errors were deemed acceptable considering the overall benefits of spot-scanning proton therapy. Errors are expected to be clinically manageable and to be safely handled in device-specific follow-up monitoring, and consequently, the decision algorithm is independent of number of fractions. As 7 mSv was the highest estimated neutron dose during any experimental scenarios, 7 mSv was used as threshold when establishing the decision algorithms, but some CIEDs may be subjected to even higher neutron exposure without experiencing not recoverable errors.

Estimation of secondary neutron dose is difficult and subject to great uncertainties. We chose to simulate the secondary neutron dose as ambient dose equivalent H*(10) using the same method as in the in-vitro

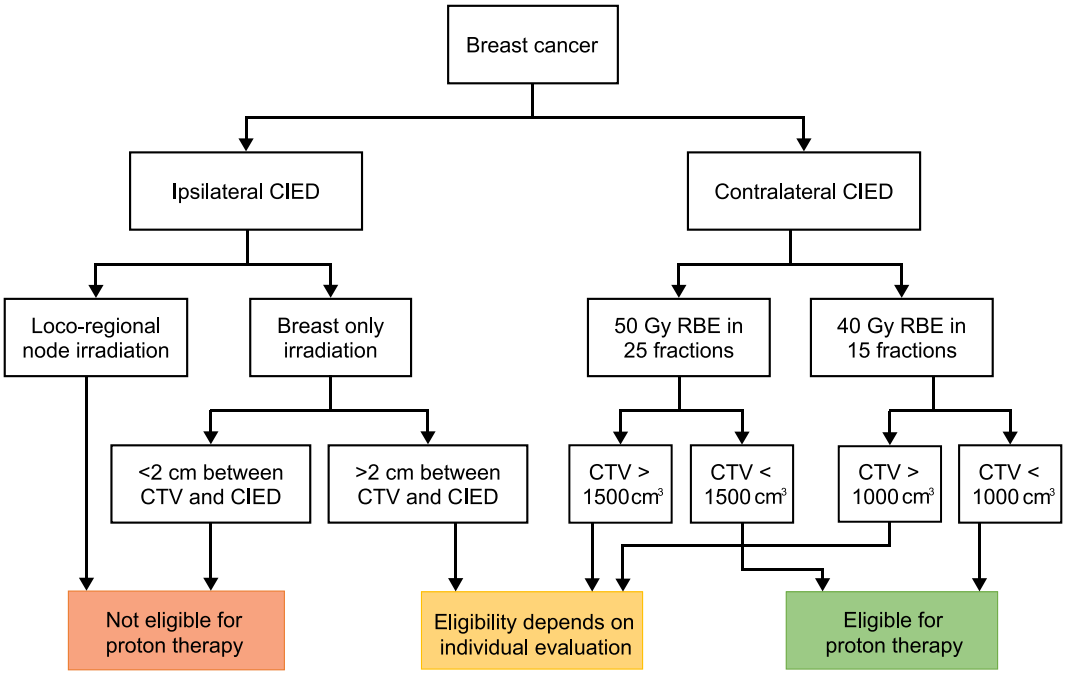

Fig. 3. Decision algorithm for evaluating if patients with breast cancer and adjacent cardiac implantable electronic devices (CIED) are eligible for proton therapy. The clinical target volume (CTV) is the total volume of all CTVs. Patients treated with simultaneous integrated boost follow the dose-fractionation scheme for non-boost target in the algorithm.

