Review paper

A review of dose calculation approaches with cone beam CT in photon and proton therapy

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ABSTRACT

Background and purpose: The use of cone beam computed tomography (CBCT) for performing dose calculations in radiation therapy has been widely investigated as it could provide a quantitative analysis of the dosimetric impact of changes in patients during the treatment. The aim of this review was to classify different techniques adopted to perform CBCT dose calculation and to report their dosimetric accuracy with respect to the metrics used.

Methods and materials: A literature search was carried out in PubMed and ScienceDirect databases, based upon the following keywords: “cone beam computed tomography”, “CBCT”, “cone beam CT”, “dose calculation”, “accuracy”. Sixty-nine peer-reviewed relevant articles were included in this review: thirty-one patient studies, fifteen phantom studies and twenty-three patient & phantom studies. Most studies were found to have focused on head and neck, lung and prostate cancers.

Results: The techniques adopted to perform CBCT dose calculation have been grouped in six categories labelled as (1) pCT calibration, (2) CBCT calibration, (3) HU override, (4) Deformable image registration, (5) Dose deformation, and (6) Combined techniques. Differences between CBCT dose and reference dose were reported both for target volumes and OARs.

Conclusions: A comparison among the available techniques for CBCT dose calculations is challenging as many variables are involved. Therefore, a set of reporting standards is recommended to enable meaningful comparisons among different studies. The accuracy of the results was strongly dependent on the image quality, regardless of the methods used, highlighting the need for dose validation and quality assurance standards.

1. Introduction

Cone beam computed tomography (CBCT) is a volumetric imaging modality currently used for verification of patient positioning in image guided radiation therapy (IGRT), and for assessing the potential need for adaptive radiotherapy (ART) [1,2]. In the patient treatment chain, kV systems mounted on linear accelerators (linacs) acquire images of the patient in the treatment position to verify the patient setup and hence enable adequate irradiation of the target. Geometrical variations of target volumes, organs at risk (OARs), weight changes (loss/gain), tumour regression and/or progression, which may occur during the overall treatment timeline, have resulted in CBCT images becoming an essential part of the process to ensure the calculated planned dose is delivered to the target and OARs. In this process, clinical staff investigate differences between the original planning CT (pCT) and CBCT acquired immediately prior to the treatment and use this information to

assess whether to reposition the patient, replan the treatment or to proceed as scheduled with the treatment.

Having these CBCT images available has made the prospect of also using them for dose calculations purposes, and dose accumulation during the entire treatment course, an attractive possibility. The potential for dose reporting and monitoring, particularly in a context of dose-guided ART, to quantify the dosimetric impact of significant changes in patients' anatomy over the course of the treatment, has been investigated [3,4]. A significant number of publications have emerged on this topic with many different approaches investigated. However, the results are highly variable due to different devices, protocols, datasets, metrics of comparison, treatment sites and treatment planning systems (TPS) being reported in the different studies.

This wide variety in the dose reconstruction methodologies and reporting methods used in this expanding field has identified a need to review the current status of the field. This work considers the current

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published studies which evaluate the accuracy of dosimetric calculations based on CBCT images. The advantages and disadvantages of the reported techniques are critically assessed with respect to metrics used for dosimetric analysis, for assessing feasibility and reproducibility with the aim of developing a set of recommendations for reporting future CBCT dosimetric studies.

1.1. Images acquisition: kV CBCT, MVCT and MV CBCT in-room imaging

Developed in the 1990's, the first CBCT scanners for dentomaxillofacial radiology were commercially available in 2001 (NewTomQR DVT 9000; Quantitative Radiology, Verona, Italy). In the mid 2000's CBCT started to be utilised in radiation therapy when Jaffray *et al.* [2] began investigating the integration of a kV x-ray source and a flat panel detector on a linac. At present, the gantry-mounted cone beam devices available are: Varian On Board Imager (OBI) (Varian Medical System, Palo Alto, USA); Elekta XVI (Elekta AB, Stockholm, Sweden); Siemens (Siemens AG, Erlangen, Germany); and Vero (BrainLAB AG, Feldkirchen, Germany & MHI, Mitsubishi Heavy Industries, Tokyo, Japan).

In 2014 the first kV CBCT was performed on a patient undergoing proton therapy at Penn Medicine's Roberts Proton Therapy Centre (USA) [5]. At present, the CBCT systems available in particle therapy can be gantry, nozzle, couch, or ceiling mounted. Proteus[®]ONE (IBA, Louvain-la-Neuve, Belgium), ProBeam[®] 360[°] Proton Therapy System (Varian Medical System, Palo Alto, USA), Sumitomo Proton Therapy System (Sumitomo Heavy Industries, Tokyo, Japan) and PROBEAT-RT Compact Single-Room Proton Beam Therapy System (Hitachi, Ltd., Tokyo, Japan) have gantry-mounted CBCT devices. Proteus[®]PLUS (IBA, Louvain-la-Neuve, Belgium) has a nozzle-mounted device and ImagingRing (MedPhoton GmbH, Salzburg, Austria) uses a couch-mounted CBCT device. In-house and commercial robotic C-arm CBCT imaging devices (Hitachi, Ltd., Tokyo, Japan) have also been developed for partial gantries and fixed beam ports (e.g. ceiling).

Megavoltage CBCT (MV CBCT) presents an alternative to the use of a kV x-ray source does not require additional equipment attached to the standard linac design. While kV imaging provides better image quality and soft tissue contrast, MV imaging is less affected by prostheses artefacts and may be better for bulky patients [6,7]. Currently, the MV CBCT systems in use on standard linac designs are the Artiste MVision[™] (Siemens AG, Erlangen, Germany) and the In-Line kView[™] (Siemens AG, Erlangen, Germany). Other linac designs include the Varian Halcyon (Varian Medical System, Palo Alto, USA), and the systems in use or available from Accuray; the TomoTherapy and the Radixact Treatment Delivery Systems (Accuray, Sunnyvale, CA), which combine the features of a linac and a helical fan beam MVCT [8]. Although the Tomotherapy unit is not a CBCT machine, four studies performing dose calculation based on TomoTherapy MVCT were found in literature and were included (separately) in this review (Table 7). An overview of the specifics of the CBCT available devices and acquisition protocols are presented in [5,9] and summarised in Appendix A1.

1.2. Image artefacts

Regardless of which imaging device/modality is used, image artefacts are generated by discrepancies between the experimental setup and the mathematical assumptions established in the chosen image reconstruction algorithm. The most widely used reconstruction algorithm for CBCT is the Feldkamp algorithm [10], either in its original form or modified [11]. From a theoretical point of view, this algorithm considers a 3D adaptation of the filtered back projection (FBP) method used in fan beam CT [12]. When using FBP, a dependency between the distance from the central plane and the image quality degradation, has been shown [13]. Consequently, when performing CBCTs on large FOVs, the larger amount of detected scatter radiation may affect the image quality. A valid strategy currently adopted to reduce the scatter contribution considers the use of a beam shaping device, such as bowtie

filters and collimators, or by placing anti-scatter x-ray grid on the detector, which decrease the primary dose but also reduces the cupping artefacts. An overview of the main CBCT artefacts, including their appearances and causes, is presented in the [supplementary material \(Table S1\)](#) while an extensive description can be found in [9].

Image artefacts may have a non-negligible impact on any dose calculation since treatment planning relies on the accurate determination of the CT numbers, which corresponds to the photons or protons attenuation inside the scanned object. Therefore, corrections techniques may be implemented and different protocols can be selected when acquiring CBCT images in order to ensure that the image artefacts are minimised. Post-processing algorithms can be used to correct for CBCT imaging artefacts such as scattering, beam hardening, ring artefacts, motion artefacts, and cupping artefacts [9,12].

Finally, the implementation of iterative reconstruction algorithms [14,15] and the introduction of machine learning techniques into the tomographic image reconstruction process [16] have more recently started being investigated to improve the image quality relative to FBP.

1.3. Treatment planning systems and dose calculation algorithms

CBCT dose calculations are typically carried out using a standard TPS. There are many different types of TPS available which may have dose calculation algorithms each of which have limitations. These limitations can depend on how well the physical interactions are modelled within the dose calculation algorithm and how well the beam modelling is carried out when commissioning the TPS [17]. Knöös *et al.* [18] grouped the model-based algorithms for TPS in external photon beam therapy into three types: Type A and B, which differ on the level of modelling of the lateral electron transport and Type C, the last generation of dose calculation algorithms, solving the electron transport either using the Boltzmann equations or Monte Carlo (MC) calculations.

Type A and B algorithms have shown to have dose < 1.0% of expected within the target in prostate [18,19], although a Type C algorithm is superior if air gaps are within the rectum [20]. In lung, improved dosimetric accuracy has been shown by employing Type B or Type C algorithms. Similar results have been observed for head and neck patients [21,22]. In proton therapy, MC has been shown to better model heterogeneities compared to the standard pencil beam model [23]. The TPS with associated dose calculation algorithms used in the identified publications included in this review are listed in the [supplementary material \(Table S2\)](#).

The choice of an appropriate algorithm is crucial to avoid inaccuracies in the dose calculation. However, when comparing the dose calculated between different studies, the beam model used should be taken into account in order to avoid biased comparisons, since beam parameters, tumour size and location may all have a non-negligible impact on the dose calculation accuracy depending on the beam model used [24]. Guidelines to follow for the commissioning of a new TPS are provided in [25], but in order to have a standard beam model for dose calculation (i.e. an unbiased comparison), beam data should be provided. The different contributions to the dose prediction errors from the beam model and the dose calculation algorithm are not separated and the evaluation of this is outside the scope of this review.

1.4. Description of the radiotherapy workflow

Radiotherapy treatment plans are typically created using pCT images, in which target volumes (gross tumour volume, GTV – clinical target volume, CTV – internal target volume, ITV – planning target volume, PTV) and OARs are contoured and plans created. A calibration curve is then used to convert the CT numbers (measured in Hounsfield unit – HU) into electron density (ED), relative electron density (RED), physical density (PD) or stopping power ratio (SPR) so that the attenuation in the object can be calculated. These curves are either

Table 1a
CBCT dose calculation studies using the pCT calibration for different tumour sites in patients, in chronological order.

Author	Make / Model	TPS	Algorithm	Site	Protocol	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Ding et al. (2007) [41]	Varian Trilogy	Eclipse	AAA	Prostate (2)	Not defined (HF, 125kV, 80mA)	Inhomogeneity (modified Batho)	n/s	pCT	$D_{\text{mean-PTV}}$	n/s	D_{mean} : Bld = 1.3, Rct = 0.6, SemVsc = 0.6, Urt = 0.7, LHip = 0.1, RHip = 0.0 D_{mean} : LPar = 0.5, RPar = 0.5, SC = 1.2
Richter et al. (2008) [35]	Elekta Synergy XVI	Pinnacle ADAC (v7.6s)	n/s	Prostate (5) Thorax (5) Head (5)	Pelvis Thorax Head	n/a	User specified CT# to PD	pCT	D_{mean}	n/s	DVH of one patient per site
Lee et al. (2008) [116]	Varian Trilogy	Eclipse	AAA	H&N (6)	n/s	n/a	User specified CT# to RED	pCT	$D_{\text{PTV-95\%}}$	n/s	D_{max} : SC = 1.0, BS < 1.1
Boggula et al. (2009) [36]	Elekta Synergy XVI	Corvus	PB	Prostate (3)	Pelvis	n/a	User specified CT# to RED	pCT	Absolute	33.3 ± 18.8 3%/3mm	n/s
Onozato et al. (2014) [42]	Varian OBI (v1.5)	Eclipse (v8.6.15)	AAA	Prostate (10)	Pelvis	n/a	User specified CT# to ED	pCT	$D_{\text{mean-PTV}}$	97.0	D_{mean} : Bld = 1.24 ± 0.91, Rct = 1.02 ± 1.11
Noufal et al. (2016) [117]	Varian Clinac IX OBI	Eclipse	AAA	Prostate (10) Brain (10)	Chest Head	n/a	User specified CT# to RED	pCT	$D_{\text{PTV-95\%}}$	91.0 ± 0.0 88.8 ± 0.1	D_{mean} : Bld < 1.5, Rct < 2.3 D_{mean} : RLens < 1.5, LLens < 1.5, ROptNrv < 1.5, LOptNrv < 2.0, Ch < 1.0, BS < 2.0 D_{mean} : RPar < 1.5, LPar < 1.0, Mnd < 1.0, SC < 2.0 Histogram – Lng-GTV(V_{20Gy}) < 2.0, D_{max} (0.1cc): SC < 2.0, Oes(V_{35Gy}) < 3.0 – D_{mean} Lng < 2.5, H < 2.5, Oes < 3.0 Histogram – Lng-GTV(V_{20Gy}) < 8.0, D_{max} (0.1cc): SC < 8.0, Oes(V_{35Gy}) < 8.0 – D_{mean} Lng < 6.0, H < 8.0, Oes < 9.0 D_{mean} : LPar = 5.42 ± 3.06
De Smet et al. (2016) [37]	Varian Truebeam STx (v1.5)	Eclipse	AXB 10.0	Lung (6)	Thorax	n/a	User specified CT# to PD	rCT	$D_{\text{mean-PTV}}$	n/s	
Arai et al. (2017) [45]	Elekta Synergy XVI (v5.0)	Pinnacle (v9.8)	n/s	Lung (10)	Clinical optimized	n/a	n/s	pCT	$D_{\text{PTV-98\%}}$	27.1 ± 31.8 3%/3mm	
Giacometti et al. (2018) [43]	Varian Clinac iX OBI 1.6	XiO-M	PB	H&N (10)	Not defined (FF, 100kV, 10mA)	n/a	n/s	pCT	$D_{\text{PTV-98\%}}$	87.8 ± 7.4	
Marchant et al. (2018) [38]	Elekta Synergy XVI (v4.5.5.0)	Pinnacle (v9.8)	n/s	Pelvis (15) Lung (15) H&N (14)	n/s	n/a Shading n/a Shading n/a Shading	User specified CT# to RED	pCT	$D_{\text{mean-PTV}}$	99.8 2% / 0.1mm (50% threshold) n/s	D_{median} : Bld = 0.0, Rct = 0.4 D_{median} : SC = -0.2, BS = -0.1 D_{max} (0.01cc): SC = 0.2, D_{max} (0.1cc): Oes = 0.1, H = 0.5 Rct(V_{40Gy}) = 9.62 ± 6.93 Rct(V_{40Gy}) = 0.09 ± 0.55 D_{max} (1cc): SC = 4.11 ± 2.59 D_{max} (1cc): SC = 0.35 ± 0.74 D_{mean} : CPar = 0.15 ± 0.58 D_{mean} : CPar = 0.10 ± 0.34

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Table 1a (continued)

Author	Make / Model	TPS	Algorithm	Site	Protocol	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Wang et al. (2019) [44]	Varian Truebeam	Eclipse (v13.6)	AAA	Prostate (10)	n/s	n/a	n/s	pCT	$D_{\text{mean-PTV}}$	1%/1mm	D_{mean} : Bld = 0.5 ± 0.3 , Rct = 0.5 ± 0.6 , Fem = 0.2 ± 0.3 D_{mean} : Bld = 0.2 ± 0.1 , Rct = 0.2 ± 0.3 , Fem = 0.1 ± 0.3 D_{mean} : BS = 0.02 ± 0.03 , OptNrv = 0.02 ± 0.05 , Ch = 0.02 ± 0.05
	Varian Truebeam (Novalis Tx)			Brain (12)		n/a				(99.0; 100.0)	D_{mean} : BS = 0.02 ± 0.03 , OptNrv = 0.02 ± 0.05 , Ch = 0.02 ± 0.05
						Scatter (machine learning [118])				(99.0; 100.0)	D_{mean} : BS = 0.00 ± 0.00 , OptNrv = 0.01 ± 0.02 , Ch = 0.00 ± 0.00
						Scatter (machine learning [118])				(99.0; 100.0)	D_{mean} : BS = 0.00 ± 0.00 , OptNrv = 0.01 ± 0.02 , Ch = 0.00 ± 0.00

TPS = treatment planning system; AAA = analytical anisotropic algorithm; PB = pencil beam; AXB = Acuros XB; H&N = head and neck; HF = half fan; FF = full fan; CT# = CT number; ED = electron density; RED = relative electron density; PD = physical density; pCT = planning CT; rCT = rescanned CT; CTV = clinical target volume; GTV = gross tumour volume; PTV = planning target volume; D_{max} = maximum dose; D_{mean} = mean dose; D_{median} = median dose; $D_{\text{PTV-50\%}}$ = dose delivered to 50% of PTV; $D_{\text{median-PTV-50\%}}$ = median dose delivered to 50% of PTV; $D_{\text{max}}(\#cc)$ = maximum dose to #cm³ of the PTV; R = right; L = left; C = contra; Bld = bladder; Rct = rectum; SemVsc = seminal vesicle; Urt = urethra; Par = parotid; SC = spinal cord; OptNrv = optic nerve; BS = brain stem; Mnd = mandible; Lng = lung; Oes = oesophagus; H = heart; Fem = femur; V(#Gy) = volume receiving #Gy or more; n/s = not supplied; n/a = not applicable.

provided within the TPS and verified during commissioning (denoted as the “TPS calibration curve”) or created by the user during commissioning (denoted as the “user specified calibration curve”). Calibration curves converting CBCT HU values into PD/RED/ED/SPR can also be generated using phantom/patient/population-specific measurements as described in Section 3.1.2.

