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Review paper

A review of cone-beam CT applications for adaptive radiotherapy of prostate cancer

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ABSTRACT

Introduction: The aim of this study was to systematize the information on adaptive radiotherapy based on cone-beam computed tomography (CBCT) imaging for patients with prostate cancers including the prostate gland only, or the prostate gland and seminal vesicles region.
Material and method: A systematic literature search was carried out using the PubMed engine, based upon the following terms: adaptive radiotherapy, intensity modulated radiotherapy, volumetric modulated arc therapy and image-guided and dose-guided radiotherapy. Overall, 58 relevant studies were included: 31 about on-line strategies of adaptation, 6 about off-line strategies, and 21 that highlighted the technical aspects of CBCT usage.
Results: The off-line strategies provide a statistical prediction for each individual patient for the rest of treatment. The on-line strategies aim to resolve the potential disagreements between a planned and delivered dose directly before the specific fraction. Both strategies need information about the movements of the irradiated region relative to the target from treatment planning and the dose delivered relative to the planned dose. Quality of CBCT is very important for the accuracy of the adaptation procedures. While the errors caused by the insufficient quality of anatomy visualisation with CBCT are currently minimized, there are still problems with the proper dose computation. The most accurate methods are able to minimize the calculation error to 3%.
Conclusion: CBCT plays a significant role in each step of adaptive radiation therapy of prostate cancers, starting from registration procedures through setting an appropriate CTV-to-PTV margin to fraction dose recalculations, and its cumulation/monitoring relative to the planned dose.

1. Introduction

The dynamic techniques of radiation therapy, such as intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) applied for treatment of prostate cancer, allow to deliver dose to the target with a higher dose gradient around the target than the three-dimensional radiation therapy [1–3]. Therefore, a proper use of dynamic techniques of radiation therapy requires consistent and accurate localisation of the prostate prior to treatment delivery provided by image guided radiation therapy (IGRT) [4]. One of the main sources of information about anatomical changes during IGRT is the kilo-voltage cone-beam computed tomography (CBCT) imaging [5–8]. The image guidance based on CBCT images, realized before each fraction or according to institutional protocols (e.g. for each fractions during the first week of treatment and followed by control one or two times per week) enables to observe anatomical changes occurring in the irradiated volume and undertake remedial actions aimed at compensating for observed changes in anatomy (differences between anatomy from the plan prepared before treatment and actual anatomy visualised during treatment). Anatomy changes may be of a progressive, random or mixed nature. While the progressive changes depend on systematic changes of the volume of irradiated structures (e.g. tumour regression), the random changes are independent on the volume changes and manifest themselves by different location of the target during radiation therapy. The changes that we refer to as 'mixed' combine both types of changes. Image guidance procedures realized on conventional accelerators allowed to observe fraction-by-fraction changes of anatomy (inter-fraction changes). It is possible to control and react automatically to changes that happen during a treatment delivery (intra-fraction changes). It is realized, for example, by tracking system implemented on non-conventional accelerators, such as CyberKnife (Accuray Inc., Sunnyvale, CA, USA) [9,10]. The changes of anatomy provided by IGRT

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do not always correspond to clinically significant changes of dose distribution. In order to access the correctness of the treatment delivery, the dose guidance procedures were proposed [11]. Conceptually, the best dose guidance procedures are based on the collection of the doses (by a detector) that are actually delivered to the patient with visualisation of these doses on three-dimensional images (e.g. CBCT) created just before the dose delivery. This method is called transit dosimetry. Although transit dosimetry has been intensively developed in recent years, it is still a research concept rather than a commercially introduced solution [12–16]. Currently used recalculation of the planned doses on images collected during the treatment is still state-of-art for dose-guided procedures [17,18]. The recalculated dose can be compared with the planning dose for a single fraction or by the accumulation of doses delivered by several fractions. Possible anatomy changes in different fractions should be accounted for by non-rigid registration algorithms and dose mapping algorithms for dose accumulation. Based on anatomical changes and the actual dose delivered to the target, it is possible to verify the agreement between the plan of the treatment and its implementation. If discrepancies are detected, the original treatment plan should be modified to the clinically significant one to meet the therapeutic objectives. This kind of actions is called adaptation and radiation therapy that includes these actions is called adaptive radiation therapy.

Another intensely developed solution of image guided radiation therapy is that based on magnetic resonance images (MR-guided RT) [19,20]. While the CBCT technology is developed by all vendors of conventional linacs [21], the MR-guided RT is implemented on Elekta linacs (Elekta Instruments AB, Stockholm, Sweden) and on cobalt units (Best Theratronics, Ottawa, Canada). Benefits include better tumour visualisation, online adaptation and the potential for image biomarker-based personalised RT [19]. Nevertheless, the dose-guidance procedures are still based on dose recalculation on CT images that are synthetically created from MR images and then non-rigidly registered with the planning CT [22,23].

