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Inter-centre variability of CT-based stopping-power prediction in particle therapy: Survey-based evaluation

Vicki T. Taasti[a,1,*], Christian Bäumer[b,1], Christina V. Dahlgren[c,1], Amanda J. Deisher[d], Malte Ellerbrock[e,1], Jeffrey Free[f,1], Joanna Gora[g,1], Anna Kozera[h,1], Antony J. Lomax[i,1], Ludovic De Marzi[j,1], Silvia Molinelli[k,1], Boon-Keng Kevin Teo[l], Patrick Wohlfahrt[m,n,1], Jørgen B.B. Petersen[a,1], Ludvig P. Muren[a,1,2], David C. Hansen[a,1], Christian Richter[m,n,1]

[a] Department of Medical Physics, Aarhus University Hospital, Aarhus, Denmark
[b] Westdeutsches Protonentherapiezentrum, Essen gGmbH, Essen, Germany
[c] The Skandion Clinic, Uppsala, Sweden
[d] Department of Radiation Oncology, Mayo Clinic, Rochester, MN, USA
[e] Heidelberg Ion-Beam Therapy Center (HIT), Medical Physics, Heidelberg, Germany
[f] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[g] EBG MedAustron GmbH, Wiener Neustadt, Austria
[h] The Henryk Niewodniczanski Institute of Nuclear Physics, Polish Academy of Sciences, Kraków, Poland
[i] Center for Proton Therapy, Paul Scherrer Institut, Villigen, Switzerland
[j] Institut Curie, Centre de Protonthérapie, d'Orsay, Orsay, France
[k] CNAO, Pavia, Italy
[l] Department of Radiation Oncology, University of Pennsylvania, Philadelphia, USA
[m] OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden – Rossendorf, Dresden, Germany
[n] Helmholtz-Zentrum Dresden – Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany

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ABSTRACT

Background and purpose: Stopping-power ratios (SPRs) are used in particle therapy to calculate particle range in patients. The heuristic CT-to-SPR conversion (Hounsfield Look-Up-Table, HLUT), needed for treatment planning, depends on CT-scan and reconstruction parameters as well as the specific HLUT definition. To assess inter-centre differences in these parameters, we performed a survey-based qualitative evaluation, as a first step towards better standardisation of CT-based SPR derivation.

Materials and methods: A questionnaire was sent to twelve particle therapy centres (ten from Europe and two from USA). It asked for details on CT scanners, image acquisition and reconstruction, definition of the HLUT, body-region specific HLUT selection, investigations of beam-hardening and experimental validations of the HLUT. Technological improvements were rated regarding their potential to improve SPR accuracy.

Results: Scan parameters and HLUT definition varied widely. Either the stoichiometric method (eight centres) or a tissue-substitute-only HLUT definition (three centres) was used. One centre combined both methods. The number of HLUT line segments varied widely between two and eleven. Nine centres had investigated influence of beam-hardening, often including patient-size dependence. Ten centres had validated their HLUT experimentally, with very different validation schemes. Most centres deemed dual-energy CT promising for improving SPR accuracy.

Conclusions: Large inter-centre variability was found in implementation of CT scans, image reconstruction and especially in specification of the CT-to-SPR conversion. A future standardisation would reduce time-intensive institution-specific efforts and variations in treatment quality. Due to the interdependency of multiple parameters, no conclusion can be drawn on the derived SPR accuracy and its inter-centre variability.

* Corresponding author at: Department of Medical Physics, Aarhus University Hospital, Noerrebrogade 44, Aarhus, Denmark.
E-mail address: victaa@rm.dk (V.T. Taasti).

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1. Introduction

The heuristic conversion from CT number to particle stopping-power ratio (SPR) is one of the main contributions to uncertainties in treatment planning of particle therapy [1,2]. The conversion between CT number and SPR is usually performed by applying a piecewise linear function, referred to as a Hounsfield Look-Up-Table (HLUT).