Before delivering the treatment, CBCT scans are typically acquired and registered (via rigid or deformable registration) onto the pCT, to verify the positioning of the patient. In case of anatomical differences between pCT and CBCT, physicists, radiographers and clinicians decide if the original plan can still be delivered or if replanning the patient is necessary, resulting in a new rescanned CT (rCT), new contours, and new plan. In this scenario, the possibility of performing a dose calculation based on CBCT images would provide a quantitative analysis of the dosimetric impact of any changes, and could be work and time saving for both clinical staff and patients. Avoidance of rescanning will also reduce the dose received by the patient.

2. Methods

2.1. Search criteria

PubMed and ScienceDirect databases were used to identify published articles reporting on the accuracy of dose calculations performed on CBCT images as compared to the chosen reference dose. Using a combination of the keywords “cone beam computed tomography”, “CBCT”, “cone beam CT”, “dose”, “calculation”, “accuracy” over one hundred peer-reviewed articles published in English between January 2006 and December 2019 were retrieved. Articles about dental CBCT, imaging dose due to CBCT, non-radiotherapy topics or those not presenting a quantitative analysis were excluded, resulting in sixty-nine peer-reviewed articles being included.

A further four peer-reviewed articles were added after including the words “tomotherapy” and “MV CT” to the keywords. Studies were excluded from the review that investigated the impact of geometric shifts or anatomical changes in on the dose calculation, reported on the additional dose delivered to the patients from the daily/weekly CBCT image acquisition or were focused on CBCT image quality, rather than presenting a method to perform dose calculations based on CBCT. Including the words “gamma knife”, “electrons”, or “heavy ion” in the search criteria identified publications in PubMed and ScienceDirect, but none of these were found to specifically investigate CBCT dose calculation methods.

2.2. Reference dose

To assess the feasibility of performing dose calculation based on CBCT, in the majority of the cases, the dose calculated on pCT or rCT (acquired on a date closer to the treatment start or during the treatment itself to monitor the response of the patient) were considered the ground truth, i.e. the reference dose to be used to evaluate the difference from CBCT dose calculations. Another possibility described in literature is the use of “virtual” CT (vCT), generated by deforming pCTs onto the geometry of CBCTs [26]. Both deformable image registration [27–29] and artificial intelligence-based methods [16,30–32] were adopted for generating vCT in dose calculation studies. Only two studies reported on the use of farmer chambers and Gafchromic films to measure the actual ground truth dose [33,34] and the measured dose was compared both with the pCT and the CBCT calculated dose.

2.3. Metrics

Since many different metrics were used, we have chosen to report only the metrics most commonly used in the literature (summarised in Appendix A.2) in order to facilitate the comparison among different studies, e.g. gamma analysis, mean/median PTV/GTV/PTV dose

Table 1b
CBCT dose calculation studies using the pCT calibration for different phantoms, in chronological order.

Author	Make / Model	TPS	Algorithm	Phantom	Protocol	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Yoo et al. (2006) [103]	Varian OBI	Eclipse	n/s	CIRS 002HAS6N small homogeneous cylindrical phantom (head)	Not defined (125kVp, 80mA)	Inhomogeneity (modified Batho)	n/s	pCT	$D_{\text{mean-phantom}}$	(−0.6; −0.3)	n/s
Lee et al. (2008) [116]	Varian Trilogy	Eclipse	AAA	CIRS 002HAS6N large homogeneous ellipsoidal phantom (body)						(−2.5; 0.7)	
Richter et al. (2008) [35]	Elekta Synergy XVI (v7.6s)	Pinnacle ADAC	n/s	CIRS 008 dynamic thorax (inhomogeneous phantom)						(−3.4; −0.3)	
Aubry et al. (2009) [101]	Siemens MVision	n/s	n/s	RANDO pelvis	n/s	n/a	User specified CT# to RED	pCT	D_{max}	< 0.5	n/s
Boggula et al. (2009) [36]	Elekta Synergy XVI (v6.2)	Corvus	PB	Pelvic phantom	Pelvis	n/a	User specified CT# to RED	pCT	$D_{\text{mean-phantom}}$	(6.8 ± 5.6; 18.4 ± 3.7)	n/s
Guan et al. (2009) [49]	Varian OBI (v1.4)	Eclipse	AAA	Pelvic phantom	Pelvis	n/a	User specified CT# to RED	pCT	$D_{\text{mean-phantom}}$	(8.8 ± 6.3; 19.9 ± 2.5)	n/s
Hatton et al. (2009) [33]	Varian 2100 IX OBI	Eclipse (v8.6)	AAA	Slabs phantom RT01 trial semi-anthropomorphic phantom	Pelvis	Cupping & missing data	User specified CT# to RED	Ionization chamber	$D_{\text{mean-phantom}}$	(−4.0; 8.0)	n/s
Qian et al. (2010) [104]	Varian Trilogy	Eclipse	AAA	Catphan 600	Not defined (HF, 125kVp, 80mA, 25ms)	n/a	User specified CT# to RED	pCT	n/s	3%/3mm	68.9 ± 5.5 n/s
Hu et al. (2011) [39]	Elekta Synergy XVI (v7.6c)	Pinnacle	n/s	Catphan 503	Not defined (120kVp, 32mA, 10ms)	n/a	User specified CT# to PD	pCT	$D_{\text{mean-PTV}}$	(−1.1; −0.2)	n/s
Wen et al. (2012) [97]	Varian Trilogy	Eclipse (v8.6)	PB	RANDO pelvis	Pelvis	n/a	User specified CT# to ED	pCT	$D_{\text{mean-PTV}}$	< 5.0	n/s
Onozato et al. (2014) [42]	Varian OBI (v1.5)	Eclipse (v8.6.15)	AAA	Pelvic phantom	Pelvis	n/a	User specified CT# to ED	pCT	$D_{\text{mean-PTV}}$	< 1.0	n/s
Ankrah et al. (2014) [107]	Varian Truebeam	Eclipse	n/s	Catphan 504 CIRS062M	Not defined (HF, 125kV, 254mA)	n/a	User specified CT# to ED	pCT	$D_{\text{mean-phantom, centre}}$	0.0	n/s
Noufal et al. (2016) [117]	Varian Clinac IX OBI	Eclipse	AAA	Catphan 504	n/s	n/a	User specified CT# to RED	pCT	n/s	(−1.8; −1.4)	n/s

D_{mean} : Bld = (−1.1; −0.4), Rct = (−0.2; 0.1)
 D_{mean} : Bld = (−0.8; −0.7), Rct = (−0.7; 2.7)
 Histogram – D_{mean} : Bld = 0.4; Rct = 0.1
 D_{mean} : ROptNrv = 0.8, LOptNrv = 0.2, Ch = 0.1, BS = 0.2
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Table 1b (continued)

Author	Make / Model	TPS	Algorithm	Phantom	Protocol	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Aral et al. (2017) [45]	Varian Clinac iX OBI 1.6	XIO-M	PB	Pelvic phantom	Pelvis	n/a	n/s	pCT	$D_{PTV,98\%}$	3%/3mm	D_{mean} : Rct = 0.58, Bld = 0.89 D_{mean} : LPar = 0.67
Marchant et al. (2018) [38]	Elekta Synergy XVI (v4.5.0)	Pinnacle (v9.8)	n/s	Alderson Rando (prostate) Alderson Rando (lung)	n/s	n/a Shading n/a Shading	n/s	pCT	$D_{mean-PTV}$	n/s	Rct(V_{40Gy}) = 24.1 Rct(V_{40Gy}) = -1.4 $D_{max}(1cc)$: SC = 4.2 $D_{max}(1cc)$: SC = -0.3

TPS = treatment planning system; AAA = analytical anisotropic algorithm; PB = pencil beam; H&N = head and neck; HF = half fan; FF = full fan; CT# = CT number; ED = electron density; RED = relative electron density; PD = physical density; pCT = planning CT; CTV = clinical target volume; PTV = planning target volume; D_{mean} = mean dose; D_{max} = maximum dose; $D_{PTV,98\%}$ = dose delivered to 98% of PTV; $D_{max}(cc)$ = maximum dose to #cc of the PTV; OAR = organ at risk; R = right; L = left; Bld = bladder; Rct = rectum; OptNrv = optic nerve; Ch = chiasm; Par = parotid; BS = brain stem; SC = spinal cord; V (#Gy) = volume receiving #Gy or more; n/s = not supplied; n/a = not applicable.

difference, and dose covering specific percentages of the PTV/CTV/GTV.

3. Results

3.1. CBCT dose calculation techniques

Sixty-nine studies were found highlighting the potential of using CBCT images for dose calculation purposes: thirty-one patient studies, fifteen phantom studies and twenty-three patient and phantom studies. The techniques adopted in these studies have been grouped in the following categories:

- 1- pCT calibration: The dose is calculated on the CBCT images using the pCT calibration curve adopted for the pCT images. The patient and phantom studies retrieved from the literature adopting this method are listed in Table 1a and 1b, respectively.
- 2- CBCT calibration: The dose is calculated on the CBCT images using the CBCT calibration curve generated via phantom/patient/population-specific measurements. The patient and phantom studies retrieved from the literature adopting this method are listed in Table 2a and 2b, respectively.
- 3- HU override: The dose is calculated on the CBCT images after overriding the CBCT HU values with either HU density or CT numbers from the CT images. The patient and phantom studies retrieved from the literature adopting this method are listed in Table 3a and 3b, respectively.
- 4- Deformable image registration (DIR): The dose is calculated on images generated by deforming the geometry of pCT/rCT images onto CBCT images via a deformation vector field (HU values are not modified). The patient and phantom studies retrieved from the literature adopting this method are listed in Table 4a and 4b, respectively.
- 5- Dose deformation: The dose is calculated by deforming/mapping dose values from an irradiated geometry (CBCT) to a reference geometry (pCT), utilising a deformation vector field. The patient and phantom studies retrieved from the literature adopting this method are listed in Table 5a and 5b, respectively.
- 6- Combined techniques: The dose is calculated by adopting a combination of the listed techniques, including CBCT calibration, HU override and DIR. The patient and phantom studies retrieved from the literature adopting this method are listed in Table 6a and 6b, respectively.

Artefact correction can be applied on the CBCT images before adopting any of these dose calculation methods.

Fig. 1 shows the number of patients (and matching publications) for whom the listed techniques were applied, grouped according to the tumour site. The main results and characteristics (CBCT device and protocol used, TPS and dose calculation algorithm adopted, patient/phantom imaged) reported in these studies are summarised in Tables 1–7.

3.1.1. pCT calibration

Table 1a and Table 1b summarise the publications retrieved from the literature for patient and phantom studies in which dose was calculated directly on the CBCT images applying the calibration curve adopted for the pCT images used for planning. This methodology does not require any extra measurements because it calculates the attenuation corresponding to the CBCT HU values by utilising the calibration curve generated with CT numbers, generated with a different imaging modality (different energies, FOVs, collimation, etc). Although discrepancies between CBCT HU values and CT numbers are known, this method has been studied in 20 out of 69 cases investigating CBCT dose calculation.

Elekta CBCT showed large differences between CBCT calculated and

Table 2a
Dose calculation studies using the CBCT calibration for different tumour sites in patients, in chronological order.