Despite a clearly stated definition of adaptive radiation therapy, there are a lot of adaptive methods for patients with prostate cancer. We propose systematization of current literature of CBCT solutions based on two criteria. Firstly, we propose the names for two classes of adaptation: actual fraction adaptation and statistical prediction; they may be equated with online and offline solutions. Secondly, in relation to changes in target geometry and organs at risk, we propose to differentiate three classes of adaptations: translational, rotational and deformational. In addition, to present full potential of using CBCT applications in adaptive RT, we analysed parameters related to CBCT, such as image quality, accuracy of dose calculations, imaging dose, and environment of CBCT processing.

2. Material and method

2.1. Information sources and search strategy

Searches were carried out in July 2018 using the PubMed searching engine that provides a free access to MEDLINE and links to full text articles when possible. If open access to the articles was restricted, they were downloaded trough our institutional access. Searching was limited to full-text articles including e-publications ahead of print, no date or language restrictions were applied. The used key words were arranged according to the following scheme: (adaptive radiation therapy and/or intensity modulated radiation therapy and/or volumetric modulated arc therapy) and prostate cancer and (image guidance and/or cone beam computed tomography) and dose-guided radiation therapy.

2.2. Eligibility criteria

English, French, and German language studies examining adaptive methods based on image-guided (with special emphasis on CBCT imaging) and dose-guided procedures during external beam radiation therapy for prostate cancer treatment limited to the prostate gland or prostate gland and seminal vesicles were included.

The quality and eligibility of the studies were assessed using three criteria: (i) Was the spectrum of patients included representative of those in clinical practice? (ii) Were the methods described in sufficient detail to permit replication of the study? (iii) Were the outcomes measured appropriate to the aims of the study?

Initial abstracts were screened for relevance by the first author, followed by assessment for eligibility of full-length articles.

Overall, 58 relevant studies were included. While 31 of them concerned on-line strategies of adaptation during radiation therapy of prostate cancer, 6 were related to off-line strategies, and 21 highlighted the technical aspects/parameters related to cone beam computed tomography and their influence on the decision-making strategy during adaptive radiation therapy.

3. Results and discussion

3.1. On-line strategies – actual fraction adaptation

In this paper, we assume that ‘online strategy’ means that all information about organs of interest, volumes and its relations is derived only from actual imaging done on-board before treatment delivery. Such procedure will be referred to as actual fraction adaptation.

In the following sections, we compared the existing knowledge about utilising three dimensional volumetric CBCT imaging for actual fraction adaptation by including translations only, translations and rotations, and strategies including procedures of non-rigid deformations and dose mapping. On-line strategies of CBCT analysis of the anatomical data allow to aperture modification for radiation therapy, segment modification for IMRT using multileaf collimator (MLC), or online inverse planning [24–27].

3.1.1. Matching by translation only

As it is impossible to track down soft tissue and localization features in planar (2D) kilo-voltage (kV) or mega-voltage (MV) imaging, the use of fiducial markers along with the CBCT or/and 2D-kV images has become a standard in image guided prostate radiotherapy [28].

In this section, we are particularly interested in the movements of the prostate gland relative to the bony anatomy. Additionally, we assume that the prostate is defined as a structure that does not deform nor change its volume during radiation therapy. This simplification enables us to identify the position of the prostate by a single point. In the case of marker-based image guidance (IG), this point is defined by a geometrical centre of fiducial markers set and, for IG, based on the volumetric information of the anatomy of the patient (e.g. CBCT imaging) this point relates to the mass centre of the prostate. Table 1 shows the published studies that compare feasibility of IG based on location of the prostate according to soft tissues that are visible on CBCT images (STB, *soft tissue-based method*) with IG based on marker-based (MB, *marker-based method*) methods of prostate localization.

There are two basic approaches to the online matching procedure – automatic and/or manual. Apart from exhaustive work [29] where 3D-3D intensity-based algorithms were found consistent with the MB method, all other automatic procedures [30–34] turned out to be inadequate for clinical situations. In the study by Hammoud et al. [29], markers (natural calcification) were evaluated on a CBCT image, not as in most cases on 2D-kV portal images, which may be the reason for the noted differences. The main reasons for a poor outcome of automatic algorithms [30–34] included insufficient quality of CBCT images and subsequent long acquisition time of images (movement of structures, blurring), high-density structures in matching ROI (markers, bones).

Manual matching methods can be divided into two groups, the first one is based on the matching of the prostate contour from planning CT to the prostate anatomy displayed on CBCT images [31,35–37] and the

Table 1
The comparison of alignments based on markers and soft tissues that were made on CBCT images for prostate gland positioning.