In general, two different approaches exist for HLUT generation, "tissue-substitute-only" [3] and "stoichiometric" HLUT definition [4]. In the first case, only measured CT numbers and SPR from tissue-mimicking materials are used, whereas in stoichiometric approach the CT number and SPRs are predicted for different (biological) tissues of known tissue composition. The CT number prediction is specific for the used scan settings and requires a calibration, again with tissue substitutes.

As photon attenuation is dependent on photon energy, the CT number for a specific tissue will depend on the X-ray energy spectrum and detector response of the CT scanner, as well as the reconstruction parameters. Furthermore, beam-hardening will lead to CT number variations, especially for high-density materials, depending on the surrounding material and the size of the entire scanned object [5]. An improved CT number constancy can be obtained by applying reconstruction algorithms with sophisticated beam-hardening correction (BHC) that distinguishes between bone- and water-like contents.

Hence, a multitude of parameters influence the CT-to-SPR conversion: (a) CT scan parameters (e.g. energy spectrum, energy filters, type of detector); (b) reconstruction parameters (reconstruction kernel, including BHC, and image smoothing); (c) HLUT definition details. This leads to a cumbersome, work intense and error-prone process, which each particle centre currently must perform individually for their specific hardware (CT scanner) and software settings. This process consists of the following steps: [1] Definition of CT scan and reconstruction protocol, ideally after its optimisation regarding image noise and contrast as well as CT number constancy for different body regions (minimising remaining beam-hardening effects); [2] HLUT definition for this CT protocol; [3] Validation of the HLUT in a realistic scenario.

Currently, 68 new particle facilities are in planning or construction phase [6]. Hence, missing standardisation in CT-to-SPR conversion and resulting inter-centre differences as well as limited accuracy in range prediction, already today a problem for centres in operation [7], are becoming even more of an issue in the near future.

To assess the inter-centre variability of CT image acquisition and reconstruction as well as calibration and validation of HLUT-based CT-to-SPR conversion, a survey-based qualitative evaluation was carried out in the framework of the European Particle Therapy Network (EPTN). Aiming to access the current status of inter-centre differences, this investigation was intended as a first step towards better standardisation of CT-based SPR derivation.

2. Material and methods

A questionnaire was sent to ten currently operational particle therapy centres connected to the EPTN, an ESTRO task group, and two operational centres in the US in the period from 1st of December 2016 to 1st of February 2017. The questionnaire concerned the conversion of CT numbers in treatment planning CT datasets to SPRs used for dose and range calculations in particle therapy. It mainly focused on (a) details on CT scanners, acquisition and reconstruction parameters, (b) HLUT definition, (c) HLUT validation, (d) body-region specific HLUT selection, (e) artifact handling and, (f) quality assurance (see Supplementary data).

As the HLUT depends on the specific scan and reconstruction parameters, a direct comparison of the different HLUTs and their respective SPR accuracy was not possible per definition. The questionnaire therefore focused on how the HLUT had been designed and how beam-hardening was handled.

The centres were also asked if they intended to change their current calibration method in the near future and their views on how the accuracy of treatment planning could be improved. Further, five upcoming innovations and technological improvements, currently under strong investigation were rated from 1 (most important) to 6 (least important) regarding their potential to improve range prediction accuracy. These five suggestions were dual-energy CT (DECT), proton CT, photon-counting-detector CT (PCD-CT), better calibration methods, and Monte Carlo based dose calculation.

3. Results

3.1. Facility specifications

Most of the centres participating in this survey had recently started clinical operation. The median operational time was three years. The most experienced centre had been treating patients since 1991. This centre implemented their current HLUT in 2001. Only one other centre had been in operation for more than ten years. One centre was not yet in operation at the time of answering the questionnaire, but has in the meantime started treating patients.