Author	Make/model	TPS	Algorithm	Site	Protocol	CBCT Calibration	Artefact Correction	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Morin et al. (2007) [102]	Siemens MVision	Pinnacle (v7.6)	n/s	NPC (1) Tongue (1)	rFOV	Phantom CBCT# to RED	Uniformity	pCT	n/s	3%/3mm 3%/3mm (30% threshold)	DVH 98.0 (78.0; 84.0)
Richter et al. (2008) [35]	Elekta Synergy XVI	ADAC Pinnacle (v7.6s)	n/s	Prostate (5)	Pelvis	Catphan(CTP503) CBCT# to PD	n/a	pCT	D _{mean}	12.7 $\pm$ 1.5 n/s	DVH
				Thorax (5)	Thorax	Population-based CBCT# to PD Patient-specific CBCT# to PD Catphan(CTP503) CBCT# to PD Population-based CBCT# to PD Patient-specific CBCT# to PD Catphan(CTP503) CBCT# to PD Population-based CBCT# to PD Patient-specific CBCT# to PD			1.3 $\pm$ 1.0 1.2 $\pm$ 0.9 6.2 $\pm$ 4.7 1.7 $\pm$ 2.4 1.7 $\pm$ 2.0 1.6 $\pm$ 2.2 1.4 $\pm$ 1.9 1.4 $\pm$ 1.9		
Cheung et al. (2009) [119]	Siemens MVision	KonRad Inverse	PB	Pelvis (2) H&N (6)	Low dose image acquisition	Phantom CBCT# – PD	Scatter [101]	pCT	D _{GTV,95%}	n/s 0.10	DVH D _{mean} : LPar = 5.8, RPar = 18.0, Lrx = 6.7, D _{1%} : SC = 2.2, Mnd = 1.8, BS = 1.1, LTMJ = –1.6, RTMJ = –0.5 Reported for individual patients
Hu et al. (2010) [58]	Elekta Synergy XVI	Pinnacle (v8.0d)	CCSC	Brain (3) H&N (3)	Not defined (S20, 100kV, 65mAs)	H&N one patient-specific CBCT# to PD	n/a	pCT	n/s	2%/2mm (10% threshold)	D _{mean} : Bld = 0.4, Rct = 0.9, FemHeads = 0.2 D _{max} : SC = –0.3, OES = 0.0, D _{mean} : Lng = 0.0 D _{max} : SC = 5.1, BS = 4.2, D _{mean} : Par = 1.5 lps lng(V ₅₀) = 0.0, H(V ₅) = 0.0
Fotina et al. (2012) [53]	Elekta Synergy XVI	iPlan (v4.5.0)	XV MC	Prostate (10) Lung (10) H&N (7)	Prostate (no bowtie) Lung (no bowtie) Head (no bowtie)	Phantom (Catphan) CBCT# to ED Phantom (Catphan) CBCT# to ED Phantom (Catphan) CBCT# to ED	n/a	Population-based CBCT# to ED	–2.0 –2.2 4.0	n/s	
Wang et al. (2013) [40]	Elekta Synergy XVI	Pinnacle (v8.0)	n/s	Breast (10)	Not defined (S20, 120kVp, 31mAs)	CBCT# to PD [58]	Scatter	pCT	D _{PTV,95%}	0.0 n/s	
Held et al. (2015) [120]	Siemens Artisite & In-Line kView MV CBCT	Pinnacle (v9.2)	n/s	Pelvis (9) Thorax (9)	eFOV eFOV	Phantom (CIRS 062 + water cylinder) CBCT# to PD – eFOV	n/a	pCT	n/s	3%/3mm (90.0; 99.0) (47.0; 100.0)	n/s
				Brain (7) Extremities (2)	rFOV rFOV	Phantom (CIRS 062 + water cylinder) CBCT# to PD – rFOV				(99.9; 100.0) (92.0; 99.0)	

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Table 2a (continued)

Author	Make/model	TPS	Algorithm	Site	Protocol	CBCT Calibration	Artefact Correction	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
De Smet et al. (2016) [37]	Varian Truebeam (v1.5)	Eclipse	AXB 10.0	Lung (6)	Thorax	Population-based (thorax) CBCT# to PD	n/a	rCT	$D_{\text{mean-PTV}}$	n/s	Histogram – Lng-GTV(V_{20Gy}) < 1.0 – D_{mean} : Lng < 1.0, H < 3.0, OES < 2.0 – D_{max} (0.1cc): SC < 1.0 – OES(V_{35Gy}) < 2.0 Histogram – Lng-GTV(V_{20Gy}) < 1.0 – D_{mean} : Lng < 1.0, H < 3.0, OES < 1.5 – D_{max} (0.1cc): SC < 1.5 – OES(V_{35Gy}) < 2.0 Histogram – Lng-GTV(V_{20Gy}) < 1.0 – D_{mean} : Lng < 1.0, H < 3.0, OES < 1.5 – D_{max} (0.1cc): SC < 1.5 – OES(V_{35Gy}) < 2.0
		Pinnacle (v9.8)	n/s	Lung (10)	Clinical optimized	Population-based (thorax) CBCT# to PD			< 1.5	< 1.0	
	Elekta Synergy XVI (v5.0)					Patient-specific CBCT# to PD			< 1.0		
Kaliyaperumal et al. (2017) [51]	Varian Clinac IX OBI	Eclipse (v10.0)	AAA	Pelvis (1) H&N (1)	Thoracic Head	Phantom (Capthan CTP404) CBCT# to ED	n/a	pCT	Absolute	n/s	D_{median} : Bld = 0.0, Rct = –0.1
Giacometti et al. (2018) [43]	Varian Truebeam	Eclipse (v13.5)	AAA	Prostate (5)	Pelvis	Phantom (Inner cylinder CIRS062M + wax + water blocks) CBCT# to RED	n/a	pCT	$D_{\text{median-PTV-99\%}}$	2%/0.1mm (50% threshold)	
				Lung (5)	Thorax	Phantom (Outer ring CIRS062M + inner cylinder low density material + wax + water blocks) CBCT# to RED			–0.7	99.6	D_{median} : SC = 0.0, BS = 0.2
				H&N (5)	Head	Phantom (CIRS062M + wax + water blocks) CBCT# to RED			–0.1	94.6	D_{max} (0.01cc): SC = 0.0, D_{max} (0.1cc): Oes = 0.0, H = 0.0
Kaplan et al. (2018) [50]	Varian Clinac IX OBI	Eclipse (v13.7.14)	AAA	Lung (12)	Low dose thorax	Phantom (CIRS062M) CBCT# to RED	n/a	sCT	D_{median} (DVH)	n/s	Box Plot – Lng(V_{20Gy}) – 0.0, H(V_{25Gy}) < 2.0, D_{max} (0.01cc): Brnc < 2.0, SC < 1.0, Oes < 1.0 D_{mean} : Bld = (–1.3; 7.9), Rct = (–2.6; 28.1)
Jarema et al. (2019) [52]	Varian Halcyon	Eclipse (v15.6.03)	AAA	Pelvis (10)	Pelvis	Phantom (CIRS062M) CBCT# to ED	n/a	pCT	$D_{\text{mean-PTV}}$	1%/1mm (10% threshold)	

TPS = treatment planning system; AAA = analytical anisotropic algorithm; PB = pencil beam; CCSC = collapsed cone superposition convolution; AXB = Acuros XB; MC = Monte Carlo; H&N = head and neck; eFOV = extended field of view; rFOV = regular field of view; CT# = CT number; CBCT# = CBCT value; ED = electron density; RED = relative electron density; PD = physical density; pCT = planning CT; rCT = rescanned CT; GTV = gross tumour volume; PTV = planning target volume; D_{max} = maximum dose; D_{mean} = mean dose; D_{median} = median dose; $D_{\text{PTV-99\%}}$ = dose delivered to 99% of PTV; $D_{\text{GTV-99\%}}$ = dose delivered to 99% of GTV; $D_{\text{median-PTV-99\%}}$ = median dose delivered to 99% of PTV; $D_{\text{max}}(\#cc)$ = maximum dose to $\#cc$ of the PTV; $D_{\#cc}$ = minimum doses received by at least $\#cc$ of the volume that received the largest dose; OAR = organ at risk; R = right; L = left; Bld = bladder; Rct = rectum; Par = parotid; SC = spinal cord; BS = brain stem; Mnd = mandible; Lng = lung; Oes = oesophagus; H = hearth; TMJ = temporomandibular joint; Fem = femur; Lrx = larynx; Brnc = bronchi; Ips = ipsilateral; V($\#Gy$) = volume receiving $\#Gy$ or more; n/s = not supplied; n/a = not applicable.

Table 2b
Dose calculation studies on several phantoms using the CBCT calibration obtained with different phantoms configurations, in chronological order.

Author	Make/ model	TPS	Algorithm	Phantom	Protocol	CBCT Calibration	Artefact Correction	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Morin et al. (2007) [102]	Siemens MVision	Pinnacle (v7.6)	n/s	Water cylinder	rFOV n/s	Water cylinder + inserts CBCT# to RED	n/a Uniformity	pCT	$D_{\text{mean-phantom}} < 5.0$ < 1.0	n/s	n/s
Yang et al. (2007) [84]	Varian Trilogy	Eclipse	PB	Catphan 600 (CTP404) CIRS002PRA (pelvic)	Pelvis	Catphan600 (CTP404) CBCT# to RED	n/a	pCT	$D_{\text{mean-phantom}} < 1.0\%$ (motion)	n/s	n/s
Richter et al. (2008) [35]	Elekta Synergy XVI	ADAC Pinnacle (v7.6s)	n/s	Catphan (CTP503)	Thorax/ Pelvis Head	Catphan (CTP503) CBCT# to PD	n/a	pCT	$D_{\text{mean-phantom}} (1.0 \pm 1.1;$ $3.2 \pm 0.7)$ $(0.8 \pm 0.8;$ $4.2 \pm 1.2)$	n/s	n/s
Petit et al. (2008) [121]	MVision Siemens MV CBCT	XiO (v4.3.3)	MGS	Small homogeneous cylinder Large homogeneous cylinder Homogeneous IMRT phantom	Low-dose rate	Phantom (water cylinder) CBCT# to ED	n/a Cupping n/a Cupping n/a Cupping n/a	pCT	$D_{\text{mean-phantom}} 0.2$ 7.1 0.4 1.0 0.9 $(-2.0; 0.9)$	n/s	n/s
Guan et al. (2009) [49]	Varian OBI (v1.4)	Eclipse	AAA	Pelvic phantom	Pelvis	NuclearAssociates76-430 + CIRS002H9K CBCT# to RED Eclipse Default CBCT# to RED Catphan Vendor CBCT# to RED	n/a	pCT	$D_{\text{mean-PTV}} (-2.0; -0.4)$ $(-0.7; -0.4)$ $(-3.4; -2.4)$ $(-4.9; -4.4)$	n/s	$D_{\text{mean}}: \text{Bld} = (-1.4;$ $0.0), \text{Rct} = (-0.6; 0.7)$ $D_{\text{mean}}: \text{Bld} = -0.7,$ $\text{Rct} = (-0.4; -0.3)$ $D_{\text{mean}}: \text{Bld} = (-1.7;$ $-1.2),$ $\text{Rct} = (-0.9; -0.7)$ $D_{\text{mean}}: \text{Bld} = (-2.0;$ $-1.5),$ $\text{Rct} = (-1.2; -0.9)$ n/s
Hatton et al. (2009) [33]	Varian 2100 IX OBI	Eclipse (v8.6)	AAA	Slabs phantom	Pelvis	Catphan500 + annulus CBCT# to RED Catphan600 (CTP404) CBCT# to RED CIRS062M CBCT# to RED CIRS062M + scattering CBCT# to RED Catphan600 (CTP404) CBCT# to RED CIRS062M CBCT# to RED CIRS062M + scattering CBCT# to RED Inner cylinder CIRS062M + water blocks	n/a	Ionization chamber	$D_{\text{mean-slabs}} < 6.0$ < 20.0 < 3.0 < 1.5 < 4.0 < 0.5 < 1.0	n/s	n/s
Rong et al. (2010) [54]	Varian Trilogy	Eclipse (v8.1)	AAA	RANDO head Lung phantom Body phantom	Not defined (FF, 125kV, 80mA, 25ms) Not defined (HF, 125kV, 80mA, 25ms) Not defined (HF, 125kV, 80mA, 25ms)	Inner cylinder CIRS062M + water blocks Outer ring CIRS062M + water blocks + low density material inner cylinder CIRS062M + water blocks Inner cylinder CIRS062M + water blocks CIRS062M + water blocks	n/a	pCT	$D_{\text{mean-PTV\&OAR}} 1.5$ 0.5 5.4 2.1 0.0	n/s	DVH: LPar < 1.0, BS < 1.0 n/s DVH: OARs < 2.0 DVH: OARs = 1.0

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Table 2b (continued)

Author	Make/ model	TPS	Algorithm	Phantom	Protocol	CBCT Calibration	Artefact Correction	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Petit et al. (2010) [57]	Siemens MVision	XiO (v4.3.4)	FSP	CIRS thorax	Low dose	Cylinder filled with water	n/a	pCT	$D_{mean-CENTRE}$	2%/2mm	n/s
							Cupping & truncation		-2.0	74.0	
				RANDO thorax					0.5	99.0	
							n/a		11.0	74.0	
Wang et al. (2013) [40]	Elekra Synergy XVI	Pinnacle (v8.0)	n/s	Anthropomorphic thorax phantom	Not defined (S20, 120kVp, 36.1mAs)	CBCT# to PD [58]	Cupping & truncation		0.0	99.0	
							n/a		6.0	70.0	
							Cupping & truncation		1.0	100.0	
							n/a	pCT	$D_{PTV-95\%}$	n/s	DVH: IpsLang(V_{30}) = 0.0, $H(V_{\frac{1}{3}})$ = 0.0 DVH: IpsLang(V_{30}) = 0.0, $H(V_{\frac{1}{3}})$ = 0.0, $Br(V_{100})$ = -6.0 (continued on next page)
							Scatter	pCT	$D_{PTV-95\%}$	n/s	

Table 2b (continued)

Author	Make/ model	TPS	Algorithm	Phantom	Protocol	CBCT Calibration	Artefact Correction	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]													
Elstrøm et al. (2014) [56]	Varian Trilogy Tx OBI (v1.4)	Eclipse	n/s	RANDO head	Standard head	Phantom (Gammex RMI467)	CBCT# to RED	n/a	pCT	$D_{\text{mean-PTV}}$	99.9 1%/3mm	D_{mean} : SC = -0.1, LPa = -0.1, RPa = -0.2, Mnd = -0.3												
												-0.4												
												99.9												
												D_{mean} : SC = -0.1, LPa = -0.2, RPa = -0.2, Mnd = -0.3												
												-0.4												
												99.8												
												D_{mean} : SC = -0.1, LPa = -0.2, RPa = -0.2, Mnd = -0.3												
												-0.5												
												99.8												
												D_{mean} : SC = -0.1, LPa = -0.2, RPa = -0.2, Mnd = -0.3												
Ma et al. (2014) [55]	Varian Trilogy	Pinnacle (v8.0)	CC	CIRS062M	Not defined (HF, 120kV, 25mA, 40ms)	CIRS062M CBCT# to RED	n/a	pCT	D_{max}	n/s	99.9 n/s	D_{mean} : SC = 0.1, LPa = 0.1, RPa = 0.0, Mnd = -0.1												
												-0.1												
												99.9												
												D_{mean} : SC = 0.0, LPa = 0.1, RPa = 0.0, Mnd = -0.1												
												-0.1												
												99.9												
												D_{mean} : SC = 0.1, LPa = 0.1, RPa = 0.0, Mnd = -0.2												
												0.1												
												99.9												
												D_{mean} : SC = 0.1, LPa = 0.2, RPa = 0.0, Mnd = 0.1												
Ma et al. (2014) [55]	Varian Trilogy	Pinnacle (v8.0)	CC	CIRS062M	Not defined (HF, 120kV, 25mA, 40ms)	CIRS062M CBCT# to RED	n/a	pCT	D_{max}	n/s	99.9 n/s	D_{mean} : SC = 0.1, LPa = 0.1, RPa = 0.0, Mnd = 0.1												
												-0.1												
												99.9												
												D_{mean} : SC = 0.2, LPa = 0.2, RPa = 0.0, Mnd = 0.0												
												0.1												
												99.9												
												D_{mean} : SC = 0.1, LPa = 0.1, RPa = 0.0, Mnd = 0.1												
												0.1												
												99.9												
												D_{mean} : SC = 0.1, LPa = 0.2, RPa = 0.0, Mnd = 0.1												
Author	Make/model	TPS	Algorithm	Phantom	Protocol	CBCT Calibration	Artefact Correction	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]	Difference (OAR) [%]												
													Eclipse	AAA	ATOM 701-G	n/a	$D_{\text{mean-PTV}}$	0.4	n/s					
																				(continued on next page)				

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Table 2b (continued)