Study	Comparison of alignment based on markers and soft tissues			
	Matching	Comment	Parameter	Result
Barney et al. [35]	Manual	Analysis of the differences between marker based and soft tissue based matches	Percentage agreement for shift < 5 mm; for each direction	AP: 72% SI: 73% LR: 97%
			Percentage agreement for shift < 3 mm; for each direction	AP: 41% SI: 49% LR: 87%
Hammoud et al. [29]	Automatic	Calcifications used as markers; comparison of mass centre (contours) and geometrical centre (markers, but on CBCT)	Average differences; for each direction	AP: 0.9 ± 0.8 mm SI: 1.4 ± 0.9 mm LR: 0.5 ± 0.3 mm
Letourneau et al. [34]	Automatic and manual	Manual delineation of CBCT and contour matching with planning CT	Average differences; for each direction	AP: 1.0 ± 1.5 mm SI: 1.1 ± 2.9 mm LR: 0.6 ± 0.8 mm
Shang et al. [38]	Manual	Analysis based on comparisons between mass centre (contours) and geometrical centre (markers)	Average difference between planning CT and manual CBCT contours; for vector	V: 1.3 ± 0.5 mm
			Average difference between marker and contours based matching; for vector	V: 6.6 ± 2.6 mm
Chiesa et al. [37]	Automatic and manual	Analysis of mass centre (contours) for planning CT and CBCT	Percentage agreement for shift < 5 mm; for each direction	AP: 19% SI: 24% LR: 13%
Maund et al. [33]	Automatic	Position of geometrical centre (markers) based on on-line and off-line analysis of CBCT	Average differences; for each direction	AP: 1.0 mm SI: 0.8 mm LR: 0.6 mm
Mosley et al. [36]	Manual	Correlation and comparison between marker based (at 2D-MV images) and soft tissue based (at CBCT images) matches	Percentage agreement for shift < 3 mm; for each direction	AP: 70.3% SI: 78.4% LR: 99.6%
			Pearson's correlation coefficient; for each direction ($p < 0.001$)	R^2(AP) = 0.49 R^2(SI) = 0.51 R^2(LR) = 0.90
		Correlation and comparison between marker based and soft tissue based (both at CBCT images) matches	Percentage agreement for shift < 3 mm; for each direction	AP: 63.7% SI: 64.1% LR: 90.8%
			Pearson's correlation coefficient; for each direction ($p < 0.001$)	R^2(AP) = 0.55 R^2(SI) = 0.41 R^2(LR) = 0.90
Logadóttir et al. [30]	Automatic	Correlation between marker based and soft tissue based matches for CBCT images	Pearson's correlation coefficient; for each direction ($p < 0.001$)	R^2(AP) = 0.483 R^2(LR) = 0.700 R^2(SI) = 0.242
Shi et al. [32]	Automatic	Analysis of the differences between marker based and soft tissue based matches	Statistically significant difference for shift > 5 mm; for each direction	AP: NO (but 28% higher than 5 cm) SI: YES ($p < 0.01$) LR: NO
Adamczyk et al. [31]	Automatic and manual	Comparison between 2D-kV registration based on bony anatomy and registration based on soft tissues (CBCT)	Statistically significant difference for shift > 3 mm; for each direction	AP: YES ($p < 0.001$) SI: NO LR: NO

AP – anterior/posterior direction; SI – superior/inferior direction; LR – left/right direction; V vector of displacement; CBCT – cone beam computed tomography; CT – computed tomography; 2D-MV – two dimensional (planar) megavoltage image.

other one on the matching of the prostate contour from CBCT images with the prostate contour from the planning CT [34,38]. Matching in the first group can be done on-line, while in the other group, the matching needs additional time for prostate contouring on CBCT images that is usually performed off-line. There is a consensus that the best agreement between both methods is in the left/right direction because of a good tissue contrast and negligible prostate movements. The conclusion is that soft-tissue matching on CBCT images could not be simply used interchangeably with the MB 2D-kV method.

The automatically react to intra-fraction changes (just like on CyberKnife [9]) is not currently possible on conventional accelerators where control of these changes is only possible by external devices (e.g. Calypso, Varian Medical Systems, Palo Alto, CA, USA) [39]. While Calypso system is beyond the scope of this review, the usage of the CBCT allows to implement interesting methods to control the CTV-to-PTV margin used during dose delivery. Gehrke et al. [40] showed methodology of markers identification on CBCT projections to assess trends in prostate movement during treatment. While this study shows in detail a unique method of tracking the prostate movement during the CBCT delivery, the possibility of extrapolation of these movements to the whole fraction of irradiation is rather controversial because the most significant factors determining intra-fraction changes have are random in nature and increase with fraction time (e.g. rectal filling/motion) [41]. Oates et al. showed in their studies [42,43] a significant correlation between the rectal diameter measured on pre-treatment CBCT and the prostate intra-fraction motion. They established that for the maximum rectum diameter (MDR) ≤ 3 cm, prostate displacement is ≤ 5 mm while for a MRD ≤ 3.5 cm prostate displacement is ≤ 5.5 mm. Correct image registration and then combining the method of predicting the intra-fraction motion of prostate [43] with one of fast on-line inverse planning methods or adaptations based on library of the plans allows a complete application of actual fraction adaptation methods. It should be noted that adaptation based on a plan library is usually used for bladder radiotherapy [44]. While for the bladder, plans included in the library differ by the CTV-to-PTV margin depending on the volume of the bladder, for the prostate the plans should differ by the CTV-to-PTV margin depending on the intra-fraction motion of the prostate.

