

REVIEW



A review of plan library approaches in adaptive radiotherapy of bladder cancer

Shane D. Collins and Michelle M. Leech 

Applied Radiation Therapy Trinity, Discipline of Radiation Therapy, Trinity College, Dublin, Ireland

ABSTRACT

Background: Large variations in the shape and size of the bladder volume are commonly observed in bladder cancer radiotherapy (RT). The clinical target volume (CTV) is therefore frequently inadequately treated and large isotropic margins are inappropriate in terms of dose to organs at risk (OAR); thereby making adaptive radiotherapy (ART) attractive for this tumour site. There are various methods of ART delivery, however, for bladder cancer, plan libraries are frequently used.

Material and methods: A review of published studies on plan libraries for bladder cancer using four databases (Pubmed, Science Direct, Embase and Cochrane Library) was conducted. The endpoints selected were accuracy and feasibility of initiation of a plan library strategy into a RT department.

Results: Twenty-four articles were included in this review. The majority of studies reported improvement in accuracy with 10 studies showing an improvement in planning target volume (PTV) and CTV coverage with plan libraries, some by up to 24%. Seventeen studies showed a dose reduction to OARs, particularly the small bowel V45Gy, V40Gy, V30Gy and V10Gy, and the rectal V30Gy. However, the occurrence of no suitable plan was reported in six studies, with three studies showing no significant difference between adaptive and non-adaptive strategies in terms of target coverage. In addition, inter-observer variability in plan selection appears to remain problematic. The additional resources, education and technology required for the initiation of plan library selection for bladder cancer may hinder its routine clinical implementation, with eight studies illustrating increased treatment time required.

Conclusions: While there is a growing body of evidence in support of plan libraries for bladder RT, many studies differed in their delivery approach. The advent of the clinical use of the MRI-linear accelerator will provide RT departments with the opportunity to consider daily online adaption for bladder cancer as an alternate to plan library approaches.

ARTICLE HISTORY

Received 8 December 2016
Accepted 18 December 2017

Introduction

Radiotherapy (RT) or radical cystectomy are the two main treatment modalities for muscle-invasive bladder cancer [1]. Radical cystectomy has been the standard treatment adopted for most patients, while RT has been reserved for those with inoperable tumours or who are medically unfit to undergo a cystectomy. Many papers have considered the choice between cystectomy and tri-modality treatment of muscle invasive bladder cancer, with a growing body of evidence suggesting that bladder preservation with tri-modality treatment leads to acceptable outcomes and should be considered a treatment option in well-selected patients [2,3]. Tri-modality treatment includes transurethral resection of the bladder tumour followed by radiation therapy and concomitant chemotherapy. However, with a significant improvement in RT delivery, the bladder-preserving potential of RT is now recognised [1].

Radiotherapy is one of the main modalities used in the treatment of muscle-invasive bladder cancer [4]. A central issue in bladder cancer RT planning and delivery is the management of organ motion. As the bladder is a mobile and

hollow organ, it changes size, shape and position during the treatment course, resulting in substantial variations in both bladder wall and tumour position, thus limiting the precision of conventional bladder RT [5–12]. Large isotropic clinical target volume (CTV) to planning target volume (PTV) margins of 1.5–2 cm are commonly used to overcome this. In most instances, the CTV includes the whole bladder plus any extravescical tumour extent. However, these margins have proven to be inadequate in many cases [7–9]. The use of such large margins to treat an organ of great positional uncertainty results in the irradiation of large amounts of normal tissue and therefore increased toxicity [13,14]. The average volume of normal tissue irradiated using a non-adaptive technique ranges from 234 to 922 cm³ (486 cm³ average) [15] and typical radical treatment doses are in the range of 60–64 Gy.

With an adaptive approach, patient-specific anatomic information is taken into consideration before each fraction of treatment. The overall aim is to improve accuracy by delivering the prescribed dose to the target while limiting dose to normal tissue through the reduction of margins [16,17]. There are a number of different methods of adaptive

radiotherapy (ART) delivery, as outlined by Thörnqvist et al. [18] but for bladder cancer, where target location and volume change are variable on a daily basis, plan libraries are prevalent. This approach is where several plans are developed for each individual patient using various probabilistic bladder volumes and the most optimal plan, based on coverage of the target volume, is selected each day [19,20]. This approach exploits the advantages of high quality 3D image acquisition using CBCT, which allows geometric corrections to be visualised and made to account for position, size and shape of the bladder at each fraction [21]. Despite this, it potentially increases patient dose due to daily imaging [22]. However, it is imperative to consider this increase in the context of the potential benefits of a more conformal and accurate treatment, which are the focus of this review [20,23].