Author	Make/model	TPS	Algorithm	Phantom	Protocol	CBCT Calibration	Artefact Correction	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]		
Barateau et al. (2015) [46]	Varian OBI (v1.5)			Standard Head		Phantom (Capthan 600 CTP404) CBCT# to RED		pCT (CT# to RED Gammex RMI467)			D _{mean} : LPar = 0.21, RPar = -0.36, D _{2%} : SC = 1.53		
						Phantom (CIRS 062M head) CBCT# to RED			-0.6		D _{mean} : LPar = -0.41, RPar = -1.09, D _{2%} : SC = -0.41		
				Standard Pelvis		Phantom (CIRS 062M body) CBCT# to RED			-1.1		D _{50%} : Bld = -1.06, Rct = -0.09		
						Phantom (Gammex RMI467) CBCT# to RED			0.4		D _{50%} : Bld = 0.00, Rct = 0.36		
Held et al. (2015) [120]	Siemens Artisite & In-Line kView	Pinnacle (v9.2)	n/s	Pelvic water phantom with inserts	n/s	Phantom (CIRS062+water cylinder) CBCT# to PD	n/a	pCT	D _{PHANTOM}	n/s	D surface region~5.0		
Held et al. (2016) [111]	Varian Truebeam	n/s	n/s	Water cylinder	Head Pelvis	Varian Truebeam CBCT# to PD	n/a	pCT	D _{mean} -PHANTOM	3%/3mm (30% threshold)	n/s		
				Water pelvic phantom	Head Pelvis								
				Head phantom	Head Pelvis								
				Thorax phantom	Thorax Pelvis								
	Elekta VersaHD			Pelvic phantom	Pelvis	Phantom (Elekta head – small – and thorax/ pelvis – large) CBCT# to PD							
				Water cylinder	Head and Neck S20								
				Water pelvic phantom	Pelvis M20								
				Head phantom	Head and Neck S20								
	Siemens MV Artisite			Thorax phantom	Chest M20								
				Pelvic phantom	Pelvis M20								
				Water cylinder	rFOV	Phantom (Artiste head, thorax and pelvis) CBCT# to PD							
				Water pelvic phantom	eFOV								
Yohannes et al. (2016) [34]	Brainlab Vero System	Pinnacle	CC	Head phantom	rFOV								
				Thorax phantom	eFOV								
				Pelvic phantom	eFOV								
				In-house cube	Not defined (80kV, 100mA)	Phantom (Capthan 504 CTP404) CBCT# to PD	n/a	Ionization chamber	D _{mean} -CHAMBER	3%/3mm	n/s		
						Phantom (Gammex RMI467) CBCT# to PD							
						Phantom (Tissue equivalent) CBCT# to PD							
						Phantom (Capthan 504 CTP404) CBCT# to PD							
						Phantom (Gammex RMI467) CBCT# to PD							
						Phantom (Tissue equivalent) CBCT# to PD							
						Phantom (Capthan 504 CTP404) CBCT# to PD							
						Phantom (Gammex RMI467) CBCT# to PD							
						Phantom (Tissue equivalent) CBCT# to PD							
						Phantom (Capthan 504 CTP404) CBCT# to PD							
						Phantom (Gammex RMI467) CBCT# to PD							
						Phantom (Tissue equivalent) CBCT# to PD							
						Phantom (Capthan 504 CTP404) CBCT# to PD							
						Phantom (Gammex RMI467) CBCT# to PD							
						Phantom (Tissue equivalent) CBCT# to PD							

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Table 2b (continued)

Author	Make/model	TPS	Algorithm	Phantom	Protocol	CBCT Calibration	Artefact Correction	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Kaliyaperumal et al. (2017) [51]	Varian Clinac IX OBI	Eclipse (v10.0)	AAA	RW 3 plates Catphan (c-shape target) Catphan (cylindrical target) Catphan (ring target) Catphan (build up region)	n/s	Phantom (Catphan CTP404) CBCT# to PD Phantom (Gammex RMI467) CBCT# to PD Phantom (Tissue equivalent) CBCT# to PD	n/a	pCT	D_{PHANTOM} $D_{\text{PTV-98\%}}$	$< 1.2\%$ -1.3 -0.3	n/s (96.0;100.0) 64.6 96.9 96.8
Kaplan et al. (2018) [50]	Varian Clinac IX OBI	Eclipse (v13.7.14)	AAA	Alderson Radiation Therapy phantom	Low dose thorax	Phantom (CIRS062M) CBCT# to ED	n/a	pCT	$D_{\text{PTV-98\%}}$	n/s $1\%/1\text{mm}$ -1.2	n/s (96.0;100.0) Structures = Normal Structures = -1.2 D_{mean} : Normal Structures = 0.5 D_{mean} : Normal Structures = 0.2 D_{mean} : Normal Structures = -0.4 D_{median} : Bmc = -2.7 , H = -0.3 , SC = 0.5, RLng = 0.15
Jarema et al. (2019) [52]	Varian Halcyon	Eclipse (v15.6.03)	AAA	Pelvis (10)	Pelvis	Phantom (CIRS062M) CBCT# to ED	n/a	pCT	$D_{\text{mean-PTV}}$	$1\%/1\text{mm}$ (10% threshold)	99.4 ± 0.2 n/s

TPS = treatment planning system; AAA = analytical anisotropic algorithm; PB = pencil beam; CC = collapsed cone; FSP = fast superposition XB; MGS = multi-grid superposition convolution; HF = half fan; FF = full fan; eFOV = extended field of view; rFOV = regular field of view; CT# = CT number; CBCT# = CBCT value; ED = electron density; RED = relative electron density; PD = physical density; pCT = planning CT; PTV = planning target volume; D_{max} = maximum dose; D_{mean} = mean dose; D_{median} = median dose; $D_{\text{PTV-}\#\%}$ = dose delivered to $\#\%$ of PTV; $D_{\#\%}$ = minimum doses received by at least $\#\%$ of the volume that received the largest dose; OAR = organ at risk; R = right; L = left; Bld = bladder; Rct = rectum; Par = parotid; SC = spinal cord; BS = brain stem; Mnd = mandible; Lng = lung; H = hearth; Br = breast; Bmc = bronchi; Ips = ipsilateral; n/s = not supplied; n/a = not applicable.

Table 3a
Dose calculation studies applying HU override on CBCT images for different patients' tumour sites, in chronological order.

Author	Make/ model	TPS	Algorithm	Site	Protocol	HU override	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Van Zijtveld et al. (2007) [61]	Elekta Synergy XVI	n/s	PB	H&N (2)	n/s	HU _{ROI}	n/a	n/s	rCT	n/s	2%/2mm (93.0; 98.0)	DVH
Boggula et al. (2009) [36]	Elekta Synergy XVI	Corvus	PB	Prostate (3)	Pelvis	Auto HU _{MLT} (3 thresholds)	n/a	User specified CT# to RED	pCT	n/s	3%/3mm (86.3 $\pm$ 5.4; 96.3 $\pm$ 4.5)	n/s
Hu et al. (2011) [39]	Elekta Synergy XVI	Pinnacle (v7.6c)	n/s	NPC (1)	Not defined (120kVp, 32mA, 10ms)	CBCT# to CT# (mathematical model)	n/a	User specified CT# to PD	pCT	D _{mean-PTV& OAR}	n/s	DVH
Fotina et al. (2012) [53]	Elekta Synergy XVI	iPlan (v4.5.0)	XV MC	Prostate (10)	Prostate (no bowtie)	Auto HU _{MLT} (7 thresholds)	n/a	User specified CT# to ED	Population- based CBCT# to ED	D _{median- PTV}	n/s	D _{mean} : Bld = 0.5, Rct = 0.1, FemHeads = 0.0 D _{mean} : Bld = 0.3, Rct = 0.0, FemHeads = 0.0 D _{max} : SC = -0.2, OES = 0.1%, D _{mean} : Lung = 0.0 D _{max} : SC = 0.2, OES = -0.1%, D _{mean} : Lung = 0.1 D _{max} : SC = -1.3, BS = 0.2, D _{mean} : Par = 0.4 D _{max} : SC = -1.3, BS = 0.2, D _{mean} : Par = 0.4 D _{mean} : Rct = -3.02, FemHeads = -2.21 D _{mean} : Rct = -0.80, FemHeads = -0.83 D _{mean} : Rct = -0.37, FemHeads = 0.19 D _{mean} : Rct = 1.84, FemHeads = 2.33 D _{mean} : Ch = -0.30, OptNrv = -1.02 D _{mean} : Ch = 1.05, OptNrv = 0.38 D _{mean} : Ch = 0.42, OptNrv = 0.26 D _{mean} : Ch = -0.18, OptNrv = 0.00
				Lung (10)	Thorax (no bowtie)	Auto HU _{MLT} (7 thresholds)	n/a			1.9	< 5.0	
						HU _{ROI}				0.1	< 5.0	
				H&N (7)	Head (no bowtie)	Auto HU _{MLT} (7 thresholds)	HU _{ROI}			< 0.5	< -3.0	
Poludniowski et al. (2012) [70]	Elekta Synergy XVI	Pinnacle (v9.0)	n/s	Pelvis (6)	Pelvis	Patient-specific CBCT# to CT#	n/a	User specified CT# to PD [122]	vCT	D _{mean-PTV}	n/s	
						Phantom CBCT# to CT#	Scatter (empirical) Scatter [122]			-2.8	-1.0	
				Brain (6)	Head	Patient-specific CBCT# to CT#	n/a			-0.2	2.1	
						Phantom CBCT# to CT#	Scatter (empirical) Scatter [122]			-0.1	1.2	
							Scatter (empirical) Scatter [122]			0.1	-0.2	

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Table 3a (continued)

Author	Make/ model	TPS	Algorithm	Site	Protocol	HU override	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Usui et al. (2013) [69]	Varian Clinac 21EX	Eclipse (v8.9)	AAA	Lung (8)	n/s	Phantom (Gammex RMI467) CBCT# to CT# Patient-specific CBCT# to CT# HU _{MLT} (3 thresholds)	n/a	n/s	pCT	D _{mean-TV}	2%/2mm	96.0 ± 2.8 n/s
Onozato et al. (2014) [42]	Varian OBI (v1.5)	Eclipse (v8.6.15)	AAA	Prostate (10)	Pelvis	Auto HU _{MLT} (3 thresholds)	n/a	User specified CT# to ED	pCT	D _{mean-PTV}	2%/2mm	98.4 98.6
Veiga et al. (2014) [71]	Varian OBI (v1.4)	Eclipse	AAA	H&N (5)	Low dose thorax	Phantom (Catphan 504) CBCT# to CT#	n/a	n/s	rCT	D _{mean} (% pD)	2%/2mm	90.3 ± 4.1
Dunlop et al. (2015) [62]	Elekta Synergy XVI (v4.5)	RayStation (v3.99)	CC	Pelvis (4)	Pelvis M10	CBCT# to CT# [70]	n/a	User specified CT# to PD [122]	pCT	D _{median- CTV}	n/s	n/s
				Lung (3)	Chest S20	CBCT# to CT# [70]				0.3		
						HU (water only)						
						HU _{MLT} (water & bone)				–1.0		
						Auto HU _{MLT} (6 thresholds)				–1.3		
						CBCT# to CT#				2.4		
						HU (water only)				–6.8		
						HU _{MLT} (water & lung)				0.4		
						Auto HU _{MLT} (6 thresholds)				–1.3		
						CBCT# to CT#				0.3		
						HU (water only)				0.4		
						Auto HU _{MLT} (6 thresholds)				–0.1		
						CBCT# to CT#						
						HU (water only)						
						Auto HU _{MLT} (6 thresholds)						
						CBCT# to CT#						
						HU (water only)						
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						Auto HU _{MLT} (6 thresholds)						
						CBCT# to CT#		</				

Table 3a (continued)

Author	Make/ model	TPS	Algorithm	Site	Protocol	HU override	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Veiga et al. (2015) [27]	Varian OBI (v1.4)	Eclipse (v10.8)	n/s	H&N (3)	Head	Phantom (Catphan 504) CBCT# to CT#	n/a	n/s	rCT	D _{RMS} (% pD) (photon plan) D _{RMS} (% pD) (proton plan) n/s	1.8 ± 1.6 n/s	DVH
Kurz et al. (2015) [72]	Elekta Synergy XVI R4.5	RayStation (v4.6)	n/s	H&N (9)	n/s	Population- based CBCT# to CT#	n/a	n/s	rCT	n/s	3%/3mm (photon plan) 3%/3mm (proton plan)	DVH
Author	Make/ model	TPS	Algorithm	Site	Protocol	HU override	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Almatani et al. (2016) [63]	Elekta Synergy XVI (v4.5)	OMP (v4.3)	PB	Prostate (1)	n/s	HU _{MLT} (5 thresholds)	n/a	TPS CT# to ED	pCT	D _{mean-PTV}	n/s	D _{mean} : Bld = -48.6, Rct = 2.6 D _{mean} : Bld = -48.8, Rct = -2.3 D _{mean} : Bld = -47.1, Rct = -2.4 D _{mean} : Bld = -49.0, Rct = -2.7 D _{mean} : Bld = -49.2, Rct = -2.6 D _{mean} : Bld = -47.4, Rct = -2.7
Arai et al. (2017) [45]	Varian Clinac IX OBI 1.6	XIO-M	PB	H&N (10)	Not defined (FF, 100kV, 10mA)	HU _{HM}	n/a	n/s	pCT	D _{PTV-98%}	3%/3mm	D _{mean} : LPar = 3.56 ± 2.35
Chen et al. (2017) [64]	Varian IX Trilogy / Truebeam	RayStation (v5.0)	n/s	Prostate (10)	n/s	Patient- specific auto HU _{MLT} (6 thresholds)	n/a	n/a (density overridden)	pCT	D _{mean-PTV}	3%/3mm	OAR 3%/3mm: (70–90% max dose) = 98.9 ± 2.5, (< 70% max dose) = 95.8 ± 5.7 OAR 3%/3mm: (70–90% max dose) = 98.7 ± 3.4, (< 70% max dose) = 98.7 ± 2.2 OAR 3%/3mm: (70–90% max dose) = 92.9 ± 5.5, (< 70% max dose) = 92.1 ± 7.2 OAR 3%/3mm: (70–90% max dose) = 100.0 ± 0.0, (< 70% max dose) = 96.9 ± 4.9 (continued on next page)
				Lung (10)							96.1 ± 5.0	
				H&N (10)							98.3 ± 1.5	
				Pancreas (10)							99.1 ± 2.4	

Table 3b
Dose calculation studies applying HU override on CBCT images for different phantoms, in chronological order.

