Adaptive radiotherapy for bladder cancer – a systematic review

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ABSTRACT

Radiotherapy has been offered as a multi-modality treatment for bladder cancer patients. Due to the significant variation of bladder volume observed throughout the course of treatment, large margins in the range of 20 – 30 mm have been used, unnecessarily irradiating a large volume of normal tissue. With the capability of visualizing soft tissue in Cone Beam Computerized Tomography, there is opportunity to modify or to adapt the plan based on the variation observed during the course of treatment for quality improvement. A literature search was conducted in May 2016, with the aim of examining the adaptive strategies that have been developed for bladder cancer and assessing the efficacy in improving treatment quality. Among the 18 identified publications, three adaptive strategies were reported: Plan of the Day, patient-specific planning target volume and daily reoptimization. Overall, any of the adaptive strategies achieved a significant improvement in reducing the irradiated volume compared to the non-adaptive approach, outweighing the additional resource required for its execution. The amount and the type of resource required vary from strategy to strategy, suggesting the need for the individual institution to assess feasibility based on the existing infrastructure in order to identify the most appropriate strategy for implementation.

List of Abbreviation

CBCT: Conebeam CT

CTV: Clinical Target Volume

DIR: Deformable Image Registration

IMRT: Intensity Modulated Radiation Therapy

OAR: Organ at Risk

PLN: Pelvis Lymph Node

POD: Plan of the Day

PS-PTV: Patient-specific PTV

PTV: Planning Target Volume

ReOpt: Daily ReOptimization

VMAT: Volumetric Modulated Arc Therapy

INTRODUCTION

The typical clinical target volume (CTV) for bladder radiotherapy consists of the pelvic lymph nodes (PLN), the entire bladder and the primary tumor [1]. High precision radiotherapy such as 3 dimensional conformal or intensity-modulated radiotherapy (IMRT) techniques have been recommended to optimize the dose to the target and the adjacent organs at risk (OAR) [2]. However, substantial internal motion of the bladder during the treatment course necessitates the use of population-based Planning Target Volume (PTV) margins in the range of 20 – 30 mm [1,3,4].

Image guidance using Cone Beam Computed Tomography (CBCT) has improved target localization via soft tissue visualization and has reduced setup errors [5]. Despite these improvements in treatment precision, there are barriers to reducing the PTV margin for bladder loco-regional radiation therapy. The radiation fields must include two independent moving targets: the PLN, which are relatively immobile, and the highly distensible bladder, which can vary in volume and position.

In the presence of two independent moving targets, adaptive radiotherapy has been demonstrated to be the best strategy in the treatment of PLN and prostate when compared to various translational correction strategies [6,7]. Adaptive radiotherapy is defined as "a closed-loop radiation treatment process where the treatment plan can be modified" by measuring an individual's target and OAR geometric variations [8]. Due to the large interfraction and interpatient variation observed for bladder cancer, various adaptive strategies have been specifically developed. A literature review was conducted with ~~T~~the purpose of ~~this paper is to d~~describing~~e~~ each of these adaptive strategies, and to compare/contrast their potential to improve treatment quality.

METHODS AND MATERIALS

A literature search was performed in May 2016 using the PubMed and the Google Scholar databases. ~~u~~Using the combination of the following keywords, ~~to identify~~ all English language peer-reviewed articles that reported on the development and efficacy of bladder cancer adaptive radiotherapy strategies using CBCT were identified: Bladder, adaptive radiotherapy, online, offline and CBCT. Only articles that were published after 2006 were included, when CBCT was widely introduced for clinical application. The reference sections of identified articles were also individually searched to include publications that were not indexed in the PubMed database. Reasons for exclusion ~~are~~were: Evaluation of CBCT; use of imaging modality other than CBCT; validation of algorithm; description of clinical trial and related training; overview on dose accumulation; accuracy on volume delineation; assessment of intrafraction motion; general overview of Genitourinary~~U~~/bladder radiotherapy, literature review on bladder adaptive radiotherapy. The PRISMA flow chart of the literature review is displayed in Figure 1.