Table 2
Adaptive strategies include deformations and dislocations of the prostate and seminal vesicles during radiation therapy.

Study	Margins	Methods of CBCT processing for dose calculations	Time	Improvement of dose distribution in comparison to	
				Rigid soft tissues correction	Classical[a], daily re-optimisation
Boggula et al. [51]	Anterior and Cranio-caudal: 12 mm Posteriorly and Lateral: 8 mm	Multi-level threshold algorithm for HU conversion from CT to CBCT.	36 min[b]	PTV: YES Bladder: NO Rectum: YES	N/A
Wu et al. [52] Thongphiew et al. [53]	5 mm	Mapping of HU between CT and CBCT by deformable methods	1–2 mins[c]	PTV: YES OARs: NO	OARs: YES
Li et al. [55]	5 mm	Mapping of HU between CT and CBCT by rigid methods	N/A	PO and SV: YES OAR: YES	PO and SV: NO OARs: YES
Qin et al. [56]	3 mm	Mapping of HU between CT and CBCT by deformable methods	N/A	PO and SV: YES OARs: YES	OARs: NO
Fu et al. [54]	5 mm	HU from not processed (raw) CBCT	10–20 min	PO: NO SV: YES OARs: YES	PO and SV: YES OAR's: NO
Crijns et al. [57]	6 mm	Mapping of HU between CT and CBCT by deformable methods	N/A[d]	PTV: NO OARs: YES	N/A

CT – computed tomography; CBCT – cone beam computed tomography; HU – Hounsfield unit; PTV – planning target volume; PO – prostate.
SV – seminal vesicles; OARs – organs at risk.
[a] Classical, means routine procedure of re-contouring, re-optimization and dose re-calculation on CT in treatment planning systems.
[b] Time include: contouring $<$ 10 min, planning $\leq$ 10 min, CBCT modification $\leq$ 1.5 min and copying original plan to modified CBCT $\leq$ 12 min.
[c] Time states for re-optimisation only.
[d] Very time-consuming mapping of HU between CT and CBCT.

3.1.2. Matching including rotations

Compared to the translations, proper identification and reconstruction of rotations using fiducial markers on coplanar 2D-kV images is not straightforward, due to its three-dimensional nature [45]. The utilization of the rotation during the procedure of patient positioning is not frequently described in literature. Moreover, our method being inconsistent with others, we decided to prepare a separate paper focusing on feasibility of using CBCT imaging (STB or MB matches) for on-line correction protocols for rotations.

Adamczyk et al. [31] measured the difference for the role of prostate rotation between the results obtained for the matching method based on bony anatomy and the method based on soft tissue (prostate gland) alignment. They established the action level for the prostate rotation at 3 degrees. In one of ten cases, the threshold was crossed. The anatomy of this patient changed considerably in comparison to CT images from planning and a re-planning procedure had to be initiated for him. Boda-Heggemann et al. [46] evaluated automatic matching between 'anatomy' structures (55 iodine seeds from brachytherapy implantation) with appropriate ‘alignment clip box’ that covers the prostate. Only tilt (rotation along the left/right direction) was possible to be reliably assessed. As a result, authors did not use on-line correction. Logadottir et al. [30] evaluated the rotations for the automatic (with manual corrections if needed) matching method based on soft tissue that covers the prostate with a 3 mm margin compared to the MB matching. The STB method gave significantly smaller random and systematic errors than the MB method. The highest correlation between rotations detected for the MB and STB methods (both on CBCT images) was for the anterior/posterior direction. For the other directions, the correlations were small, and the difference between the obtained rotation vectors was statistically significant. It should be noted that the authors of this study analysed rotations higher than 3 degree. They showed that rotations lower than 3 degrees do not significantly affect the distribution of doses deposited in the prostate and organs at risk (OARs). Similar solutions based on the strategy 'check visually and if it's necessary then re-plan it' are presented by Bratengeier et al. [47] and Holubyev et al. [48]. For each daily fraction, authors checked anatomy alignment between PTV contoured on the planning CT images, and prostate visible on CBCT images. In the case of non-compliance (prostate outside PTV), patient was replanned on a new CT, using a simplified procedure of IMRT optimization, which changes only the segment shape and preserves monitor units for every field. Chiesa et al. [37] evaluated the utilization of CBCT together with 6 degrees of freedom trans-rotational correction system (couch 6D). CBCT was manually or automatically matched to planning CT using only bony structures. Authors suggest that the relevance of 6D patient repositioning is important in the case of non-spherical targets and organs far from the isocenter. Charret et al. [49] used the automatic STB matching of CBCT to CT images used during planning. Translational correction and correction of two rotations: roll (longitudinal axis) and pitch (lateral axis), were analysed. Their study shows that rectal distension has no significant impact on pitch and roll angles of the prostate. Shang et al. [38] evaluated different online MB position correction strategies utilizing CBCT imaging. MB alignments (automatic and automatic with manual corrections), which include translations and rotations, were analysed in relation to soft tissue alignment that includes translations only and is based on contours of the prostate. All methods of alignment were performed on CBCT images. MB alignment that includes manual corrections is better than MB automatic only alignment. Including rotations leads to the increase in the difference between MB alignment and STB alignment. Moreover, large rotations lead to the increase in false identification of markers (e.g. rotation by 6 degree resulted in 2 mm migration of the markers). The authors show additionally that soft tissue (contours) based alignment provides the best prostate dose coverage.