Author	Make/ model	TPS	Algorithm	Phantom	Protocol	HU override	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Boggula et al. (2009) [36]	Elekta Synergy XVI	Corvus	PB	Pelvic phantom	Standard Pelvis	Auto HU _{MLT} (3 thresholds)	n/a	User specified CT# to RED	pCT	n/s	3%/3mm	97.2 ± 0.7 n/s
Hu et al. (2011) [39]	Elekta Synergy XVI	Pinnacle (v7.6c)	n/s	Caplan 503 RANDO head	Not defined (120kVp, 32mA, 10ms)	Mathematical model for CBCT# to CT#	n/a	User specified CT# to PD	pCT	D _{mean- PHANTOM} D _{mean-PTV}	(−0.2; 1.9) n/s 0.1	n/s D _{mean} : LPar = 1.5, RPar = 1.2, SC = −6.1, BS = −0.4% n/s
Usul et al. (2013) [69]	Varian Clinac 21EX	Eclipse (v8.9)	AAA	ImRT phantom	n/s	Phantom (Gammex RMI467) CBCT# to CT#	n/a	n/s	pCT	D _{mean- TARGET}	0.0 2%/2mm	100.0 n/s
Onozato et al. (2014) [42]	Varian OBI (v1.5)	Eclipse (v8.6.15)	AAA	Pelvic phantom	Pelvis	Phantom-specific CBCT# to CT# HU _{MLT} (3 thresholds)	n/a	User specified CT# to ED	pCT	D _{mean-PTV}	0.2 0.1	n/s n/s n/s
Liu et al. (2015) [65]	Varian Trilogy	Pinnacle (v8.1)	n/s	RANDO pelvis RANDO lung RANDO head	n/s	HU _{MLT} (5 thresholds)	n/a	n/a (density overridden)	pCT	n/s	2%/2mm	(96.0; 98.0) (97.0; 99.0) (99.0; 100.0)
Park et al. (2015) [68]	Elekta Synergy XVI	XiO	PB	Pelvic phantom	Not defined (M15, 120kV, 40&64mA, 40ms)	Phantom-specific (soft tissue-based) CBCT# to CT#	n/a Scatter (uniform)	TPS CT# to RSP	pCT	n/s	3%/3mm (10% threshold)	94.8 92.4 n/s
Arai et al. (2017) [45]	Varian Clinac iX OBI 1.6	XiO-M	PB	Thorax phantom	Not defined (M20, 120kV, 40&64mA, 40ms)	n/a Scatter (uniform)	n/a Scatter (uniform)	n/a	pCT	n/s	3%/3mm	97.3 99.7 D _{mean} : Rct = 0.14, Bld = 0.75 D _{mean} : LPar = 0.56
Arai et al. (2017) [45]	Varian Clinac iX OBI 1.6	XiO-M	PB	Abdomen phantom	Not defined (M20, 120kV, 40&64mA, 40ms)	HU _{HM}	n/a Scatter (uniform)	n/a	pCT	D _{PTV-98%}	0.2 2.7	97.3 99.7 D _{mean} : Rct = 0.14, Bld = 0.75 D _{mean} : LPar = 0.56
Arai et al. (2017) [45]	Varian Clinac iX OBI 1.6	XiO-M	PB	Head phantom	Not defined (S20, 100kV, 10mA, 10& 20ms)	HU _{HM}	n/a Scatter (uniform)	n/a	pCT	D _{PTV-98%}	0.2 2.7	97.3 99.7 D _{mean} : Rct = 0.14, Bld = 0.75 D _{mean} : LPar = 0.56
Arai et al. (2017) [45]	Varian Clinac iX OBI 1.6	XiO-M	PB	Pelvic phantom	Not defined (S20, 100kV, 10mA, 10& 20ms)	HU _{HM}	n/a Scatter (uniform)	n/a	pCT	D _{PTV-98%}	0.2 2.7	97.3 99.7 D _{mean} : Rct = 0.14, Bld = 0.75 D _{mean} : LPar = 0.56

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Table 3b (continued)

Author	Make/ model	TPS	Algorithm	Phantom	Protocol	HU override	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Rafic et al. (2018) [66]	Varian OBI (v1.6)	Eclipse	n/s	Alderson RANDO	Not defined (HF, 125kVp, 80mA)	HU local correction – Stitch 1	n/a	n/s	pCT	$D_{\text{mean-TARGET}}$	3%/3mm (reference to global dose)	D_{mean} : Bld = (1.2; 1.9), LFemHeads = (-1.5; -0.7), RFemHeads = (-0.8; 0.0), Vrt = (-0.2; 0.5) n/s
Schröder et al. (2019) [48]	Elekta Synergy XVI 5.0	XiO (v4.3.4)	n/s	Alderson Rando (pelvis) Alderson Rando (prostate) Alderson Rando (lung) Alderson Rando (H&N)	Not defined (M, 32mA, 40ms)	Phantom (CIRS062M body) CBCT# to CT#	Scatter (uniform)	User specified CT# to PD	pCT	$D_{\text{mean-PHANTOM}}$	n/s	D_{mean} : Bld = (1.7; 2.3), LFemHeads = (-2.9; -2.2), RFemHeads = 0.8; Vrt = (-2.0; -1.2) n/s
					Not defined (S, 16mA, 40ms)	Phantom (CIRS062M lung) CBCT# to CT#			pCT	$D_{\text{mean-PHANTOM}}$	3.4 $\pm$ 2.1 2.4 $\pm$ 1.8 1.4 $\pm$ 2.8 2.6 $\pm$ 10.1	(99.9; 100.0) (96.8; 99.2) (99.9; 100.0) (96.9; 99.2)

TPS = treatment planning system; AAA = analytical anisotropic algorithm; PB = pencil beam; H&N = head and neck; HF = half fan; FF = full fan; CT# = CT number; CBCT# = CBCT value; MLT = multilevel-threshold; HM = histogram matching; ED = electron density; RED = relative electron density; RSP = relative stopping power; pCT = planning CT; PTV = planning target volume; CTV = clinical target volume; D_{max} = maximum dose; D_{mean} = mean dose; $D_{\text{PTV, \# \%}}$ = dose delivered to #% of PTV; OAR = organ at risk; R = right; L = left; Bld = bladder; Rct = rectum; Par = parotid; SC = spinal cord; Vrt = vertebrae; BS = brain stem; Fem = femur; n/s = not supplied; n/a = not applicable.

Table 4a
Dose calculation studies on different tumour sites in patients adopting deformable image registration (DIR), in chronological order.

Author	Make/ model	TPS	Algorithm	Site	Protocol	DIR algorithm	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Yang et al. (2007) [84]	Varian Trilogy	Eclipse	PB	Prostate (3)	n/s	Free form BSpline	n/a	User specified CT# to RED	CBCT	$D_{\max}$ Prostate < 2.0	n/s	n/s
Disher et al. (2013) [73]	Varian OBI (v1.4)	Pinnacle	CC	Lung (1) Lung (3)	Thorax	ANIMAL	n/a	User specified CT# to RED	pCT	$D_{\text{PTV-95\%}}$ (4.0; 13.0)	n/s	n/s
Onozato et al. (2014) [42]	Varian OBI (v1.5)	Eclipse (v8.6.15)	AAA	Prostate (10)	Pelvis	BSpline (CBCT deformed topCT)	n/a	User specified CT# to ED	pCT	$D_{\text{mean-PTV}}$ 1.2 ± 0.5	2%/2mm	D_{mean} : Bld = 0.54 ± 0.42 , Rct = 0.66 ± 0.58
Veiga et al. (2014) [71]	Varian OBI (v1.4)	Eclipse	AAA	H&N (5)	Low dose thorax	BSpline (NiftyReg)	n/a	n/s	rCT	$D_{\text{PTV-95\%}}$ 0.7 ± 0.2	2%/2mm	97.1 ± 4.3 DVH of one patient & histograms for BS, SC, LPar, RPar
Landry et al. (2015) [79]	Elekta Synergy XVI R4.5	CERR-based	MC	H&N (6)	H&N	Morphons (REGGUI, Matlab)	n/a	User specified CT# to PD	rCT	n/s	2%/2mm	DVH: differences[Gy] rCT, physician and DIR contours
Landry et al. (2015) [78]	Elekta Synergy XVI R4.5			H&N (1)			n/a				3mm/2mm WET	n/s
Kurz et al. (2015) [72]	Elekta Synergy XVI R4.5	RayStation (v4.6)	n/s	H&N (9)	n/s	Morphons	n/a	n/s	rCT	n/s	3%/3mm (photon plan)	DVH of one patient
Veiga et al. (2015) [27]	Varian OBI (v1.4)	Eclipse (v10.8)	n/s	H&N (3)	Head	BSpline + Velocity field (NiftyReg)	n/a	n/s	rCT	$D_{\text{RMS}}(\% \text{pD})$ (photon plan) 0.6 ± 0.1	n/s	D_{mean} to OARs (SP, BS, Par) = 0.2 ± 0.1 & DVH of one patient
Kurz et al. (2016) [74]	Elekta Synergy XVI or Versa HD (v4.5)	RayStation (v4.6)	n/s	Prostate (4)	Not defined (M15, 120kVp, 64mA)	Morphons (REGGUI, Matlab)	Scatter (priori CT-based) [68,123]	n/s	vCT	$D_{\text{RMS}}(\% \text{pD})$ (proton plan) $(1.0 \pm 0.3;$ $2.6 \pm 0.6)$	2%/2mm	D_{mean} to OARs (SP, BS, Par) = 1.3 ± 2.5 ; $1.8 \pm 1.7\%$ & DVH of one patient
Huang et al. (2017) [75]	Varian OBI	Eclipse (v13.5)	CC	Liver RIDL (7) Liver (16)	Not defined (HF, 120kVp, 40mA, 40ms)	Gradient- based free form	n/a	n/s	pCT	$D_{\text{mean-}}$ NORMAL LIVER $(-7.8; 15.7)$ $(-35.3;$ $-12.1)$	n/s	n/s
Veiga et al. (2016, 2017) [29]	IBA (v1.4)	Eclipse (v11.0)	n/s	Lung (20)	Not defined (HF, 110kVp, 1142mAs)	Morphons	n/a	User specified CT# to RSP	rCT	$D_{\text{mean}}(\% D_{\max})$ -0.5 ± 0.9	n/s	n/s

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Table 4a (continued)

Author	Make/ model	TPS	Algorithm	Site	Protocol	DIR algorithm	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Thing et al. (2017) [76]	Elekta Synergy XVI or Versa HD (v4.5-5.0)	Pinnacle	CC	Lung (21)	Clinical 4D	BSpline (NiftyReg)	n/a	User specified CT# to ED	rCT	n/s	2%/2mm	Box Plot: median γ 2%/2mm: Lung > 80.0, H ~ 100.0, Oes ~ 100.0, SC ~ 100.0
Cole et al. (2018) [77]	Varian OBI (v1.4)	Eclipse	AAA	Lung (7)	Low dose thorax	BSpline + Velocity field (NiftyReg)	n/a	n/s	rCT	$D_{\max}$ -CTV + 1 cm	n/s	Box Plots: median γ 2%/2mm: Lung ~ 100.0, H ~ 100.0, Oes ~ 100.0, SC ~ 100.0 D_{mean} : Lung-GTV(V_{20Gy}) = 0.8 ± 1.2 , H(V_{40Gy}) = 2.0 ± 2.9 , SCnl + 5mm = 2.2 ± 3.3 D_{median} : Bld = 0.0, Rct = 0.1
Giacometti et al. (2018) [43]	Varian Truebeam	Eclipse (v13.5)	AAA	Prostate (5) Lung (5) H&N (5)	Pelvis Thorax Head	n/s	n/a	User specified CT# to RED	pCT	D_{median} -PTV- 99%	2%/0.1mm (50% threshold)	D_{median} : SC = 0.0, BS = -0.1 D_{max} (0.01cc): SC = -0.2, D_{max} (0.1cc): Oes = 0.1, H = -0.1 D_{max} (0.01cc): BS = 0.0 $\pm$ 1.2, SC = -3.0 $\pm$ 3.3, D_{mean} : LPar = 0.3 $\pm$ 2.4, RPar = 0.2 $\pm$ 3.1
MacFarlane et al. (2018) [67]	Varian Clinac iX -Truebeam OBI	Pinnacle (v9.7)	CC	H&N (15)	Standard & Low dose head	Fast- symetric Demon (Pinnacle)	Inhomogeneity	n/s	rCT	D_{mean} -TV	3%/3mm	$Rct(V_{40Gy}) = -0.16 \pm 0.66$ $Rct(V_{40Gy}) = -0.11 \pm 0.52$
Marchant et al. (2018) [38]	Elekta Synergy XVI (v4.5-5.0)	Pinnacle (v9.8)	n/s	Pelvis (15)	n/s	BSpline (Elastix) Free form BSpline (NiftyReg)	n/a	n/s	pCT	D_{mean} -PTV	n/s	D_{max} (1cc): SC = 0.31 $\pm$ 1.14 D_{max} (1cc): SC = 0.15 $\pm$ 1.27
				Lung (15)		BSpline (Elastix) Free form BSpline (NiftyReg)						
				H&N (14)		BSpline (Elastix) Free form BSpline (NiftyReg)						D_{mean} : CPar = 0.28 $\pm$ 0.20 D_{mean} : CPar = 0.00 $\pm$ 0.30
Hansen et al. (2018) [30]	Elekta Synergy XVI (R5.0.2)	RayStation (v4.99)	CC	Prostate (8)	Not defined (M20, 40mA)	n/s	Shading (machine learning)	n/s	Shading corrected CBCT	n/s	2% (50% threshold) (photon plan)	n/s
			PB								2% (50% threshold) (photon plan)	

TPS = treatment planning system; AAA = analytical anisotropic algorithm; PB = pencil beam; CC = collapsed cone; MC = Monte Carlo; H&N = head and neck; HF = half fan; CT# = CT number; ED = electron density; RED = relative electron density; PD = physical density; RSP = relative stopping power; pCT = planning CT; CBCT = cone beam CT; vCT = virtual CT; rCT = rescan CT; PTV = planning target volume; CTV = clinical target volume; GTV = gross tumour volume; D_{max} = maximum dose; D_{mean} = mean dose; D_{median} = median dose; $D_{\text{PTV-99\%}}$ = dose delivered to 99% of PTV; $D_{\text{median-PTV-99\%}}$ = median dose delivered to 99% of PTV; $D_{\text{mean(\%)}}$ = mean dose as percentage of the prescribed dose; $D_{\text{RMS(\%)}}$ = root mean square as percentage of the prescribed dose; $D_{\text{max}(\#cc)}$ = maximum dose to #cm³ of the PTV; $D_{\text{mean}(\%D_{\text{max}})}$ = mean dose normalized to the maximum dose; OAR = organ at risk; R = right; L = left; C = contra; Bld = bladder; Rct = rectum; Par = parotid; SC = spinal cord; SCnl = spinal canal; Oes = oesophagus; BS = brain stem; Lung = lung; SP = spine; H = hearth; V(#Gy) = volume receiving #Gy or more; n/s = not supplied; n/a = not applicable.

Table 4b
Dose calculation studies on different phantoms adopting deformable image registration (DIR), in chronological order.