After reviewing the publications, each was categorized as one of the following adaptive strategies: Plan of the Day (POD), Patient-specific PTV (PS-PTV) and daily reoptimization (ReOpt). Details of the various studies were then extracted and organized to develop a detailed description of individual strategy, contrasting the strategy with the other approaches and highlighting its pros and cons.

FINDINGS

A total of 18 published studies that investigated various adaptive strategies for bladder radiotherapy are included in this review and are summarized in Table 1.

Plan of the Day (POD)

Based on the large and random variation in bladder volume observed during treatment, it is hypothesized that the single distribution generated based on an expansion on the planning bladder would lead to either a geographical miss of the target or over-irradiation of normal tissue. In order to resolve this, a POD library consisting of multiple distributions generated based on PTV of various sizes was proposed. Different approaches in generating the POD library are discussed below but generally, CBCT are acquired prior to daily treatment delivery, and the smallest PTV that can encompass the target volume on that day is selected. The corresponding POD distribution is then used to deliver the dose of the day. Burridge et al. (2006) were the first to report the use of CBCT for selecting the POD based on the bladder size prior to daily treatment [9]. This strategy has subsequently been investigated by various groups to assess its efficacy in OAR sparing and target coverage [10-23].

There are various methods of constructing the different sized PTVs for the POD library, which could be based on a single image or multiple images. For single-image based, a standard PTV is first generated by expanding the bladder by a population margin in the range of 15 – 30 mm. A library of 3-6 PTVs is then created by applying an isotropic margin in increments of 5mm to the bladder [14], or by changing the margin in the superior and/or anterior directions in which bladder exhibits greater variation [9,11,17]. In the study by Vestergaard et al. (2010), various isotropic margins that would provide coverage for 50%, 70%, and 90% of the population were applied to generate the POD library [10]. Although this method is simple, the use of a single image in generating the POD library lacks the ability to characterize individual's bladder filling and irregular deformation pattern, diminishing its ability to fully compensate for volume variations.

The use of anatomical information from multiple planning images enables the generation of a POD library that is more patient-specific and is able to account for the significant inter-patient variability in bladder variation observed in this group of patients. Lalondrelle et al. (2011) first reported the generation of a POD library using bladder delineated on multiple successive CTs acquired at different time intervals, starting with an empty bladder [12]. This strategy has been investigated by a few other groups [11,17,19]. In general, the irradiated volume was reduced when compared to using a population-based static PTV approach. However, depending on the filling rate and the length of time in which the successive CTs were acquired, target under-dosage was observed in >20% of cases, demonstrating the inadequacy of this approach in capturing the whole range of bladder volume [11,12,17]. Instead of scanning an empty bladder first, Meijer et al. (2012) acquired the first CT with a full bladder and acquired the second one after the patient had voided [16]. Six different PTVs were then generated based on information provided from these two scans. This increased the target coverage to 100% and achieved the same goal of reducing the irradiated volume based on qualitative evaluation. Although multiple CTs were acquired, some argue that this was still insufficient to capture the full spectrum of anatomical deformation of bladder observed through the course of treatment, nor does it address systematic differences between bladder volumes at planning and treatment [20,22,24].

The inclusion of CBCTs acquired at the beginning of the treatment course when generating the POD library was proposed and investigated [10,12,13,15,18,21,22]. In this approach, bladder was delineated on the planning CT and first 4-5 CBCTs. The POD library was generated based on different combinations and/or numbers of volumes. For example, in Vestergaard et al. (2010), the smallest PTV was derived based on the combination of the 2 smallest volumes, medium based on all combined volumes and large by expanding a population margin on the bladder on CT [10]. When comparing the POD library generated based on multiple CTs vs. combination of CT and CBCTs, a larger irradiated volume resulted from the former method. However, the inclusion of CBCTs achieved better target coverage with a smaller irradiated volume [22]. Images acquired on multiple days captured the volume variation for bladder and the positional variation based on changes in rectal filling [3]. Furthermore, less time is required at the time of planning to acquire multiple CTs.