Material and methods

The search process included a database search, selection of relevant studies, assessment of their quality and subsequently, data extraction. As the focus of the review was bladder cancer and ART in the form of plan libraries, the search terms used were: Adaptive Radiotherapy AND bladder cancer [MeSH], Adaptive Radiotherapy AND bladder cancer AND accuracy [MeSH], Adaptive Radiation therapy AND bladder cancer [MeSH], as well as plan library AND bladder cancer [MeSH]. Search terms were screened under the title and/or abstract components of studies indexed in EMBASE, Pubmed, Science Direct and Cochrane databases. Duplicate studies were excluded.

Abstract screening, using the inclusion and exclusion criteria specified in Appendix A (supplementary data) was performed on the resulting list of citations. Following screening, chosen literature underwent a full text assessment. The reference lists of the selected studies were searched to identify further possible studies, ensuring all relevant publications were included.

Prospective and retrospective studies were included in this review. Studies published in abstract form only were excluded as were studies or reviews that focused on the use of plan libraries for sites other than bladder cancer or for multiple sites.

Results and discussion

The primary search identified 365 articles through the selected databases. Following initial title and abstract screening, subsequent full text assessment and a second hand search of the reference lists, 24 studies were identified as eligible. A histologically-proven diagnosis of bladder cancer with ART using plan library selection as the main modality of treatment was required for the study to be included in this review. All stages of disease excluding palliative disease were considered and both male and female participants were included. A plan library was defined as the production of several RT treatment plans, with the optimal plan chosen on the day. Publications on plan libraries for bladder cancer were excluded if they did not consider at least one of treatment

accuracy or feasibility comparison or investigated interventions other than plan libraries.

Data were extracted from resulting eligible studies and presented accordingly as outcomes of using plan libraries and factors affecting outcomes (Tables 1 and 2 and Supplementary Appendix B). Studies have been noted as retrospective or prospective in Table 1.

Accuracy of plan libraries for bladder cancer

Margins and geometric miss

As part of a plan library approach, daily geometric verification is used [11,13,14,16,19,23–34] which enables correction of positional and deformational errors of the target [29]. Different methods of developing a plan library have been trialled with varied success. Lalondrelle et al. [14] found that with an adaptive-predictive organ localisation technique, bladder displacement outside of the PTV where the cumulative 95% isodose covered <95% of the volume, was reduced from 51% of fractions to 27%, with a mean volume of 8.5% being excluded, which was a greater reduction than using a conventional plan. Tuomikoski et al. [28] reported that for four fractions where the bladder exceeded the PTV, tumour coverage was assessed by the radiation oncologist and approved. Two cases of geographical miss were caused by confusion due to incorrect plan selection because of duplicate plan names. In eight cases, suboptimal CBCT image quality resulted in misses in the caudal and anterior portions of the bladder and one patient was affected by moving intestinal gas [28].

The occurrence that no plan is suitable is frequent among different plan library strategies [14,16,28,29,32,35]. This in practical terms results in three options: the radiation oncologist approves the insufficient coverage, the patient empties their bladder and plan selection is repeated or a conventional plan is used. The absence of a suitable plan has a negative effect on the workflow of the unit, a decrease in patient satisfaction due to longer treatment times and counteracts the benefit of an adaptive strategy. One retrospective analysis found that the standard conventional plan (medium-sized bladder) was deemed most suitable for the majority (58%) of patients [23].

Intra-fraction motion

While daily imaging may correct for anatomical variation, it alone cannot account for intra-fraction motion. Studies examining direction and magnitude of bladder filling found an increase in intra-fraction bladder volume of up to 150 cm³ [36] mainly in the anterior and cranial directions [7–9]. Use of plan libraries is made more complex by intra-fractional bladder filling. Murthy et al. [33] found for 16% of patients, the bladder had expanded outside of the treatment field by the end of treatment as well as a risk of geographical miss due to intra-fractional bladder filling in six directions, with the exception of the inferior direction. Foroudi et al. [29] reported that in 5.5% of fractions the CTV had expanded beyond the chosen plan in conventional RT, with the use of concomitant chemotherapy being cited as a reason for this

Table 1. Summary of included studies.