Author	Make/model	TPS	Algorithm	Phantom	Protocol	DIR	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Landry et al. (2015) [78]	Elekta Synergy XVI R4.5	n/s	MC	PMMA deformable phantom modelling H&N anatomical changes	n/s	Morphons (REGGUI)	n/a	User specified CT# to PD	rCT	Average range	< 1.0	n/s
Park et al. (2015) [68]	Elekta Synergy XVI	XiO	PB	Pelvic phantom	Not defined (MI5, 120kV, 40&64mA, 40ms)	n/s	Scatter (priori CT-based)	TPS CT# to RSP	pCT	n/s	3%/3mm	98.4
				Thorax phantom	Not defined (M20, 120kV, 40&64mA, 40ms)							98.6
				Abdomen phantom	Not defined (M20, 120kV, 40&64mA, 40ms)							99.7
				Head phantom	Not defined (S20, 100kV, 10mA, 10 & 20ms)							99.5
Niepel et al. (2018) [85]	Elekta Synergy XVI R4.5	RayStation (v4.99)	n/s	Moving phantom based on ex vivo porcine lungs	Chest	Morphons (REGGUI)	n/a	User specified CT# to RSP	4DCT	n/s	3%/3mm	(89.0; 99.0)

TPS = treatment planning system; PB = pencil beam; MC = Monte Carlo; H&N = head and neck; CT# = CT number; ED = electron density; RED = relative electron density; PD = physical density; RSP = relative stopping power; pCT = planning CT; rCT = rescan CT; OAR = organ at risk.

reference dose in a number of publications using this methodology [35–39] although dosimetric improvements up to 7.4% were observed when artefact corrections were applied [38,40].

In almost all cases, differences from the reference dose using Varian CBCT have been within 1.5% [37,41–44]. As expected, the largest differences were observed for lung images compared to the other tumour sites. This is most likely due to heterogeneities although this raises the question about the accuracy of different dose calculation algorithms. Another explanation is described in [37] where Elekta and Varian CT vs CBCT calibration curve are plotted. The two curves are almost overlapping for Varian while they are different for Elekta, thus explaining the higher dosimetric discrepancies.

In the case of proton treatments, differences up to 27.1% in the dose to 98% of the PTV were observed for proton dose calculated on the acquired CBCT [45]. Authors attributed these differences to discrepancies between HU values in CBCT and pCT image that could cause a significant impact on the calculation of the proton range (and therefore in the dose calculation) when converted to relative proton stopping power.

The advantage of using the pCT calibration approach is that it is fast and does not require any extra measurements. The disadvantage is that although this method may work for small objects, it is not reliable for larger and heterogeneous objects (and particularly for patient scans) due to the different amounts of scatter radiation present during the pCT and the CBCT acquisitions.

3.1.2. CBCT calibration

A new calibration curve with PD/RED/ED/SPR as a function of the HU values in the CBCT can be generated based on the CBCT images using phantom/patient/population-specific measurements (Table 2a and 2b). CT and CBCT calibration curves have been plotted and compared in several studies [35,37,43,46–48]. While for negative HU values (lower density tissue) CT and CBCT calibration curves are in good agreement, for positive HU values the calibration curves are quite different, independent of the treated site.

Several phantoms, briefly described in the supplementary material (Table S3), have been used to generate CBCT calibration curves. Errors up to 20.0% were calculated when using diagnostic CT scanners quality assurance phantoms [33,35,49–53]. This can be attribute to the size of these phantoms (about 15 cm in diameter), which, due to the collimation used in standard CT scans, are of limited depth. If used for CBCT measurements, the imaging field can extend beyond the depth of the phantom and thus underestimate the scatter contribution which occurs during a patient CBCT acquisition. This lack of scatter causes dosimetric inaccuracies when undertaking dose calculations for objects/patients larger than the phantom size (diameter and depth).

Commercial phantoms are now available that provide additional material perpendicular to the CT slices (depth), although a number of authors [33,43,54,55] have reported mimicked this by adding additional material either side of the standard electron density phantoms described above. Differences from the reference dose of less than 0.8% were reported using the Gammex RMI467 phantom [34,46,56] and generally less than 2.0% using CIRS062M phantom when used with extra slabs of water equivalent material to increase the scatter [43,54]. Hatton et al. [33] reported mean dose differences up to 22.0% from ionisation chamber measurements when applying a calibration curve from a large diameter phantom to a smaller object, and up to 12.0% when a calibration curve from a small phantom was used for a larger object. This suggests that a site-specific approach may be more appropriate than a one-size-fits-all solution. Rong et al. [54] confirmed that the HU uniformity deterioration increases with the size of the scanned objects, mostly due to scatter contamination, and the authors claimed this issue could be addressed using smaller cone angles. Indeed, differences from the reference dose between –1.2% and 1.0% were calculated when using site-specific CBCT phantoms for the calibration [34,43,54], better mimicking the radiation response of the

Table 5
Dose calculation studies on different tumour sites in patients via dose deformation by means of a deformation vector field, in chronological order.

Author	Make/ model	TPS	Algorithm	Site/Phantom	Protocol	Dose Warping	Artefact Correction	Calibration Curve	Reference	Difference	γ -analysis [%]	Difference (OAR)
Wen et al. (2012) [97]	Varian Trilogy	Eclipse	n/s	Prostate (5)	n/s	DIR + WARP (Bspline)	n/a	n/s	pCT	D _{mean-PTV}	-1.9 ± 0.1%	D _{mean} [%]: Bld = (10.9; 42.4), Rct = (-3.4; 30.7)
Garcia Molla et al. (2015) [98]	Elekta Synergy XVI (v4.2.1)	RayStation (v4.0.1.4)	n/s	H&N (5)	n/s	DIR + WARP (Hybrid algorithm)	n/a	n/s	pCT	DVH	40 ± 40cGy	DVH[cGy]: TMJ = 99 ± 70, BS = 100 ± 100, B = 20 ± 20, Lrx = 50 ± 10, Jaw = 40 ± 30, SC = 110 ± 80, OptNrv = 36 ± 2, E = 20 ± 20, Par = 80 ± 40 D _{mean} [%] SC = 0.4 ± 0.6, BS = 0.6 ± 0.8 Par = 0.6 ± 0.3 D _{mean} [%] SC = 0.4 ± 0.6, BS = 0.6 ± 0.8 Par = 0.3 ± 0.4 D _{mean} [%] SC = 0.5 ± 0.4, BS = 0.5 ± 0.4 Par = 0.9 ± 0.5 DVH of three patients
Veiga et al. (2015) [86]	Varian OBI (v1.4)	Eclipse	AAA	H&N (5)	Low dose thorax	DIR(sas) + WARP(sas) DIR(sas) + WARP(inv) DIR(tcs) + WARP(tcs)	n/a	n/s	DIR(svf) + WARP(svf)	D _{99%} (% pD)	7.0 ± 3.0% 7.0 ± 3.0% 9.0 ± 5.0%	
Veiga et al. (2016, 2017) [28,29]	IBA (v1.4)	Eclipse (v11.0)	n/s	Lung (20)	Not defined (HF, 110kVp, 1142mAs)	DIR + WARP (Morphons)	n/a	User specified CT# to RSP	rCT	D _{mean} (% D _{max})	-0.4 ± 1.0%	

TPS = treatment planning system; AAA = analytical anisotropic algorithm; H&N = head and neck; HF = half fan; CT# = CT number; RSP = relative stopping power; pCT = planning CT; rCT = rescan CT; PTV = planning target volume; D_{mean} = mean dose; D_{9%}(%pD) = minimum doses received by at least 9% as percentage of the prescribed dose; D_{max}(#cc) = maximum dose to #cm³ of the PTV; D_{mean}(%D_{max}) = mean dose normalized to the maximum dose; OAR = organ at risk; R = right; L = left; Bld = bladder; Rct = rectum; B = brain; Par = parotid; SC = spinal cord; OptNrv = optic nerve; BS = brain stem; TMJ = temporomandibular joint; E = eye; Lrx = larynx; Lung = lung; Sas = standard asymmetric registration; Inv = inverse; Ics = inverse-consistent symmetric; Svf = symmetric registration parameterized by a stationary velocity field; n/s = not supplied; n/a = not applicable.

Table 6a
Dose calculation studies using a combination of techniques for different tumour sites in patients, in chronological order.

Author	Make/ model	TPS	Algorithm	Site	Protocol	Dose Calculation Method	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Disher et al. (2013) [73]	Varian OBI (v1.4)	Pinnacle (v3.5)	CC	Lung (3)	Thorax	DIR (CBCT to pCT) + CBCT calibration curve	n/a	Phantom (Gammex RMI467) CBCT# to RED	pCT	$D_{PTV-95\%}$ (−5.0; 6.0)	n/s	n/s
Jin et al. (2013) [47]	Elekta Synergy	RayStation (v3.5)	n/s	NPC (10)	Not defined (120kVp, 25mA, 40ms)	DIR + Auto HU_{MLT} (4 thresholds)	n/a	User specified CT# to RED	pCT	(1.0; 9.0)	n/s	D_{mean} : Lpar < 10.3, Rpar < 11.0, SC < 5.4, BS < 2.5
Onozato et al. (2014) [42]	Varian OBI (v1.5)	Eclipse (v8.6.15)	AAA	Prostate (10)	Pelvis	Auto HU_{MLT} (4 thresholds) + DIR	n/a	Phantom (Caplan CTP503) CBCT# to PD	pCT	$D_{mean-PTV}$ 0.8 ± 0.4	2%/2mm	D_{mean} : Bld = 0.55 ± 0.33 , Rct = 0.61 ± 0.49
Liu et al. (2015) [65]	Varian Trilogy	n/s	n/s	Prostate (1) Lung (1)	n/s	HU_{HIM} + DIR	n/a	User specified CT# to ED	pCT	0.8 ± 0.2	n/s	D_{mean} : Bld = 0.26 ± 0.37 , Rct = 0.39 ± 0.42 DVH
Aral et al. (2017) [45]	Varian Clinac IX OBI 1.6	XiO-M	PB	H&N (10)	Not defined (FF, 100kV, 10mA)	DIR + HU_{MLT} (5 thresholds)	n/a	n/a (density overridden)	pCT	D_{mean} < 1.0	n/s	D_{mean} : LPar = 3.5 ± 2.4
MacFarlane et al. (2018) [67]	Varian Clinac IX Truebeam OBI	Pinnacle (v9.7)	CC	H&N (15)	Standard & Low dose head	DIR + Patient- specific CBCT# to CT#	Inhomogeneity	n/s	pCT	$D_{PTV-98\%}$ 5.7 ± 4.1	3%/3mm	D_{mean} : LPar = 3.5 ± 2.4
Landry et al. (2019) [31]	Elekta Synergy XVI (R5.0.2)	RayStation (v4.6)	CC	Prostate (8)	Not defined (M20, 20ms, 20mA)	CBCT# to CT# [68] + DIR	Intensity (machine learning)	n/s	rCT	$D_{mean-TV}$ -0.5 ± 0.8	3%/3mm	D_{max} (0.01cc): BS = 0.6 ± 1.0 , SC = -2.0 ± 2.5 , D_{mean} : LPar = 0.7 ± 1.5 , RPar = 0.5 ± 2.2
									Shading corrected CBCT [30]	n/s	2%/2mm	(85.0; 100) n/s

(continued on next page)

Table 6a (continued)

Author	Make/ model	TPS	Algorithm	Site	Protocol	Dose Calculation Method	Artefact Correction	Calibration Curve	Reference	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Schröder et al. (2019) [48]	Elekta Synergy XVI 5.0	XiO (v4.3.4)	n/s	Pelvis (28)	Not defined (M, 32mA, 40ms)	Anti-scatter grid + Phantom (CIRS062M body) CBCT# to CT#	Scatter (uniform)	User specified CT# to PD	vCT	n/s	2%/1mm (20% threshold)	DVH
							Scatter (iterative)				> 90.0	> 90.0
							Scatter (uniform)				> 90.0	> 90.0
				Prostate (26)	Not defined (M, 16mA, 40ms)	Anti-scatter grid + Phantom (CIRS062M lung) CBCT# to CT#	Scatter (uniform)				> 85.0	> 85.0
							Scatter (iterative)				> 95.0	> 95.0
							Scatter (uniform)				> 60.0	> 60.0
				Lung (24)	Not defined (M, 16mA, 40ms)	Anti-scatter grid + Phantom (CIRS062M lung) CBCT# to CT#	Scatter (iterative)				> 80.0	> 80.0
							Scatter (uniform)					
							Scatter (iterative)					
				H&N (32)	Not defined (S, 16mA, 40ms)	Anti-scatter grid + Phantom (CIRS062M head) CBCT# to CT#	Scatter (uniform)				> 90.0	> 90.0
							Scatter (iterative)				> 85.0	> 85.0

TPS = treatment planning system; AAA = analytical anisotropic algorithm; PB = pencil beam; CC = collapsed cone; H&N = head and neck; NPC = nasopharyngeal carcinoma; FF = full fan; DIR = deformable image registration; MLT = multilevel-threshold; HM = histogram matching; ROI = region of interest; CT# = CT number; CBCT# = CBCT value; ED = electron density; RED = relative electron density; PD = physical density; pCT = planning CT; CBCT = cone beam; CT; vCT = virtual CT; rCT = rescan CT; PTV = planning target volume; GTV = gross tumour volume; D_{max} = maximum dose; D_{mean} = mean dose; D_{PTV, #%} = dose delivered to # % of PTV; D_{GTV, #%} = dose delivered to # % of GTV; OAR = organ at risk; R = right; L = left; C = contra; Bld = bladder; Rct = rectum; Par = parotid; SC = spinal cord; BS = brain stem; n/s = not supplied; n/a = not applicable.

Table 6b
Dose calculation studies using a combination of techniques for different phantoms, in chronological order.

Author	Make/ model	TPS	Algorithm	Phantom	Protocol	Dose Calculation Method	Artefact Correction	Reference	Calibration Curve	Difference [%]	γ -analysis [%]	Difference OAR [%]
Moteabbed et al. (2014) [88]	Elekta Synergy XVI	RayStation	n/s	Pelvis full bladder	n/s	DIR on original images (Bspline/Demons) + DIR (Bspline)	n/a	pCT	n/s	$D_{\text{mean-PROSTATE}}$	2%/2mm	D_{mean} : Bld = (2.3; 2.9), Rct = (0.5; 2.9)
						DIR on original images (Bspline/Demons) + Phantom-specific CBCT# to CT#			0.5	D_{mean} : Bld 0 = -0.2, Rct = (0.2; 0.4)		
						DIR on original images (Bspline/Demons) + Phantom-specific CBCT# to CT# + DIR (BSpline)			0.2	D_{mean} : Bld = -0.3, Rct = (0.0; 0.1)		
				Pelvis half full bladder		DIR on original images (Bspline/Demons) + DIR (Bspline)			(3.0; 3.2)	D_{mean} : Bld = (2.2; 3.0), Rct = (0.6; 2.2)		
						DIR on original images (Bspline/Demons) + Phantom-specific CBCT# to CT#			0.5	D_{mean} : Bld = (-0.7; 0.2), Rct = (0.2; 0.3)		
						DIR on original images (Bspline/Demons) + Phantom-specific CBCT# to CT#			0.2	D_{mean} : Bld = (0.2; 0.4), Rct = (0.0; 0.2)		
						DIR on original images (Bspline/Demons) + Phantom-specific CBCT# to CT# + DIR (BSpline)			(3.2; 3.6)	D_{mean} : Bld = (7.8; 9.1), Rct = (1.1; 2.6)		
						DIR on original images (Bspline/Demons) + Phantom-specific CBCT# to CT#			0.6	D_{mean} : Bld = (-0.1; 0.6), Rct = (0.3; 0.4)		
						DIR on original images (Bspline/Demons) + Phantom-specific CBCT# to CT#			0.2	D_{mean} : Bld = (0.0; 1.4), Rct = (0.0; 0.2)		
						DIR on original images (Bspline/Demons) + Phantom-specific CBCT# to CT# + DIR (BSpline)			n/s	n/s		
Schröder et al. (2019) [48]	Elekta Synergy XVI 5.0	XIO (v4.3.4)	n/s	Alderson Rando (pelvis)	Not defined (M, 32mA, 40ms)	Anti-scatter grid + Phantom (CIRS062M body) CBCT# to CT#	Scatter (uniform) Scatter (iterative)	pCT	User specified CT# to PD	$D_{\text{mean-PHANTOM}}$	2.0 ± 1.4	n/s
						Anti-scatter grid + Phantom (CIRS062M lung) CBCT# to CT#	Scatter (uniform) Scatter (iterative)				1.2 ± 1.1	
						Anti-scatter grid + Phantom (CIRS062M head) CBCT# to CT#	Scatter (uniform) Scatter (iterative)				1.1 ± 1.0	
				Alderson Rando (lung)		Anti-scatter grid + Phantom (CIRS062M lung) CBCT# to CT#	Scatter (uniform) Scatter (iterative)				1.2 ± 1.1	
						Anti-scatter grid + Phantom (CIRS062M lung) CBCT# to CT#	Scatter (uniform) Scatter (iterative)				1.2 ± 1.6	
						Anti-scatter grid + Phantom (CIRS062M lung) CBCT# to CT#	Scatter (uniform) Scatter (iterative)				1.2 ± 1.4	
						Anti-scatter grid + Phantom (CIRS062M head) CBCT# to CT#	Scatter (uniform) Scatter (iterative)				1.0 ± 3.5	
						Anti-scatter grid + Phantom (CIRS062M head) CBCT# to CT#	Scatter (uniform) Scatter (iterative)				1.1 ± 3.6	
						Anti-scatter grid + Phantom (CIRS062M head) CBCT# to CT#	Scatter (uniform) Scatter (iterative)					
						Anti-scatter grid + Phantom (CIRS062M head) CBCT# to CT#	Scatter (uniform) Scatter (iterative)					

TPS = treatment planning system; H&N = head and neck; DIR = deformable image registration; PD = physical density; CT# = CT number; CBCT# = CBCT value; pCT = planning CT; CBCT = cone beam; CT; D_{mean} = mean dose; OAR = organ at risk; R = right; L = left; C = contra; Bld = bladder; Rct = rectum; n/s = not supplied; n/a = not applicable.