All centres had the ability to treat with pencil beam scanning (PBS); however, five centres also used passive double-scattering (DS). The following treatment planning systems (TPSs) were used: Eclipse (Varian Medical Systems, Palo Alto, CA, USA; six centres), RayStation (RaySearch Laboratories, Stockholm, Sweden; four centres) and Syngo RT Planning (Siemens Healthineers, Forchheim, Germany; two centres). Two centres using RayStation also used XiO (Elekta, Stockholm, Sweden).

All centres treated tumours situated in the brain, the head-and-neck region, and the pelvis area (Fig. 1). Other common treatment sites were abdomen (nine centres), thorax (eight), and extremities (seven). Less common treatment sites were ocular tumours (five), and breast tumours (three).

A relative range uncertainty margin (RUM) of 3.5% of the total particle range was applied by seven institutions. An additional absolute RUM of 2 mm or 1 mm was used by two and one centre, respectively. One centre chose the additional margin based on the delivery technique, 1 mm for PBS plans and 3 mm for DS plans. Another centre, also using a relative RUM of 3.5%, increased their RUM in some cases, e.g. for cranio-spinal irradiations. A relative RUM of 3% was used by a

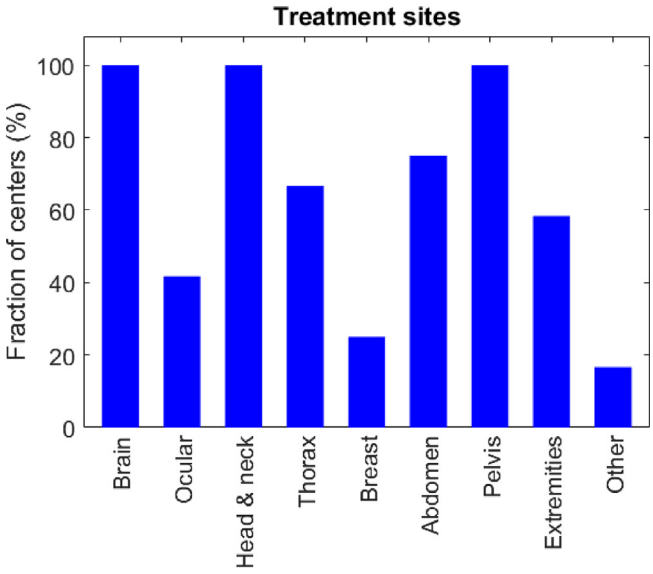

Fig. 1. Anatomical sites treated at the different particle therapy centres. The category "Other" includes cranio-spinal treatments and irradiations close to the spine.

Table 1
CT scanner specification used at the twelve different institutions. *Abbreviations*: BHC: Beam-hardening correction; FBP: Filtered back-projection. 2 ×/4 ×: Two/four CT scanners of the same model.

Institution number	Scanner model	Scan and reconstruction protocol		
		Tube potential (kVp)	Reconstruction	
			Type	Type of BHC
1	Siemens Sensation Open	120, 140	FBP	Bone-BHC for head Water-BHC for abdomen
2	Philips Brilliance Big Bore	120	FBP	Water-BHC
3	Philips Brilliance Big Bore	120, 140	FBP	Water-BHC
4	i. Toshiba Aquilion LB	i. 100, 120, 135	i. FBP	i. Water-BHC
	ii. Siemens Definition AS	ii. 100, 120	ii. Iterative	ii. Bone-BHC for head/Water-BHC for abdomen
	iii. Siemens Sensation Open	iii. 120	iii. FBP	iii. Bone-BHC for head/Water-BHC for abdomen
	iv. GE LightSpeed RT16	iv. 120, 140	iv. FBP	iv. Water-BHC
5	Siemens Definition AS	120	FBP	Water-BHC
6	i. Siemens Sensation Open ii. Siemens Definition – part of PET/CT Biograph40 iii. Siemens Confidence iv. Siemens Sensation Open	120	FBP	Bone-BHC for head Water-BHC for abdomen
7	Siemens Definition AS	120	FBP	Water-BHC
8	4 × Siemens Definition AS	120	Iterative	Water-BHC
9	Siemens Sensation	120	FBP	Water-BHC
10	i. Siemens Sensation Open ii. Philips TF Big Bore PET-CT	120	FBP	Water-BHC
11	2 × Siemens Definition AS	SECT: 120 DECT: 80/140	Iterative	Bone-BHC
12	Siemens Definition AS	120 for adults 80 for children	Iterative	Not provided