Author, year, study type	Patient no.	ART method	Library size	Additional time (min)	Technique used	Partial/whole bladder	Full/empty bladder
Ⓢ Burridge 2006 [19]	20	Different CTV-PTV margins applied	3	Recognised as necessary but not specified	3DCRT	–	Empty
Ⓢ Foroudi 2009 [27]	5	Boolean, mean and smallest CTV	3	7	3DCRT	Whole bladder	Empty
Ⓢ Lalondrelle 2009 [14]	15	Three successive CT scans	3	15–20 overall	3DCRT	Whole bladder	Emptied before first scan
Ⓢ Foroudi 2010 [16]	27	Composite	3	5–8	3DCRT	Whole bladder	Empty
Ⓢ Wright 2010 [44]	2	Based on planning and four CBCT	5	–	IMRT	Whole bladder + integrated boost	–
Ⓢ Vestergaard 2010 [26]	10	3 methods	3	–	IMRT	Whole bladder	Empty
Ⓢ Kron 2010 [20]	27	Composite	3	–	3DCRT	Whole bladder	Empty
Ⓢ Tuomikoski 2011 [28]	5	Four successive CT scans	3–4	5–10	VMAT	Whole bladder + partial boost	Emptied and drank water
Ⓢ Murthy 2011 [33]	10	Isotropic PTVs	6	21 overall	Helical tomotherapy	–	Both
Ⓢ Hutton, 2012 [23]	10	Composite volume	3	7	–	Both	Empty
Ⓢ Kuyumcian 2012 [46]	26	Composite method	3	Recognised but not specified	3DCRT	–	Empty
Ⓢ Meijer 2012 [35]	20	Two planning CT and interpolation	6	12	IMRT	Whole bladder + SIB	Full
Ⓢ Tuomikoski 2013 [30]	5	Four successive CT scans	3–4	–	VMAT	Both	Emptied and drank water
Ⓢ McDonald 2013 [13]	25	Composite	3	<14 min	3DCRT	–	Empty
Ⓢ Vestergaard 2013 [24]	7	Composite	3	–	IMRT	–	Empty
Ⓢ Webster 2013 [39]	20	Comparison of plan library and composite	4	Recognised as necessary but not specified	3DCRT	Whole bladder	Empty
Ⓢ Foroudi 2014 [29]	50	Composite	3	–	3DCRT	Whole bladder	Empty
Ⓢ Vestergaard 2014 [38]	13	DVF vs. composite	3	–	–	–	Empty
Ⓢ Vestergaard 2014 [25]	20	Composite	3	8	VMAT	–	Empty
Ⓢ Gronberg 2015 [32]	9	Composite CTV (planning and CBCT)	3	Recognised as necessary but not specified	VMAT	–	Empty
Ⓢ Lutkenhaus 2015 [37]	10	Two planning CT and interpolation	5	Recognised as necessary but not specified	VMAT	Whole bladder + lymph nodes	Full
Ⓢ Murthy 2015 [34]	44	Anisotropic PTV margins	3 or 6	Recognised as necessary but not specified	Tomotherapy based IMRT	Whole bladder ± SIB	Both
Ⓢ Tuomikoski 2015 [28]	10	Comparison (multiple CT vs. CBCT scans)	CT = 4 CBCT = 3	–	–	Whole bladder	CT = full CBCT = empty
Ⓢ Canlas 2016 [31]	8	CTV based on CT with five anisotropic margins.	5	Recognised as necessary but not specified	–	Whole bladder	Empty

Ⓢ: retrospective study; Ⓢ: prospective study.

Table 2. Summary of review endpoints.