Although the POD strategy has been demonstrated as effective at improving plan dosimetry when compared with a non-adaptive approach, there are some acknowledged challenges with this adaptive strategy. Depending on the number of PTVs available and how they are generated, the planning resource burden could be heavy. Acquisition of multiple CT scans exposes patients to additional dose and adds procedural time to both the patient and the department. Resources invested to construct the POD library and the associated multiple treatment plans is considered wasted when some of the PTVs are not used or are selected in low frequency. For example, 6 different distributions were generated for the 6 PTVs in the POD library reported in Murthy et al. (2011). However, only 3 out of the 6 PTVs were eventually selected for treatment [14].

Patient-Specific PTV (PS-PTV)

Similar to the multiple image POD strategy, information from the CT and CBCTs can be incorporated to derive a single patient-specific PTV (PS-PTV). A PS-PTV can be generated by creating a structure by combining the volumes of bladder delineated on the planning CT and the first few CBCTs, then adding a small expansion margin to incorporate additional uncertainties. Instead of selecting different distributions based on the bladder of the day (POD strategy), a single distribution is generated based on the PS-PTV and is used to deliver the remaining course of treatment [17,25-27]. This approach is therefore more logistically viable than the multiple plan POD approach. Moreover, all studies reported a significant decrease in the irradiated volume when compared to a standard PTV. It is important to note that the target coverage ~~rate~~ was reported to be >95% when the PS-PTV was derived based on a full bladder and inclusion of 5 CBCTs [25,26], whereas it ~~the rate~~ decreased to 50% when it was derived based on an empty bladder and inclusion of 3 CBCTs [17]. A disadvantage of the PS-PTV strategy is that changes observed during the beginning of the treatment course cannot be corrected immediately due to the need of information gathering from the first few treatments. In addition, if the bladder is significantly smaller in subsequent fractions compared to the first 4-5 fractions, the efficacy of PS-PTV in OAR sparing could be reduced. Conversely, a larger bladder volume in the later part of treatment could result in geographical miss of the target. Therefore, despite significant dosimetric and logistical advantages, the efficacy of the PS-PTV approach is reliant on the bladder volumes from the first few fractions being representative of the bladder filling variation throughout the remainder of the treatment course.

Daily Re-optimization (ReOpt)

Since there are large and random variations in bladder volume and shape from fraction to fraction, it is hypothesized that daily re-optimization (ReOpt) would be the best strategy to achieve optimal target coverage and OAR sparing. This can be achieved by acquiring daily CBCT and performing online modification of the plan prior to treatment delivery based on the anatomy visualized on the CBCT [28] and has been demonstrated to be feasible for palliative and pelvic radiotherapy, with acceptable dosimetric accuracy and timeframe [29,30]. Vestergaard et al. (2013) performed a comparison between a standard PTV and the POD and ReOpt strategies for bladder radiotherapy [18]. The reduction of the irradiated volume achieved by ReOpt was significantly greater than POD. For a total prescription of 60Gy, ReOpt reduced the volume receiving ≤45Gy by 58% whereas POD reduced it by 20% compared to a standard PTV [18]. However, the requirement to delineate the bladder while the patient is on the couch and the generation of a new distribution for every fraction can be resource intensive. The cost-benefit of adopting this strategy has yet to be critically assessed to determine the feasibility of implementing it clinically and its impact on departmental resources.

DISCUSSION

This comprehensive and systematic literature review identified three major adaptive strategies for the treatment of bladder cancer described and/or evaluated in 18 studies:

POD, PS-PTV and ReOpt. Each strategy has been demonstrated as effective at reducing the irradiated volume when compared to a non-adaptive approach but with considerable variation in the magnitude of that effect. A number of factors can have an impact on the efficacy of these strategies: Bladder status at the time of planning and treatment, accuracy and precision of bladder delineation on CT and/or CBCT, and reproducibility in image assessment.