single centre, but this was increased to 5% when large uncertainties were foreseen, e.g. due to hardware, CT number uncertainty, or exact tumour location. Three institutions only used fixed RUMs, ranging from 2 to 7 mm. Here, different RUMs were used for different treatment situations, e.g. one centre used smaller margins (4 mm) for children compared to adults (5–7 mm).

3.2. CT scanner specification

Most centres had a CT scanner from either Siemens Healthineers (nine centres) or Philips (Philips Healthcare, Cleveland, OH, USA) (four centres). A GE (General Electric, Fairfield, CT, USA) and a Toshiba CT scanner (Toshiba Medical Systems, Ohtawara, Japan) were available at one institution each. A few CT scanners were integrated PET/CT scanners (Table 1).

Six centres were equipped with a scanner with DECT capabilities (Siemens Definition AS). However, only one centre used the DECT capability for a subgroup of their patients (brain and pelvic region). For body regions with potential body and/or organ motion, single-energy CT (SECT) was applied at this institution. All other centres exclusively used SECT for treatment planning. Treatment planning on contrast-enhanced CT datasets was not performed at any participating institution.

For SECT scans, a tube potential of 120 kVp was used by all participating institutions. In addition, four centres applied different tube potentials between 80 and 140 kVp depending on the patient group (Table 1).

The CT datasets were reconstructed using Filtered Back-Projection (FBP) in eight centres, while three institutions applied iterative reconstructions; one centre applied either FBP or iterative reconstruction based on the specific scanner used. One centre used a reconstruction protocol with bone-BHC for all patients, while four other centres limited the bone-BHC to head-and-neck cases and applied a water-BHC for all other cases. The remaining seven centres used water-BHC in all situations.

3.3. Influence of beam-hardening

Nine centres had examined the impact of setup variations on CT number stability, while the three other centres had not investigated the influence of beam-hardening. The most commonly performed test was to acquire CT scans of tissue substitutes placed in phantoms of different sizes. Two centres had investigated the influence of different positions of the tissue substitutes within the field-of-view (FOV). Other investigated parameters included tube potential (kVp), tube current-time product (mAs), detector settings, pitch, rotation time, reconstruction algorithm, slice thickness, and FOV.

3.4. HLUT definition

All centres applied an in-house defined HLUT. For one planning system (RayStation), the conversion from CT number to mass density needed to be specified, as a hardcoded conversion from mass density to particle SPR is applied internally using so-called core-materials.

The stoichiometric and tissue-substitute-only method was used by eight and three centres, respectively. One institution applied a combination of the stoichiometric method and experimental SPR measurements of tissue substitutes (Table 2). All centres used either inserts from CIRS (Norfolk, VA, USA) or Gammex (Middleton, WI, USA) for either the scanner-specific calibration of the stoichiometric or for their tissue-substitute-only calibration. It should be noted that mostly standardised electron density phantoms including the respective tissue surrogate inserts were chosen that are optimised for tissue-equivalence for photons, in contrast to other available tissue substitute materials optimised for proton-tissue-equivalence.

The HLUTs were defined by two to eleven linear line segments, either based on linear interpolation between data points or on step-wise linear fits for different CT number regions. For one institution, the individual linear fits were connected using connecting lines, while three centres joined the linear fits in the intersection of the two adjacent fits. A single centre, using a stoichiometric curve with three linear segments, placed their two intersection points at specific reference human tissue data points. Two centres forced their conversion curve through the data point for water.