3.1.3. Matching including deformations

Strategies including deformations consider target as a non-rigid structure consisting of the prostate gland and seminal vesicles. Due to the fact that the seminal vesicles can move, rotate, and deform regardless of the prostate gland [48,50], it is not possible to use any surrogate (fiducial markers) to properly track down the target structure. Table 2 shows the frequently used methods of standardization and related results.

Boggula et al. [51] present results of using module Active-Rx™ from research version of Corvous treatment planning system (TeamBest®, Pittsburgh, PA, USA). Daily adaptation is based on manual isodose shaping to achieve the required result. Based on the changes of isodose, the adaptation tool included in Active-Rx™ alters either monitor units

or segments of treatment fields (adequate for step and shoot IMRT) without changing the isocentre of the treatment. The group from the Duke University Medical Centre [52,53] used their in-house model of linear programming for daily adaptation. The model minimizes the weighted sum of deviations of the delivered dose from the prescribed dose through modification of the MLC movements for the best coverage by the dose of the prostate and seminal vesicles. Fu et al. [54] presented a similar methodology with the main difference that online MLC modification adapts daily fraction for translations and deformation based on contours of the prostate and seminal vesicles that are delineated manually on CBCT images, while the studies from the Duke University were based on non-rigid registrations of the images. The methodology of the study proposed by Fu et al. [54] assumes that the total monitor units for each beam and for each segment are kept unchanged. Li et al. [55] show a hybrid approach called 'AIGRT' (adaptive image guided radiation therapy). The AIGRT is based on the methodology described by the Duke University group [52,53] with one important exception: the fraction dose is not modified by MLC movement but is selected from a library of plans. Plans included in the library cover main potential deformations and dislocations of the prostate and the seminal vesicles. The library increases during the course of radiation therapy by daily re-optimized plans. Taking into account the information about the difference in anatomy displayed on planning CT images and CBCT images, the most-fitting plan to compensate these differences is chosen automatically from the library. Different hybrid approach was evaluated by Qin et al. [56]. In this study, the authors associate daily marker-based correction (translations only) with an offline adaptive strategy. After the first week of radiation therapy, a new plan was generated using 5 daily post fraction CBCT images. The last method of adaptation is directly applied to end products of the optimisation of monitor units and generated optimal fluences. Corrections that include optimal collimator rotation, jaws position and isotropic scaling are generated based on projected fiducial points and, in the next step, are automatically applied to the plan [57,58].

3.2. Off-line strategies – statistical prediction

Off-line strategies mean that information gathered during the first few fractions is used to make some assumptions about forthcoming behaviour (statistical prediction) for individual patients and, in contrast to the classic solutions (population analysis) [59–61]. Off-line strategies allow individualizing CTV-to-PTV margins to create a new treatment plan based on personalized margins.

First off-line strategies assume the possibility of individualization of the CTV-to-PTV margin based on the generation of average contours [62,63]. During the first few fractions (e.g. 6 fractions as in Nijkamp et al. [62] study), the patient was treated with a treatment plan that took into account the literature based CTV-to-PTV margin (10 mm). Each fraction was guided by CBCT. On every set of CBCT images, the prostate and rectum were delineated using methods of automatic localization. In the next step, the contours sets were exported and displayed on the planning CT images. Envelopes of the prostate and rectum contours were defined as new adapted contours and used for plan re-optimization. As a result, the CTV-to-PTV margin was reduced from 10 mm to 7 mm, which corresponds to a decrease of the PTV by 29%. From dosimetrical point of view, the volume of the rectum that received dose > 65 Gy was reduced by 19%. Unfortunately, the procedure [62] is time consuming and needs approximately 7 h for each patient. The same methodology but for proton therapy of patient with prostate cancer was used by Góra et al. [64]. Their adaptive strategy, based on creating a treatment plan for the PTV being an envelope of CTV contours generated for the first five fractions, was compared with a standard planning strategy when 10 mm CTV-to-PTV margin is used. To include intra-fraction motion, the PTV was additionally enlarged by 5 mm in the anterior/posterior direction and by 3 mm in the lateral and superior/inferior direction. While the dose distribution in the prostate was comparable in adaptive and standard strategies, the adaptive strategies guaranteed improved sparing of the rectum. Also, authors clearly state that it is not recommended that fiducial markers are used in proton beams due to their possible dose perturbations. In contrast to previously described studies, the group of Vanasek et al. [65] based their study on the average isocenter position that was computed from the first ten fractions where CBCT imaging for daily online prostate matching was performed. During the first ten fractions, CTV-to-PTV margins were, respectively, 8 mm for the anterior/posterior direction and 6 mm for the superior/inferior and left/right directions for each patient. The shifts data collected during the first ten fractions were used for calculations of systematic and random errors of prostate position. In the second phase of treatment (after first ten fractions), an average isocenter position was set and used for the rest of the fractions. In this phase of treatment, isotropic CTV-to-PTV margin was created individually to each patient. The size of CTV-to-PTV margins corresponded to the random errors of prostate position and were 6 mm if a random error was smaller than 2.5 mm, 8 mm when a random error ranged from 2.5 mm to 5.0 mm and 10 mm for random errors higher than 5.0 mm. In the second phase of radiotherapy, the setup verification was based only on two orthogonally placed 2D-kV pelvic images.