Some institutions adopt the empty bladder protocol for better bladder volume reproducibility, improved patient comfort and reduction of irradiated volume [9-13,15,17-22,27] whereas others prefer the use of full bladder preparation for improved sparing of normal tissue [16,23,25,26]. Webster et al. (2013), reported poor target coverage using the PS-PTV strategy and an empty bladder protocol [17], whereas those studies that evaluated PS-PTV in combination with a full bladder protocol report excellent target coverage statistics [25]. It may therefore be suggested that full bladder is more efficacious if a PS-PTV strategy is to be employed, especially when there is difficulty achieving an empty bladder towards the end of treatment due to swelling and incomplete emptying due to toxicity. To date, there is no direct comparison of the impact of full or empty bladder on the efficacy of the other two adaptive strategies.

Bladder delineation is a critical task in the adaptive process and variability among observers and between CT and CBCT is unavoidable. The single image based POD strategy could be less affected by delineation variability since the PTVs are generated using a single bladder contour delineated on the highest quality image (planning CT) resulting in small delineation variability [31]. For the multiple image based POD, the PS-PTV and the ReOpt strategies however, the PTVs are derived based on the multiple bladder contours delineated on often poor quality image datasets (CBCT) and are thus susceptible to a higher degree of observer variability [32]. Auto-segmentation tools will have an important role to play in the improvement of both efficiency and precision of bladder adaptive strategies that require multiple bladder contours delineated on poor quality images [33,34].

Excellence in CBCT assessment is necessary to accurately distinguish the bladder from the adjacent normal tissue when selecting the appropriate PTV for treatment using the POD strategy. Prior to the implementation of the POD strategy, Foroudi et al. provided a training workshop and that educational intervention was deemed to be effective in improving the quality of POD-based treatment delivery by reducing the plan selection variability [35]. Similarly, very high skill levels are required for the soft-tissue CBCT matching necessary for the PS-PTV, particularly when the PTV is highly irregular or when complex 3D surface-based matching surrogates are required. The clinical application of ReOpt will require the greatest level of skill in CBCT image assessment. Where treating radiation therapists may be required to recontour and replan on-the-fly while the patient is on the couch, there is opportunity for scope expansion in which high-level clinical skills in image interpretation and delineation of treatment volume are to be developed and applied.

There are a number of limitations in the findings of the various studies reviewed. The majority of the studies considered only the reduction of the geometric PTV volume as the benefit of using adaptive radiotherapy without reporting the actual dose to the target and/or OARs [9,12,13,15-17,19,25,26]. The benefits postulated are predicated on the assumption that the volume receiving the prescribed dose and the defined target volume is a perfect overlap. However, despite the use of highly conformal techniques such as IMRT and VMAT, perfect conformity is rarely clinically achievable. This can result in an over or under estimation of the differences between the adaptive strategies. For studies that included a dosimetric comparison, the dosimetric differences were calculated without accounting for any OAR anatomical changes exhibited during treatment [10,11,23,27]. This is problematic since the OARs adjacent to the bladder dome can be in a different location from fraction to fraction. With this lack of accounting for the dosimetric effect of OAR positional changes, it is clear that no study to date can accurately predict the dosimetric differences between any of these adaptive strategies. Deformable image registration (DIR) has been previously used to account for the significant changes in volume and shape of the bladder and the adjacent OARs between the planning CT and CBCTs [36]. Certainly, the application of DIR techniques to accurately discriminate between bladder adaptive strategies is urgently necessary.

CONCLUSION

Three adaptive strategies [36]have been developed for bladder cancer radiotherapy to address the large interpatient and interfraction bladder volume variation observed. All strategies have demonstrated significant improvement in reducing the irradiated volume without compromising target coverage, yet definitive dosimetric evaluations that incorporate the effect of OAR motion are currently lacking. In lieu of compelling dosimetric evidence, individual institutions should adopt the strategy that best fits their clinical processes and existing infrastructure based on the strengths and limitations of each strategy.

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