Table 2
Specification of CT-to-SPR conversion (HLUT). Institution numbers are the same as in Table 1. *Abbreviations*: N/A: not applicable; WET: water-equivalent thickness. TPS: Treatment planning system.

Institution number	Calibration procedure	Calibration phantom	Reference human tissue data	# of line segments	# of HLUT	Same HLUT for multiple scanners	Validation procedure
1	Tissue substitutes	CIRS	N/A	10	6	No	WET of tissue substitutes
2	Tissue substitutes	CIRS	N/A	11	6 (3 for adults and 3 for children)	No	WET of tissue substitutes and animal tissues
3	Tissue substitutes	Gammex	N/A	2	3	No	WET of tissue substitutes and animal tissue, stoichiometric calibration
4	Stoichiometric	CIRS + Gammex	[24–26]	7	12 (4 different anatomical regions; different CT scanners and different kVp settings)	No	WET of custom-made phantom of organic skull, fat and air
5	Stoichiometric	CIRS	[24,25]	11	2 (head and body)	No	No. Only relative inter-comparison of calibrations at different hospitals using radiological phantoms
6	Stoichiometric	Gammex	[24,25]	7	2 (head and body)	No	WET of animal tissues and human bone tissue. Also WET for half of an Alderson head phantom and a frozen pig head
7	Stoichiometric	CIRS	[24–26]	3	1	No	WET of tissue substitutes and head phantom
8	Stoichiometric	CIRS	[26]	8	1	Yes	WET of porcine and bovine tissues, and for two beam paths through a human cadaver in a cranium (bone + brain) and a thigh (muscle + adipose) region
9	Stoichiometric	CIRS	[26]	4	1	No	WET of animal tissues
10	Stoichiometric	CIRS	[24,25]	7	1	Yes	None
11	Tissue substitutes + stoichiometric	CIRS + Gammex	[24,25]	3	1 SECT + 1 DECT	Yes	WET of different phantoms (tissue substitutes)
12	Stoichiometric	CIRS	[27]	NA	3 (head, body and children)	No	Proton radiography of animal tissues

HLUT re-assessment was performed yearly in four institutions. Other centres only checked for CT number stability. From the provided feedback, re-calibration seems to be necessary only very seldom. Two centres would check their HLUT after CT scanner repair and maintenance.

3.4.1. Multiple HLUTs

As beam-hardening can cause CT numbers to differ depending on the size of the object being scanned, it was assessed whether the same HLUT was applied for all anatomical sites or different HLUTs were used. Between one and six different HLUTs were applied. A common strategy was to have two different calibration curves allowing for a differentiation between head and abdomen. Five institutions also applied a dedicated HLUT for large and/or paediatric patients. E.g. one institution had three different HLUTs for children, differentiating between head, pelvis, and infants. Five institutions used a single HLUT for all treatment sites. One of them had minimised the influence of beam-hardening by using bone-BHC in all scans and verified the applicability of a single HLUT.

In centres with multiple CT scanners, either the same HLUT was used (two centres with the same CT scanner model and one centre with CT scanners from different vendors) or individual scanner-specific HLUTs were applied (four centres).

3.4.2. Experimental HLUT validation

All but two institutions had experimentally validated their CT-to-SPR conversion. The validation usually was performed with water-equivalent thickness (WET) measurements for tissue-substitute materials (six centres) and/or animal tissues (seven centres). One institution had also measured the WET for two beam paths through a human cadaver, resulting in a slight adjustment of their original HLUT effecting adipose tissue (Table 2).

3.5. Metal artifacts

For the assessment of metal artifacts, eight centres contoured the affected region and manually assigned the appropriate CT number, SPR or mass density. One institution assigned all metals to titanium. Three centres used metal artifact reduction (MAR) reconstruction algorithms. One of them applied it for all treatment planning scans.