Different approach, called 'hybrid strategy', was shown by Qin et al. [56]. In this study, a CTV-to-PTV margin was 3 mm. The relatively small margin enforced daily correction of the prostate and seminal vesicles (CTV) that was based on the correction of the position of the markers in the prostate gland. The second component of the hybrid strategy was off-line adaptive inverse planning performed by using in-house software. Delivered dose was presented as the sum of the doses calculated on CBCT images for the first five fractions. The composite dose from the first five fractions was built by non-rigid mapping algorithms and was displayed on the CT planning image. To allow comparison with the planned total dose, the composite dose from the first five fractions was extrapolated to total prescribed dose. Hybrid technique achieves a similar result as daily online re-planning (Table 2). Finally, the group of Adamson et al. [66] showed that using off-line strategies allowed in most clinical cases to reduce the CTV-to-PTV margin after the first 4–5 fractions below the population-based level. Their specific results suggest that it is possible for 73% of patients.

3.3. Parameters related to cone-beam computed tomography

3.3.1. CBCT image quality

The quality of the CBCT images is very important because daily CBCT images in prostate cancer cases are utilized either for manual or automatic OARs delineation or to determine their temporal position. The overview of possible artefacts or loss in image quality is given by Barrett et al. and Schulze et al. [67,68]. In the context of these publications, we could divide possible issues into two groups.

The first group included situations where images are not good enough for further processing and there was no way to improve them by current tools for modification of CBCT images. The occurrence of high-density objects (hip prosthesis) in the field of view (FOV) lead to artefacts resulting from beam hardening, artefacts concerning exponential edge or extinction/scattering processes. These artefacts lead to poor quality by reducing the contrast, obscuring structures and impairing the detection of areas of interest. While there were attempts to introduce some algorithms to reduce these artefacts [69,70] or use megavoltage energies for creating CBCT images [71], the current state of reduction of these artefacts does not allow the use of CBCT images for adaptive applications for patients with hip prosthesis. However, hopes are now placed on new, iterative CBCT reconstruction methods called iCBCT (Varian Medical Systems, Palo Alto, CA, USA) [72]. Another reason for low quality patient motion. Due to relatively long time of acquiring, CBCT imaging of the abdomen is sensitive to rectal gas movement. Nijkamp et al. [62] showed that 9% of CBCT images were overruled due to quality issues caused by rectal gas movement. Because there is no

software-based solution for this issue, one possible way is to introduce strict dietary protocols. Smitsmans et al. [73] showed improvement for the adequacy of automatic matching procedure from 83% to 94% ($p < 0.001$) when dietary protocol was applied during patient's radiotherapy. Truncation or truncated view artefacts are inherently related to CBCT imaging. They occur because the size of FOV is smaller than the size of object being imaged. Abdominal imaging is especially prone to this effect because of the body size. There are attempts to introduce reconstruction algorithms; nevertheless, there is still no working clinical application [74]. Unlike hip prosthesis situation, most truncation artefacts do not unambiguously exclude patients from adaptive/IGRT protocols.

Second group is related to parameters that can be controlled and/or improved by the quality assurance process. Several guidelines are available on this topic for CBCT [75,76]. This study focuses on parameters related to adaptive protocols in prostate cancer. First parameter is low contrast visibility (LCV) related to soft tissue contrast, which is crucial for the prostate region. According to Stock et al. [77] and Lehmann et al. [78], CT is superior to CBCT and no time trend for CBCT's LCV to CT's LCV in 16 months period is observed. Nevertheless, there is a strong relation between LCV, protocol used, and the presence of bow-tie filter [77]. Similar results were obtained by Yoo et al. [75] who evaluated LCV using a standard Catphan 504 phantom with low-resolution disks (The Phantom Laboratory, Salem, NY, USA). The CBCT images acquired using a full-fan were superior to a half fan and results were reproducible over a four-month period [75]. Second parameter is Hounsfield unit (HU) linearity and uniformity which is related to dose calculation capability. According to Yoo et al. [75], over a four-month period all materials from a Catphan 504 phantom were reconstructed with ± 40HU accuracy with fluctuations within the limits. Next parameter is in-slice spatial linearity, which is a simple distance measure for geometrical distortions that can influence organ relations in the reconstructed image. It is recommended to keep a 1% tolerance (0.5 mm) that should be stable over a 16-month period [75]. Last parameters highlighted in Yoo's study are related to noise. These are signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR). SNR was 26% less for CBCT than for CT and CNR was 51.1% higher for CT than for CBCT. There was no time trend observed either for SNR or CNR.