TECHNIQUES USED FOR DIFFERENT TUMOUR SITES TOTAL PATIENTS IN PUBLISHED PAPERS

Fig. 1. Total number of patients for which the CBCT dose calculation was evaluated using different techniques (1 – pCT calibration, 2 – CBCT calibration, 3 – HU override, 4 – DIR, 5 – Dose deformation, 6 – Combined techniques). The number of publications matching the number of patients in each bar is reported in the table underneath the plot.

corresponding real tissues in both phantom studies and patient studies.

According to Richter *et al.* [35], the CBCT dose calculation accuracy could be further improved using patient-specific or population-based CBCT calibration curves rather than phantom ones, and this was later confirmed in [37,53]. The differences from the reference dose were generally less than 2.0% and there were minimal differences between patient-specific and population-based dose calculations.

No trend can be observed between different CBCT models, although Siemens MVision reported the highest difference from the reference dose: up to 11.0% for the uncorrected CBCT that noticeably improved (up to 2.0%) with artefact correction [57].

No proton studies were found in the literature which reported using CBCT calibration curves for dose calculations.

The CBCT calibration approach shows better results than the pCT calibration method, particularly for patient studies. Patient-specific CBCT calibration curves provided better results than using calibration phantoms [35,37,58], but the disadvantage of this approach is not generalizable and is carried out on a patient by patient basis. It is therefore time consuming and not clinically feasible without automation.

3.1.3. HU override

Another aspect to take into account when performing dose calculation based on CBCT is the variability of the HU values in the acquired images, which is attributable to acquisition parameters, object size and presence of inhomogeneities in the object itself. In addition, the increased scatter radiation can also cause an incorrect calculation of the photon attenuation, and consequently of the correspondent HU value and density. Thomas *et al.* [59] reported that a difference of 8.0% in bone electron density corresponds to a dosimetric error of 1.0% for typical radiotherapy beams. A good indicator of the performance of a

CBCT system is the stability of HU over time. Schröder *et al.* [60] investigated the HU reproducibility for an Elekta CBCT scanner (Synergy, XVI 5.0) over a period of 10 months, finding that the dosimetric change caused by the HU variability was less than 1.0%.

To reduce the influence of CBCT artefacts and HU variability on the dose calculation, several studies have suggested overriding the density of the structures in the CBCT image with average HU values from the corresponding structures on the pCT/rCT [36,42,66,67,43,45,53, 61–65]. Some other studies generated a linear conversion curve to match the HU values in the CBCT images with the HU values in the pCT images [27,39,68–72] (Table 3a, 3b). In many publications, the CBCT HU values to CT numbers conversion curves are labelled “calibration curve”, not to be confused here with the CBCT calibration curve mentioned in the Section 3.1.2.

Simple methods, such as applying a single HU value, equivalent to water, to the entire outline have been shown to give small median dose differences to the CTV for pelvis (0.3%) and head and neck (0.4%) but larger differences of 6.8% in lung patients [62]. Using an additional “lung” HU override combined with the water override, reduced this difference to 0.4%.

Thresholding tools are available in the TPS to allow automatic contouring of structures with different densities. The segmentation of the images can be done using multilevel-threshold (MLT), based on algorithms that classify CBCT voxels with similar HUs into several ranges, based on the grey level. The thresholds can be generated automatically using specific software (here referred as “Auto HU_{MLT}”) [36,42,43,53,62–64] or manually [62,63,65,69]. Dunlop *et al.* [62] recommended the use Auto HU_{MLT} rather than segmenting manually individual tissue (e.g. water/bone or water only), because it is faster, simpler and therefore easier to integrate into a typical clinical workflow. Better results were reported for head and neck and prostate

Table 7
Dose calculation studies for different tumour sites in patients and for different phantoms in tomotherapy MVCT adopting different methods, in chronological order.

Author	Make/model	TPS	Algorithm	Site/Phantom	Protocol	Method	Artefact Correction	Reference	Calibration Curve	Difference [%]	γ -analysis [%]	Difference (OAR) [%]
Langen et al. (2005) [124]	Tomotherapy Hi-Art	Tomotherapy Planning Station	MC	CIRS Thorax Phantom (rigid & distorted)	n/s	MVCT calibration	n/a	pCT	Phantom (Gammex RMI467) MVCT# to RED	$D_{\text{Target-95\%}}$ 0.50	n/s	DVH
Crop et al. (2012) [125]	Tomotherapy Hi-Art (v4.0.3)	n/s	n/s	H&N Gammex RMI phantom Pelvis (6)	n/s	MVCT calibration	n/a	kV CT	Author's model MVCT# to PD Phantom (Gammex RMI467) MVCT# to PD	$D_{\text{PTV-50\%}}$ 0.20 $D_{\text{DVH-50\%}}$ < 3.20	n/s	n/s
				H&N (6)					Author's model MVCT# to PD Phantom (Gammex RMI467) MVCT# to PD	0.40		
									Author's model MVCT# to PD Phantom (Gammex RMI467) MVCT# to PD	< 1.40		
Held et al. (2016) [111]	Accuray Tomotherapy	n/s	n/s	Water cylinder phantom Water pelvis phantom Anthropomorphic head phantom Anthropomorphic Thorax phantom Anthropomorphic pelvic phantom	n/s	MVCT calibration	n/a	pCT	Author's model MVCT# to PD User specified MVCT# to PD	D_{mean} -0.4 ± 3.7 -0.3 ± 0.6 -1.7 ± 6.1 -1.0 ± 9.0 0.2 ± 4.9	3%/3mm 97.0 100.0 99.5 99.2 100.0	n/s
Branchini et al. (2017) [126]	Accuray Tomotherapy	Tomotherapy DQA Station (v5.1.0.4)	n/s	H&N (10)	n/s	MVCT calibration DIR (3B-SplinesFree Form)	n/a	kV CT	User specified MVCT# to PD	n/s	2%/2mm 95.7 $\pm$ 0.4 94.8 $\pm$ 0.8	n/s

TPS = treatment planning system; MC = Monte Carlo; H&N = head and neck; DIR = deformable image registration; MVCT# = MVCT number; RED = relative electron density; PD = physical density; pCT = planning CT; PTV = planning target volume; D_{mean} = mean dose; OAR = organ at risk; n/s = not supplied; n/a = not applicable.

cancer, compared to thorax and abdomen [43,53,62,64].

Alternatively, a direct match between CBCT and pCT image cumulative histograms (HU_{HM}) was proposed by Onozato *et al.* [42]: pCT and CBCT HU values were normalised, so that the HU values of the CBCT images matched the HU values in the pCT histogram. In this study, HU_{MLT} and HU_{HM} yielded to similar results both for prostate patients and for a pelvic phantom.

For proton treatments, the HU_{HM} method was employed by Arai *et al.* [45] for a proton plan for head and neck patients revealed a dose difference of 5.7% to 98.0% of PTV when performing a CBCT dose calculation. According to the investigation conducted by the authors, in regions with large artefacts, HU_{HM} could not improve the CBCT dosimetric accuracy, thus generating potential problems in making histograms of HU values in proton beam therapy. Improved results were observed when the dose calculation was performed on a CBCT for pelvic (0.2%) and head and neck (2.7%) phantoms [45].

Another possible option, here referred as “ HU_{ROI} ”, consists in segmenting structures (ROI's) in the pCT and then transferring them to the CBCT images. The HU in the delineated ROI's is manually assigned to the mean HU value of the same regions in the pCT images [53,61,67]. The direct comparison between HU_{MLT} and HU_{ROI} presented by Fotina *et al.* [53] shows that similar results were obtained for prostate and lung, but for head and neck the results are 2.5% more accurate with HU_{MLT} .

For proton treatments, independently of whether HU_{MLD} , HU_{HM} , or HU_{ROI} are adopted, when applying the HU override technique in proton studies, similar gamma pass rates to photon studies were reported [68,72] but slightly higher dose differences to 98% of PTV (up to 5.7%) [27] and root mean square of the dose difference (up to 3.3%) were measured. According to the authors, these differences can be explained by the limited FOV of CBCT, missing important geometrical information necessary for adaptive proton therapy and by the higher proton plans sensitivity to inaccuracies in the image registration. The poor results for the caudal head and neck cases in [72] were explained by the artefacts and shadowing in the shoulder regions causing dosimetric inaccuracies both in IMRT (hotspots) and IMPT (distortions) plans.

Stitching CBCT techniques to cover an entire phantom body were investigated by Rafic *et al.* [66] using an anthropomorphic phantom: mean dose differences < 0.7% and gamma pass rates above 99.8% were measured. This is an interesting development as often a limitation of CBCT calculations are the limit to the FOV in the cranial-caudal direction.

HU override techniques show results comparable to those achieved with the CBCT calibration method [43,53]. However, this method can provide unreliable dose distributions when a large variation in densities occurs within a segmented tissues (e.g. lungs) [37,43,53,62].

3.1.4. Deformable image registration

Deformable image registration (DIR) is a technique that consists in geometrically deforming one image into another applying mathematical algorithms (eg. B-spline, Demons, etc). For CBCT dose calculation purposes, DIR is used to deform either the original pCT or the rescan rCT to match one of the patient's CBCT images [27,29,76–79,38,42,43,67,71,73–75]. Thus, a deformation vector field (DVF) defining the voxel-to-voxel mapping between pCT and CBCT is generated. The outlined structures are propagated from pCT to CBCT according to the DVF and the new deformed image are referred to as vCT. Finally, the pCT plan is applied to the vCT and the dose delivered is calculated.

DIR allows monitoring the organ deformation during the course of the treatment, particularly when daily or weekly CBCT scans are acquired. If anatomical changes, intra- or inter-fraction, are not corrected, they can lead to underdosage or overdosage to the target and OARs when using the planning dose distribution. Therefore, DIR can be used to propagate the planning segmentations to the images acquired on the day of the treatment (e.g. CBCT), thus giving an estimate of the dose

delivered to the deformable structures and a prediction of the toxicity to the OARs [80].

For all the previously described methods, the correct way of calculating the dose delivered to the CBCT was to apply the pCT plan to the CBCT images. When performing DIR, a meaningful comparison between pCT and CBCT dose calculation can be reported only if small anatomical changes occurred in the patient between acquiring the pCT and acquiring the CBCT, otherwise it is not possible to establish which one is the actual reference image and dose. Thus, for most of the studies reported here using the DIR method (Table 4a), the reference dose is calculated on an rCT acquired on a date close to the CBCT. The rest of the studies chose pCT as reference because the CBCT images were chosen to match closely the pCT [43] or the contours were copied from the pCT as in [73]. In other cases it was explicitly stated that a larger spread of errors were due to larger discrepancies between vCT and CBCT anatomy [38], or that pCT was chosen as a reference to iteratively compare the planned objectives while the treatment was progressing [75].

DIR tools are available in many TPS's; one of DIR main advantages is that vCT images are not affected by HU inaccuracies because the original CT numbers are not modified by the deformation. On the other hand, one of DIR main challenges is its quantitative verification, often not possible because of the difficulty in determining the ground truth. In the Task Group 132 [81] report, published by the Therapy Physics Committee of the American Association of Physicists in Medicine (AAPM), the role of image registration in treatment planning is discussed and guidelines to perform quality assurance for deformable and rigid image registration are provided. In particular, site-specific recommendations for performing qualitative assessments, and to ensure the clinical acceptability of the registration in routine clinical practice are supplied, since there is no comprehensive ground truth when dealing with DIR in patients. The tolerances indicated for DIR were 1–2 voxels for relevant structures when planning, and visible boundaries within PTV and OAR's margins during the treatment; for digital phantom test cases 95.0% of voxels has to be within the phantom within 2 mm and the maximum error must be < 5.0 mm.

The use of DIR for CBCT dose calculation was investigated on 202 patient cases (Table 4a) and on deformable phantoms (Table 4b).

Many different DIR algorithms are available and their accuracy has been discussed in [82,83]. BSpline and Morphons algorithms were observed to be the most commonly used both for patient and phantoms studies, but BSpline has been shown to perform better on patients, independent of the delivery technique [27,38,42,71,77,84]. Improved results were reported for prostate and head and neck cancer, compared to lung and liver [38,43,75,84]. The large mean dose difference reported by Huang *et al.* [75] between the dose calculated in the liver in week 1 and week 3 was explained by the anatomical changes which occurred during the treatment; the authors suggested prompt adaptive re-planning to avoid liver overdose. Veiga *et al.* [27,71] used the re-plan rCT (acquired approximately one week before the treatment) to evaluate the accuracy of recalculating the dose using CBCT images to avoid dosimetric errors due to the time gap between pCT and CBCT acquisitions (mean value for dose difference as percentage of the prescribed dose < 0.7% for photons, and < 2.6% for protons).

No trend can be observed between different CBCT manufacturers/models (described in Appendix 1) within this review.

For proton therapy, the most accurate result (dose difference normalized to the maximum dose of $-0.5\% \pm 0.9\%$) was reported in the only publication retrieved from the literature using a gantry-mounted CBCT clinical system for protons [29]. All the other publications on proton therapy CBCT dose calculation used CBCT datasets acquired on linacs, where DIR proved to be a valid technique for CBCT dose recalculation [27,29,45,68,72,78,79,85] where other methods were often suboptimal.