Four institutions reported that they tried to avoid beam directions through metals and streak artifacts, one centre specified that they especially avoided beam directions parallel to streak artifacts. Another centre reported that patients would be referred to photon therapy if CT image quality was not sufficient due to metal artifacts in the beam path. This is probably the case in other centres too.

3.6. Future improvements

3.6.1. Planned changes

Seven of twelve institutions had specific plans for changing/updating their calibration process. For six of them, these updates included the use of DECT, though to varying degree. Some of these centres were awaiting results for validation of DECT-based range prediction in organic tissues and quantification of its gain in accuracy. One centre specifically wanted to use DECT to reconstruct pseudo-monoenergetic datasets similar to Ref. [5]. Other intended changes were the use of multiple HLUTs depending on the patient size, use of additional high-density tissue substitutes for HLUT definition, and implementation of bone-BHC. One centre intended to shift from a tissue-substitute-only to the stoichiometric approach.

3.6.2. Suggestions for further improvement

When the centres were asked to score given upcoming techniques regarding their potential to improve range prediction accuracy, a large spread was found for some techniques (Fig. 2). However, DECT and

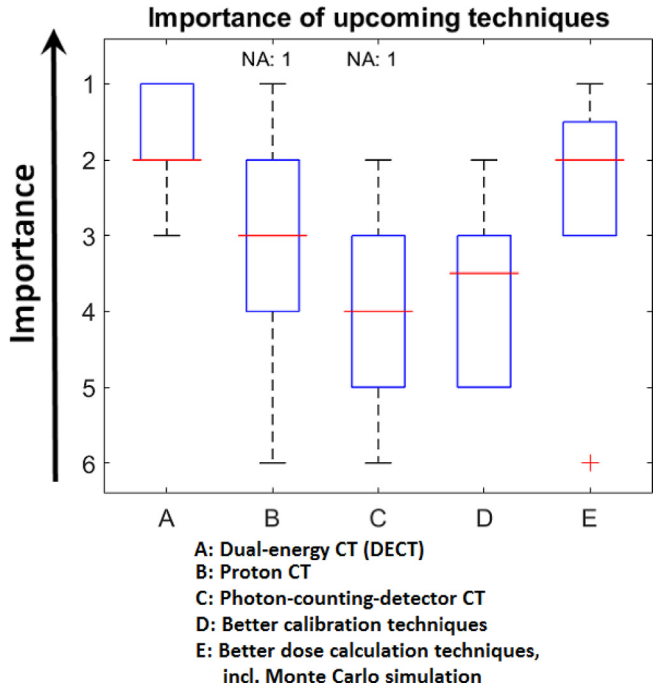

Fig. 2. Scored importance for SPR calculation in proton treatment planning. Importance score definition: 1: most important, 6: least important – more techniques could be scored equally. The median is shown by the red lines, and the blue boxes extend from the 25% to the 75% percentile. Abbreviation: NA: No answer. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

better dose calculation algorithms (including Monte Carlo dose calculations) were scored relatively high by all institutions. Other ideas, provided in free-form comments, included optimisation of CT protocols concerning image noise and beam-hardening, robust optimisation and adaptive therapy. In-vivo range verification was also suggested by five centres, including prompt-gamma, PET and proton range probes. One institution intended to investigate patient-specific HLUT adaptations. For one centre, it was important to deal with the largest sources of errors first, which they considered to be anatomical changes in the patient, therefore their most important improvement would be to change to an adaptive regime, with regular, maybe even daily, adaptations.

4. Discussion

The current status of CT-to-SPR conversion for particle treatment planning was assessed for twelve centres. Although mostly 120 kVp CT scans were used, a large inter-centre variability in implementation of CT scans, image reconstruction and especially in CT-to-SPR conversion was found. All participating institutions applied a heuristic HLUT which can therefore be seen as current gold standard.

This is in line with a previously performed HLUT inter-comparison at proton centres in USA [7], where large deviations were also found between the centre-specific conversion curves and a study-specific reference HLUT. However, also this study was unable to provide conclusions on SPR accuracy [7].