3.3.2. Dose calculation using CBCT

In addition to the visualization properties (which are affected by the parameters described above), one of the main challenges of CBCT imaging is the dose calculation capability, and there are still many doubts abound the quality of final dose distributions. In the next paragraphs, we will omit discrepancies caused by artefacts and focus on studies comparing CT and CBCT dose calculation results.

Yoo and Yin [79] analysed the dose distributions calculated on CBCT images in relation to the doses computed on conventional CT images. Sets of CBCT images used in the study were generated by Varian On Board Imager system (OBI®, Varian Medical Systems, Palo Alto, CA, USA). The doses were computed on CBCT that were gathered in different combination of filtering and imaging mode (full and half fan mode of imaging with and without a bowtie filter). All computations were performed for a CIRS phantom (CIRS, Norfolk, VA) with a Hounsfield units density curve that was gathered from CT measurements. In a homogenous phantom with lateral static 6MV and 15 MV beam, setup, dose differences higher than 1% computed on CT images and on CBCT images when a half fan mode without a bowtie filter was used. Similar results were observed for an inhomogeneous phantom to simulate a lung case. Richter et al. [80] as well as Fotina et al. [81] compared different constructions of Hounsfield-units-to-density tables for dose calculation on CBCT data sets for Elekta XVI system (Elekta Instruments AB, Stockholm, Sweden). Dose calculated on CBCT images was compared with a dose calculated on CT images. They showed that for CBCT dose computations using standard tables (the Hounsfield units from CT) or phantom based tables (phantom based Hounsfield units curve for CBCT) lead to unacceptable differences between doses calculated on CT and on CBCT that are higher than 5%. The use of patient individual tables allows to decrease these differences to less than 3%. Additionally, they showed the dependence between the slope of Hounsfield-units-to-density table and the tube voltage.

3.3.3. Imaging dose considerations

The number of images collected during image guided radiation therapy is much greater than in the case of a standard, non-image guided radiation therapy. Therefore, for most adaptive procedures, information about the dose delivered to the patient during imaging should be noted [82].

Basic guidelines that concern the management of imaging dose during image-guided radiotherapy are reported by the Task Group 75 appointed by the American Association of Physicist in Medicine [83]. The general rule of thumb for any dose is ALARA, which assumes that the dose should be as low as reasonably achievable. Specific recommendations for CBCT are: (1) scanning only as much anatomy as necessary for desired task by reducing cone angle in the axial direction; (2) considering if CBCT is consistent with image quality and information needed for treatment decision to be made and (3) evaluate total dose patient-by-patient. Moreover, the imaging dose should be analysed individually for each patient. It results from the fact that in order to obtain good quality images with the lowest dose, both patient's data (e.g. patient's size and anatomy and difficulty of positioning) and imaging device's data (e.g. field of view, voltage, time and the mode of CBCT imaging) should be taken into account.

For radiotherapy patients, we want to know the dose cumulated in organs at risk for the whole course of treatment, including imaging dose. Unfortunately, there are only indirect methods to estimate imaging doses. Wen et al. [84] considered the doses from CBCT imaging during the treatment of prostate cancer patients on Varian machines (Varian Medical Systems, Palo Alto, CA, USA). The doses were measured using TLD's and Rando pelvic phantom. The normal tissue integral dose for 40 fractions was ranged from 1.3 Gy in the central area of the phantom to 2 Gy in peripheral parts of the phantom. Dose to the left femoral head can be higher than 4 Gy for the whole treatment course. Ding et al. [85] simulated and evaluated the 3D dose from Varian CBCT (125 kVp, 80 mA and 25 ms with a half-fan filter, whole rotation) by VMCBC (Vanderbilt Monte Carlo Beam Calibration) algorithm. Two extreme situations for a prostate case, such as a large adult patient (lateral and vertical dimensions: 24 cm and 38 cm) and 31-month pediatric patient (lateral and vertical dimensions: 17 cm and 11.5 cm) were examined. Doses from one therapeutic imaging session (one CBCT) for femoral heads ranged from 6 to 7 cGy for adults and from 15 to 17 cGy for pediatric patients. For soft tissues, the range of doses was from 2 to 3 cGy for adults and from 6 to 8 cGy for pediatric patients. Moreover, authors show that the minimum doses received by 50% of the imaged body of adults or pediatric patients were, respectively, 3 or 7 cGy. Islam et al. [86] provided comprehensive information about doses for CBCT imaging on Elekta XVI system. They showed that the imaging dose depends on the chosen field of view (FOV). For example, the surface dose cumulated for one cycle of imaging (full rotation, 120kVp and 30 cm diameter of the body phantom) was 1.8 cGy for 5 cm × 26 cm FOV, while for 26 cm × 26 cm FOV it was 2.3 cGy. With changing the kilovoltage peak from 120 to 140 kVp, the surface doses increased from 1.8 to 2.8 cGy for 5 cm × 26 cm FOV and from 2.3 to 3.5 cGy for 26 cm × 26 cm FOV. They showed also that imaging dose depends on the number of projections used to image reconstruction. Full rotation of the imaging gantry in Elekta system needs 622 projections. Measurements performed for phantom with 30 cm diameter show that for the range of projections from 100 to 600, the imaging doses linearly increase with the number of projections.