The advantage of DIR is that it is fast to use and promising results have been reported. However, large changes in anatomy may lead to

discrepancies between the CBCT and the vCT that consequently can affect target and OAR delineations and their dosimetric evaluations. This is particularly relevant when substantial anatomical differences occur at tissue-air interfaces (e.g. bowel or lung) [38,67].

3.1.5. Dose deformation

A further step in the use of DIR in radiotherapy consists of using a DVF to map back the calculated dose to the reference anatomy (dose warping). First, the pCT is mapped to the CBCT geometry using DIR and the dose is calculated on the deformed pCT. Then, the recalculated dose is warped to the original pCT using the same deformation matrix (dose warping) [86].

This technique presents a new challenge: while with all the previous methods it was possible to see/measure the effects of the modifications on the original images (CT or CBCT) and to correlate those changes to the recalculated dose, the dose deformation is not visible or measurable, therefore harder to interpret. Thus, the accuracy of dose warping for dose accumulation has been widely investigated both with physical and digital models, taking into account both DIR and DVF accuracy [87–90].

DIR and DVF were found to depend on the location and on the dose gradient in that location: small DVF errors in a high gradient region may lead to a larger dose error than large DVF errors in a region with homogeneous dose or no dose [91,92].

The appropriateness of deforming the dose in ART was discussed in a point/counter point debate published in 2012 [93–95]. Experimental measurements conducted using deformable gel phantoms [90,96] showed that DIR algorithms can be very accurate in reproducing the contours of the objects but less accurate in representing the low contrast region inside the contours. This was confirmed by the results presented by Veiga *et al.* [86], in which the regions with reduced contrast and increased noise or with higher dose gradient typically presented larger uncertainties in dose mapping. The choice of the DIR algorithm and the flexibility of the control parameters play a key role in dose warping but, independently from the algorithm chosen, the propagation of large deformation errors leads to large dosimetric errors [95]. Therefore, the lack of metrics for assessing the accuracy of DIR and the inability to measure the deformed dose are main limitations for evaluating the effectiveness of this method.

Few publications [29,86,97,98] were found in literature investigating the effects of using dose warping for CBCT dose calculations (Table 5). In the study conducted by García-Molla *et al.* [98] the difference between pCT and warped dose from the DVHs was reported in cGy and therefore was not comparable with the other results. Wen *et al.* [97] presented a study on PTV margin reduction for prostate cancer in which the dose calculated using the CBCT images is warped to the pCT images to determine the actual dose given to the patient. They calculated a mean dose difference to the PTV of -1.9% . Veiga *et al.* [86] tested the dose contribution from different combinations of algorithms for DIR and dose warping: the 99th percentile of the dose difference distribution as a percentage of the prescribed dose was 7.0% and 9.0% in the treated volume for the different combinations. Two years later the same author [29] applied dose warping on twenty lung cancer patients treated with proton therapy and reported a dose difference normalized to the maximum dose of -0.4% . The latter results highlighted the necessity of understanding the effect of DIR on dose warping by establishing the impact of the DVF uncertainties on dose mapping [99].

Dose deformation has been shown to be quite an accurate technique and potentially a very useful tool in radiotherapy, but the lack of an objective metric for assessing the correctness of the registration and the inability of tracking voxels for measuring the deformed dose is still a problem to be solved [93]. Clinical studies are recommended for validating DIR algorithm in terms of deformation parameters, in order to define specific tolerances to integrate DIR and dose warping into the clinical workflow [87,95,99]. Emerging studies on the use of gel

dosimetry for direct measurements of deformed dose [96] may provide insights into strategies for performing dose warping QA.

3.1.6. Combined techniques

Several of the studies combined two or more of the techniques previously described (Table 6a and Table 6b). While the most accurate method for calculating dose on CBCT could not be established, improvements were reported when combining the advantages of each specific method [38,48,88].

Kong *et al.* [100] suggested using “DIR + HU override” for both volume delineation and dose computation: DIR to facilitate the auto segmentation and HU override to overcome the lower CBCT image quality. This combination was investigated on a number of patient studies [42,45,65,67,73]. The most accurate results were reported in [42,67]: $< 0.8\%$ of mean dose difference to the PTV. While the least accurate result was reported in [73]: up to 9.0% for the dose difference delivered to 95% of PTV. Moteabbed *et al.* [88] adopted “DIR + HU override” on an anthropomorphic pelvic phantom. Both pelvic phantom CT and CBCT were deformed beforehand using two realistic patient-based deformation fields and an improvement of about 3.0% in the mean dose for prostate was achieved with the combination “HU override + DIR”, instead of using either HU override or DIR alone.

Another technique reported is to combine “DIR + CBCT calibration”, DIR (CBCT deformed onto pCT) to better match CBCT and pCT voxels, CBCT calibration to generate a calibration curve exploiting this match [47,73]. While the dose differences reported by Disher *et al.* [73] are quite large (between -5.0% and 6.0% for the dose delivered to 95% of PTV), Jin *et al.* [47] calculated a dose difference inferior $< 1.0\%$ to 95% of GTV.

No trends can be found in the results presented in Table 6a and Table 6b, but Arai *et al.* [45] once again showed larger dose differences for proton beams ($5.7 \pm 4.1\%$ for the dose to 98% of PTV) compared to the photon delivery techniques.

3.2. Artefact correction

It has been observed that artefact correction combined with any other techniques generally improved the dose calculation accuracy. Better results (with improvements up to 6.0%) were achieved both for patients and phantoms studies when artefact correction was applied before calculating the dose via pCT calibration [32,38,40,41,44,57,62,101,102]. Artefact correction applied before CBCT calibration [57,102], HU override [68,70], and DIR [68,76] improved the dosimetric accuracy by up to 10.0% . Poludniowski *et al.* [70] developed an in-house scatter correction algorithm that was combined with patient-specific CBCT HU values to CT numbers conversion to improve the calculated dosimetric accuracy up to 2.6% .

Schröder *et al.* [48] presented the only study investigating the effect on the dose calculation of a beam shaping device for scatter reduction (i.e. a hardware solutions to collimate/block the beam such as bowtie filters, anti-scatter grid, etc.). It was reported that using an anti-scatter grid, the calculated median gamma pass rate improved by 10.0% – 15.0% . Finally, machine learning based methods to correct CBCT images have recently started to be investigated and promising results were reported using different deep learning models (gamma pass rates $1\%/1\text{mm}$ improved from 88.2% to 96.3% [32] and from 94.5% to 99.0% [44]).

Motion artefacts can also cause notable dosimetric inaccuracies in dose calculations based on CBCT images [36,76,84,103] and undermine the DIR performance [74,79]. Thing *et al.* [76] verified that the presence of motion artefacts in CBCT but not in CT images led to an enlargement of the tumour, and consequently to lower gamma pass rates for the PTV than for any other delineated structure, because such artefacts may be observed around the moving target. Yang *et al.* [84] compared the effects of the motion artefacts between lung and prostate cancer: for lung cases, errors up to 3.0% were calculated, while for

prostate cancer, presenting little motion artefacts, the errors were found to be < 2.0%.

3.3. Dose calculation algorithms

Only one study was found in literature directly comparing the performances of different algorithms in CBCT dose calculation [63]. The authors reported on the results for one prostate patient: MC algorithm (Type C) improved the dose calculation by 1.0% in respect to a pencil beam (PB) algorithm (Type A) and by 0.5% in respect to a collapsed cone (CC) algorithm (Type B). Although only one site and one patient were investigated, the reported results reflected an important point when considering the previously reported techniques. The studies that used a PB algorithm reported the highest discrepancies between the CBCT and the reference dose [30,36,45,68]. Although, when using HU override method with the PB algorithm, the patients results reported in [45] and [36] were substantially improved (dose difference to 98% of PTV for ten head and neck cases improved from 27.1% to 5.7% and gamma pass rate 3%/3mm for three prostate cases improved from 33.3% to 92.8%, respectively).

Dose difference less than 5.0% were measured when using MC algorithms [37,53,63,79], but different metrics were used to reports the results (mean and median dose to the PTV, dose to 95% of the target volume, average range, WET) therefore it is difficult to identify trends or similarities between those studies.

The majority of the studies reported here, used Type B algorithms, and in particular the analytical anisotropic algorithm (AAA). Lung studies [43,62,69,73,86] reported larger dosimetric differences from the reference dose (dose difference to 95% of PTV up to 9.0%), probably because of the presence of low density media and heterogeneities [22].

The impact of which is the optimal dose calculation algorithm to use for CBCT calculations requires further investigation in a way which can separately consider the different techniques for CBCT calculations discussed above. Currently it is difficult to establish the optimal dose calculation algorithm for each technique based on the reported literature.

3.4. Physical limitations

Physical limitations such as the small FOVs coverage of CBCT (which causes partial irradiation when imaging large volumes), can affect dosimetric measurements performed using CBCT images. In order to enlarge the CBCT FOV, artificially stitched CBCT images could be generated taking CBCT acquisitions at different table positions [27,66,104]. Considering that the periphery of the CBCT images show reduced HU values, Yoo *et al.* [103] suggested not to set the isocentre of the stitched image in the edge of the CBCTs, emphasizing the limitation of CBCT-based planning in cases of larger treatment volumes. Alternatively, the image data of the pCT could be used outside of the FOV of the CBCT, enabling analysis of dose coverage of larger targets [37,43,76].

Another CBCT hardware limitation is given by the limited linac gantry rotational speed which increases the acquisition time thus making CBCT images more susceptible to motion artefacts. Boggula *et al.* [36] applied anisotropic safety margins to compensate for organ motion when calculating the dose distribution. Immobilisation techniques and retrospective sorting in a subset of projections belonging to different breathing phases (4D CBCT) are strategies currently adopted to reduce CBCT motion artefacts together with post-processing algorithms [105,106].

In many studies, customised protocols were chosen [37,40,107,41,47,48,55,58,66,75,104], adding extra variables to be considered when comparing the techniques adopted to perform CBCT dose calculation. Therefore, site-specific protocols for each machine model cannot be specified in this review for an optimal CBCT dose

calculation.

4. Discussions and recommendations

CBCT for IGRT and ART has been proven to improve radiotherapy treatments for several treatment sites (head and neck, lung, prostate, etc) [108–110]. CBCT enables imaging of the patient directly before the treatment, in the treatment position, thus showing changes in anatomy (tumour shrinkage, patient weight loss, etc.) and gives the possibility of adjusting the treatment if necessary to account for changes in the target position. Currently radiotherapy treatment plans are typically created using pCT, but the use of CBCT images for dose recalculation has been widely investigated.

This review has identified numerous studies evaluating the accuracy of dose calculations using CBCT. Most studies have focused on head and neck, lung and prostate cancer. A key aim of this review has been to investigate if the most accurate method to calculate dose on CBCT images could be identified. Although this has not been possible because of the many variables involved, the adoption of artefact correction techniques improving the CBCT image quality, and consequently the calculated dose, is recommended.

Since improving the CBCT image quality may lead to achieving better dose calculation results, it would be advisable to identify new site-specific standardised imaging protocols to use when acquiring CBCT images for dose calculation purposes. However, by following practices that aim to minimize the dose to the patient (ALARA principle), the noise in the images may increase and thus reduce the accuracy of the dose calculation.

4.1. Challenges when comparing studies on CBCT dose calculation results

Comparison between studies is challenging due to the many variables involved (e.g. image acquisition protocol, tumour site, TPS algorithm, etc) and the various metrics used for evaluating the dose difference compared to the reference dose.

Any metric used must be relevant and its use fully justified. Gamma analysis is often adopted but dose threshold and reference dose (local or global) for the γ -index calculation were only specified in eight articles [30,43,48,52,58,68,102,111]. Diamantopoulos *et al.* [112] published a review article on the dose comparison methodologies for treatment plan verification. Gamma analysis was found to be often adopted in the literature as the gold standard. It has, however, been suggested to strive for a better metric, taking into account statistical and clinical parameters rather than continuing to use the familiar gamma index because of its limitations and challenges in calculation [113,114].

A comparison of the results reported in the studies presented here is also challenging because of the lack of a common ground truth for the reference dose. Typically, authors want to minimize the contribution of geometrical changes (from anatomical and posture changes) when comparing reference and CBCT calculated dose and experimental measurements can provide a common ground truth for comparisons. However, some studies have reported a way to exploit the variations in anatomy on the CBCT images by using the dose delivered to OARs on the CBCTs as an indicator to decide whether replanning the patient is necessary or not [36,47,115].

4.2. Set of reporting standard for CBCT dose calculations

Since many different parameters are involved, a set of common reporting standards for CBCT dosimetric studies is recommended to enable meaningful future comparison and it is imperative that the following are reported as a minimum:

- i. Linear accelerator:
 - Manufacturers, model, version and software version.
 - Imaging acquisition parameters, protocols (e.g. filter, collimator,

energy, FOV, gantry rotation) and software version; the use of standard protocols provided by the vendors is recommended.

- Delivery technique.
 - Artefact corrections.
- ii. TPS:
- Dose calculation algorithm and software version number.
 - Image registration technique (rigid or deformable registration) and software version used – if applicable.
 - Segmentation method adopted and software used – if applicable.
 - Calibration curve chosen – if applicable.
 - Time taken between pCT and CBCT acquisition.
 - pCT scanner, make model and software version.
- iii. Treated targets and OARs:
- Tumour site (target volumes for phantoms).
 - Number of cases investigated.
 - OARs.
- iv. Phantom used for the CBCT calibration and for the dose calculation – if applicable:
- Vendor and model.
 - Inserts specifics (size and composition).
- v. Comparison metrics:
- Analysis software and version.
 - Ground truth upon which calculating the reference dose.
 - Gamma analysis threshold – if applicable.
 - Gamma analysis reference dose (local or global) – if applicable.
 - Median absorbed dose to targets and OARs – if applicable.

5. Conclusions

With the increasing adoption of CBCT pre-treatment verification and the rapid increase in the use of ART, this review demonstrates a variability in methods used to quantify dose on pre-treatment CBCT images for photon and proton therapy. CBCT image quality has significantly improved through advances in hardware and software, and this review has shown that irrespective of the method utilized this has resulted in improved dose calculation accuracy. This highlights the need for dose validation and quality assurance standards to allow an accurate assessment of CBCT-based dose calculation.

CBCT dose recalculations are often used as a trigger to rescan and/or re-plan the patient using a pCT. However, depending on the accuracy required for this trigger point, or if new plans are created based on the CBCT dose calculation, these doses should be subject to the same validation and quality assurance standards as those on a pCT. Moreover, CBCT dose recalculations have been typically compared to pCT dose calculations as the reference, assuming that the dose algorithm is accurate. More studies evaluating measured data, rather than comparisons with doses calculated on pCTs, are recommended.

This review revealed insufficient reporting of parameters (such as hardware, software, calculation algorithms, acquisition protocol, delivery techniques), and methods of reporting results varied significantly across studies. Since many parameters are involved, this review establishes a set of reporting standards for studies on CBCT dosimetric accuracy in order to allow meaningful comparisons among different Institutes.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejmp.2020.06.017>.

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