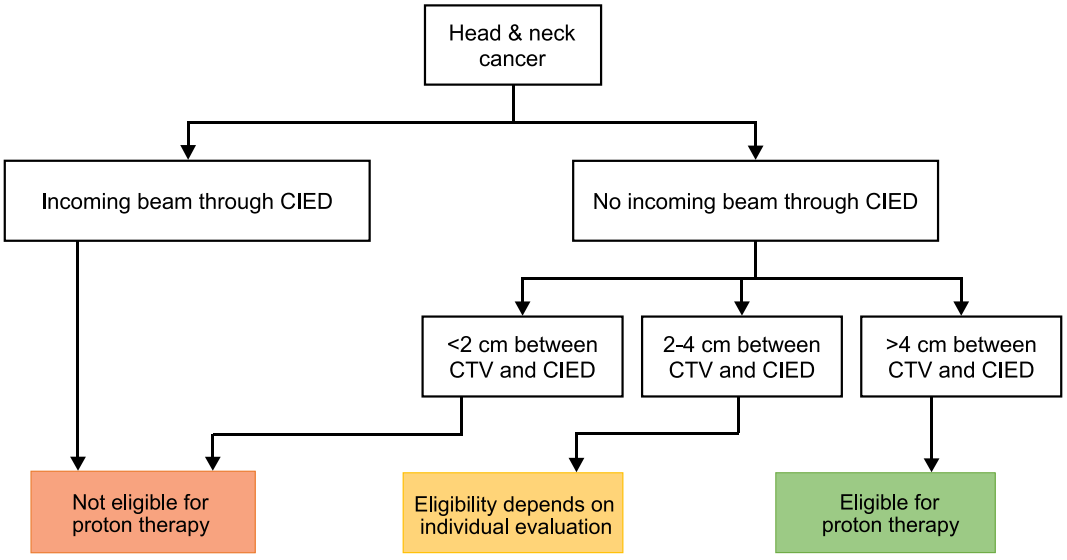

Fig. 4. Decision algorithm for evaluating if patients with head & neck cancer and an adjacent cardiac implantable electronic devices (CIED) are eligible for proton therapy.

study to minimise uncertainties from different simulation methods. We acknowledge that translating in-vitro measurements using a specific estimation method of secondary neutron dose into clinical practice is complex and it should be done with great caution. Consequently, we have established a clinical database for prospective follow-up of patients with CIED treated according to this algorithm at our institution.

The standard dose-fractionation scheme for adjuvant breast cancer patients requiring loco-regional irradiation was recently (September 2021) changed in Denmark from 50 Gy in 25 fractions to 40 Gy in 15 fractions. Secondary neutron dose was simulated for the 5.2 Gy RBE per fraction scheme and considered in this study because of the results from the FAST-Forward trial [23]. It is, however, currently not a standard dose-fractionation scheme used in Denmark, and we did consequently not include the scheme in the decision algorithm, but secondary neutron dose increased considerably (doubled) with this fractionation schedule. It should be stressed that the decision algorithm for eligibility for proton therapy in Fig. 3 is based on limited data with a moderate correlation between CTV size and secondary neutron dose; the distribution of neutron exposure is dependent of patient anatomy, and the neutron exposure of the CIED is dependent of the location of the CIED. Consequently, the decision algorithm was created to include these uncertainties by recommending individual evaluation of eligibility for a large range of CTV sizes. Simultaneous integrated boost for patients with breast cancer has increased dose per fraction to the boost CTV which will result in an increased amount of secondary neutrons, but we assumed that the boosts will not influent greatly since the boost CTV is a small

volume compared to the rest of the CTV.

All proton therapy plans in this study were created using a range shifter of 57 mm water equivalent thickness. A thinner range shifter would result in fewer secondary neutrons, so we recommend considering a thinner range shifter if the superficial parts of the target can be sufficiently covered.

For devices very close to the proton beam, artefacts on the planning CT scan may interfere with the proton therapy planning to a great extent such that patients may not be eligible for proton therapy due to CT artefact and not the risk of device malfunctions. Artefacts from CIED leads are limited compared with artefacts from the device. However, for patients with breast cancer, the CIED lead is often located near the internal mammary nodes, but it can be handled in the proton therapy planning by overriding the stopping power to tissue in this limited area and by increasing the beam range uncertainty in the robust optimisation. At our institution, scattering effects for two different type of CIED leads using silicone-based 3D radiochromic dosimeters and gafchromic films have been investigated, and no substantial scattering or under- or overdosage were observed (work in progress by Barbosa et al). The CIED leads are widely considered to be insensitive to radiation [10,24].

Spot scanning proton therapy is feasible for patients with pacemakers or implantable cardioverter defibrillators, even when the target is adjacent to the device. The risk of device malfunctions for cancer sites distant from the CIED location, e.g. pelvic, abdominal or brain cancers, is low.

The next step is to expand these decision algorithms for breast and H&N cancer targets with adjacent CIEDs to include other adjacent sites such as thyroid cancer, mediastinal lymphoma and lung cancer.

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.

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