3.3.4. Environment of CBCT processing

The environment where CBCT is processed during IGRT is just as

important as the well-chosen CBCT parameters. The CBCT images appear in many operational places of the radiation therapy line, starting from treatment planning system (TPS) through recording and verification (R&V) system to CBCT imaging system. Therefore, there is a need to automate the flow of the imaging and dose data between these places. While Accuray developed commercially available solution for Tomotherapy units (Accuray Inc., Sunnyvale, CA, USA) to manage the adaptive process included in PreciseART™ module in Precise TPS v 2.0 [87], this solution is still commercially unavailable for conventional linacs. Recently, one of interesting in-house solutions of anatomical and dose data management was proposed by Qin et al. [88]. The system developed by them monitors the R&V system and, when CBCT images are reconstructed, generates pseudo-CT based on non-rigid registration between planning CT and CBCT images. Finally, the dose for respective fraction is recalculated on pseudo-CT and considered in the evaluation of agreement between planned dose and dose delivered during the radiation therapy. Considering the need to validate automatic systems for monitoring changes in anatomy and their impact on dose distributions, it should be noted that such solutions significantly shorten the time of data processing and facilitate the routine implementation of adaptive procedures in radiotherapy.

4. Conclusion

While the rigid registration of the prostate only region visualised on planning CT and on CBCT images during radiation therapy allows to initiate adaptive procedures, the registration of the region of the prostate and seminal vesicles needs to use non-rigid procedures. For full implementation of adaptive strategies, both above scenarios need additional information connecting the shift data of the target with the dose delivered to the actual anatomy. There are a few in-house methods proposed to do this in an on-line regime. Nevertheless, more popular are off-line strategies that allow dose calculation procedures that are not limited by the operational time. Off-line strategies allow individualizing the CTV-to-PTV margin and to create a new treatment plan using individual margins. While the off-line strategies are statistical prediction for each individual patient for the rest of treatment (typically treatment during the first week based on a population-based margin), the on-line strategies tried to resolve the potential disagreements between planned and to be delivered dose before the specific fraction. Despite methodological differences, both on-line and off-line methods need information about the potential movements of the irradiated region relative to the anatomy from treatment planning and the dose delivered relative to planned dose. Methodology of prediction of intra-fraction motion of prostate showed by Oates et al. [43] seems to be an optimal method that connects the on-line and off-line strategies. While it allows to set an adequate CTV-to-PTV margin (just like the off-line strategies), it is implemented in the on-line regime. The quality of CBCT images directly affects the accuracy of the adaptation procedures. While the errors based on the quality of anatomy visualisation based on CBCT images are currently minimized, there are still problems with proper dose computation. The most accurate methods minimize the calculation error to 3%. Implementation of the new solutions of the CBCT image reconstruction (e.g. iCBCT) will probably enable further minimizing of the treatment dose calculation errors while reducing non-therapeutic, imaging doses that cumulate in the visualised region during the adaptive procedures. Currently, the methodology proposed by Qin et al. [88] seems to be the most appropriate methodology of dose recalculation and subsequent monitoring during the radiotherapy. It is based on generation of pseudo-CT (as a result of non-rigid registration between planning CT and CBCT), dose recalculation on pseudo-CT, and finally on the monitoring of delivered dose (cumulated fraction-by-fraction in a non-rigid regime) in the light of planned dose.

Combining the most relevant methods, the optimal adaptation scheme should include (1) online components, such as (a) accurate registration of CBCT to planned CT (marker-based method with prostate rotations smaller than 3 degrees and soft tissue-based method with rotations higher than 3 degrees), (b) on-line estimation of most appropriate CTV-to-PTV margin (based on prediction model of intra-fraction movement), (c) if the estimated margin differs from that currently used, application of the fast on-line inverse planning method or adaptations based on the library of plans, (d) fraction dose delivery, and (2) offline components, such as (e) generation of pseudo-CT, (f) dose recalculation on pseudo-CT, and its monitoring (cumulated fraction-by-fraction in the non-rigid regime) in the light of planned dose.

Conflict of interest

None.

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