Endpoint	Studies that support endpoint	Studies that refute endpoint
1. Plan libraries improve accuracy for bladder cancer.	<p>The plan library approach overcame intra-fractional bladder filling [27,30–32,37].</p> <p>Allowed for geometric verification [11,13,14,16,19,23–34].</p> <p>The conventional plan was used in small number of patients only [14,16,29].</p> <p>A plan library of three plans is uncomplicated, safe and efficient [19,34,46].</p> <p>Plan library reduces the incidence of a geometric miss [14].</p> <p>No significant intra-fraction movements or changes in bladder filling [35].</p> <p>Better and/or improved PTV coverage [19,23,25,31,32,35,38].</p> <p>Improved CTV coverage [14,16,31,39].</p> <p>Minimises dose to organs at risk [13,14,16,19,23–25,27,32–35,38,44].</p> <p>Minimises dose to small bowel at high dose levels [27,30,31,37].</p> <p>Imaging dose can be adjusted [19,20,26,28].</p> <p>Potentially improves the therapeutic ratio [13,19,25,34,35].</p>	<p>Risk of geographical miss due to intra-fractional bladder filling [33].</p> <p>Risk of geometric miss [47].</p> <p>Inaccuracies in matching to skeletal surrogates [27].</p> <p>The conventional plan was deemed most appropriate in the majority of patients [27].</p> <p>No plan in the plan library was deemed suitable [14,16,28,29,32,35].</p> <p>Geographical misses caused by confusion [28,35].</p> <p>In appropriate plan choice [29,35].</p> <p>Bladder CTV after treatment had expanded outside the chosen plan [29,33].</p> <p>Fails to account for rectal and bowel filling [26,37,47].</p> <p>No significant difference between adaptive and non-adaptive strategies in terms of target coverage [37,39].</p> <p>Poor CTV coverage (offline protocol) and insufficient coverage in 9% of patients (online protocol) [29].</p> <p>Dose constraints could not be met [25].</p> <p>Higher integral dose due to increased frequency of imaging (if 5 cGy) [20].</p> <p>Higher integral dose due to numerous CT imaging [28,30].</p> <p>Any gain from the individualised approach is offset by the less conformal conventional plan used at the start [46].</p> <p>Not suitable for all patients [14,24,25].</p> <p>A large inter-observer variability for plan choice after training [46].</p> <p>Difficulties with choosing a plan for partial bladder irradiation [27].</p> <p>Availability of technology may hinder its implementation [27,33,39,47].</p> <p>Additional training was given, which costs time and money [11,12,32,37,39].</p> <p>Increased treatment time [16,21,22,25–27,29,37].</p> <p>Resource implications, daily workflow is affected due to longer treatment slots and treatment planning [19,27,34,39,47].</p> <p>Failure of pilot to multi-centre study [29].</p>
2. Plan libraries are feasible in the clinical setting for bladder cancer.	<p>High concordance of plan selection among therapists [13,14,19,23,31].</p> <p>Technology is available to allow plan libraries to be used in the clinical setting [11].</p> <p>Concluded plan library to treat bladder cancer is feasible [13,14,23,25,28].</p>	

intra-fractional motion. The use of intensity modulated radiotherapy (IMRT) or hypo-fractionated treatment schedules heightens the importance of margins or choosing a plan with sufficient coverage to allow for known intra-fraction motion. Bladder infection and inability to void may exacerbate intra-fraction motion and hinder the use of an adaptive plan [29].

Five studies have found that plan libraries can overcome intra-fraction bladder motion by appropriate plan selection, the addition of a patient-specific margin or a population-based margin [27,30–32,37].

Target coverage

Many studies report improved PTV [19,23,25,31,32,35,38] and CTV coverage [14,16,31,39] using plan libraries (see Appendix B for detailed results). All four studies by Vestergaard et al. support an improvement in PTV coverage, with improved conformity [26], no target compromise [24], target coverage achievement in 97% of fractions [38] and an average PTV reduction of 183 cm³ [25]. A 2016 study by Canlas et al. [31] reported successful positive fraction coverage of the CTV (V95% ≥98%), with the average volume excluded outside the PTV at 0.1 cm³/0.1% (worst case scenario 0.4 cm³/0.5%).

A total dose of 60–64 Gy is typically used for radical RT of bladder cancer [40], yielding local control rates of 30–50% [41]. As urothelial cancers are considered radiation-sensitive tumours [42], a higher total dose would likely be more optimal, with Pos et al. [41] reporting a relative increase in local control from 1.44 to 1.47 with an increase in total dose of 10 Gy. However, the safe delivery of higher doses to the bladder without a plan library approach is hindered by the close proximity of organs at risk (OARs) such as small bowel. The use of a plan library should allow for dose escalation with acceptable levels of toxicities [34]. Murthy et al. [34] among others [13,19,25,35,39], illustrated that plan libraries have the potential to improve the therapeutic ratio.

Conversely, three studies reported no significant difference between adaptive plan libraries and non-adaptive strategies in terms of target coverage [16,37,39]. Webster et al. [39] found that the difference was not statistically significant, with two failures to achieve target coverage. Lutkenhaus et al. [37] reported V95 was 98% for both strategies. Similarly, Foroudi et al. reported insufficient CTV coverage in the plan library arm in 9% of patients [27] with a further two studies reporting that the bladder CTV after treatment had expanded outside the chosen plan [29,33]. It appears that while plan libraries may improve CTV coverage, 100% of the CTV may still not be covered.