This study was not only helpful to derive the status-quo in CT-based SPR determination, but it could also be of immediate interest for particle centres in the start-up phase. Many particle therapy centres will have to define their HLUT in the near future. Currently, 42 proton and four carbon-ion centres are under construction and 22 proton facilities are in the planning phase [6]. From this fact and the large variability in CT-based SPR prediction found in this study, the benefit of a future standardisation of is obvious: It would reduce time-intensive institution-specific efforts. More important, harmonised SPR prediction would reduce variations in treatment quality, which would be of benefit when conducting multi-centric clinical trials. Hence, standardisation is highly demanded in particle therapy. It would be beneficial, if individual particle therapy centres, leading organisations as PTCOG, AAPM, ESTRO as well as CT manufacturers and TPS providers would put their efforts together to work towards this goal. Of course, such standardisation is not trivial, not only due to the dependence on CT scanner hardware. Nevertheless, CT manufacturers could provide scan and reconstruction protocols optimised for the demands in particle therapy (e.g. minimising remaining beam-hardening) and the particle therapy community could formulate a recommendation for HLUT-based CT-to-SPR conversion.

The majority of the participating institutions had addressed beam-hardening, either by using different HLUTs for different body regions (e.g. head and abdomen region) or by using sophisticated BHC. On the other hand, not all institutions with a single one-fits-it-all HLUT had investigated the size dependency. As a recommendation, the influence of beam-hardening should be quantified and addressed, especially for particle therapy centres relying on a single HLUT. If no bone-BHC is applied, the use of dedicated HLUT for specific body regions should be considered. Most centres had performed an experimental validation of their HLUT (Table 2), see Refs. [8–12].

In the near future, most participating centres expect a benefit for SPR prediction from DECT. However, only one institution has implemented DECT scans for clinical treatment planning, still applying a HLUT based on pseudo-monoenergetic CT datasets. No centre has so far implemented direct, patient-specific DECT-based SPR prediction. However, from recent investigations the evidence concerning the benefit of DECT for more accurate and patient-specific SPR prediction is growing [10,13–22]. The additional information derived from DECT-based SPR prediction can be used to either adapt the heuristic HLUT or to directly use it for fully patient-specific SPR prediction. Particle therapy centres that are currently in the phase of CT scanner procurement should consider having a DECT option available. Moreover, a large fraction of the participating institutions deemed proton CT and PCD-CT as of intermediate importance, even though no substantial experimental evidence for a clinically realistic scenario has yet been proven for either of these techniques. The use of proton radiography or range probe measurements [12,23] seems to be a pragmatic and promising alternative research avenue.

A limitation of this study was that only two centres outside Europe participated. Furthermore, several questions were in free-form format, which made it difficult to compare answers in those cases. Other questions were in multiple-choice format with only a few response options which potentially could limit the responses even though most of these questions were supplied with a text field for other answers. A principle limitation of the study is its qualitative nature, which for example did not allow a quantification of range prediction accuracy and its inter-centre variability. Note that different calibration curves for different CT hardware as well as scan and reconstruction settings can result in the same SPR prediction and (more importantly) vice versa. Therefore, a dedicated inter-centre comparison of SPR prediction accuracy will be performed using a ground-truth phantom and applying the institution-specific hardware- and software solutions in an end-to-end-test-scenario as a next step within the EPTN.

A large inter-centre variability in implementation of CT scans, image reconstruction and especially in HLUT definition was found in this survey-based study. It reveals that no standard procedures exist in terms of scan- and reconstruction-parameter optimisation, mitigation of beam-hardening artefacts and HLUT definition. All these issues are of importance and should be addressed with care by each particle therapy centre. Hence, a standardisation of CT-based SPR prediction is highly recommended.

Disclosure of conflicts of interest

The institution of CR and PW has an institutional research agreement with Siemens Healthineers in place. The authors have no further conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phro.2018.04.006.

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