Integral dose and plan selection

It is often argued that increased integral dose associated with daily imaging offsets any potential gain from normal tissue sparing. However, four studies reported that imaging dose can be optimised, reducing the overall integral dose [19,20,28,30]. When using a library of plans, concerns over organ delineation on CBCT are redundant, which subsequently reduces the need for higher CBCT dose for organ

contrast. The dose per CBCT scan is estimated at 40 mGy, with a cumulative dose of 1.4 Gy to the imaging volume, which equates to 2% of the overall dose [28]. Furthermore, as the age of bladder patients tends to be >65 years with significant comorbidities, the risk of secondary malignancy is decreased [28].

A study by Kron et al. [20] found a reduced integral dose with plan libraries compared to conventional treatment using a uniform CTV to PTV expansion of 1.5 cm. However, this was only at an imaging dose of 3 cGy and they concluded that there was a higher integral dose, due to increased frequency of imaging, if 5 cGy was used. Although this study recognises the ability to reduce or adjust the imaging dose, image quality sufficient to select the optimal plan, must be considered. The approach to plan library creation can also impact on integral dose with a higher dose contribution from using multiple CTs compared to a CBCT on-set approach [28,30].

Sparing of normal tissue

Toxicity is of concern during bladder-preserving RT. Using conventional RT, a large amount of small bowel is at risk of exposure. Plan libraries using IMRT reduce the volume of small bowel irradiated [43]. Overall, many studies report a reduction of dose to OARs using a plan library approach [13,14,16,19,23–25,27,32–35,38,44]. However, many describe the reduction of OARs in qualitative rather than quantitative terms, making comparison across studies difficult. Exceptions are Lutkenhaus et al. [37], who found a significant reduction in V30Gy and V40Gy for small bowel and Canlas et al. [31], who reported similar results with significant reductions in the V45Gy and V50Gy of small bowel ($p < .01$).

A reduction of dose to OARs can be achieved due to a reduction of the PTV volume and highly conformal nature of a plan library [38]. Vestergaard et al. [25] report a reduction in small bowel V45Gy by 100 cm³ and V10Gy by 180 cm³ and a reduction in the rectal V30Gy by 10%. Details of individual OAR dose reductions per study are given in [Supplementary Appendix B](#). A limitation of the current data is a lack of long-term follow-up. The RAIDER trial [45], a large scale international phase II randomised trial should consolidate the current evidence base with a long follow-up period.

Some studies employ an empty bladder protocol for better bladder volume reproducibility, a reduction of the irradiated volume and increased patient comfort [13,14,16,19,24–28,39,46,47]. However, other studies have opted for a full bladder for improved normal tissue sparing [11,35,37] (see [Table 1](#)). It must be noted that an empty bladder protocol may be difficult to achieve towards the end of a treatment course due to swelling and incomplete emptying due to toxicity [48]. To date, there is no study that compares the impact of a full or empty bladder on the efficacy for a plan library. Likewise, patients may find holding a full bladder difficult, especially as treatment progresses; thus reproducibility may be affected.

Feasibility of plan libraries for bladder cancer. There are many studies that base the library of plans on the first week of CBCT scans. Using this method may involve using a conventional plan for the first 5–7 fractions, which is typically

20% of the treatment course. Kuyumcian et al. [46] concluded that any gain from the use of plan libraries thereafter is offset by the less conformal conventional plan used at the start of treatment.

Plan libraries are not suitable for all patients [14,24,25], with Vestergaard et al. reporting that for one in seven patients, the conventional plan was used for the entire treatment course, although it is not specified as to why this was the case [24]. Similarly, for patients whose bladders do not expand significantly, use of plan libraries did not improve target coverage nor normal tissue sparing [14]. In a further study, Vestergaard et al. [25] reported that two out of 20 patients would have benefited from further adaptation of the library of plans due to a systematic change in bladder shape during the treatment course. Foroudi et al. [16] suggested that treatment-induced irritation could cause more frequent bladder voiding, resulting in smaller bladder volumes and thereby impacting on plan selection.

Observer variability in plan selection

The studies in this review reported conflicting results on observer variability in plan selection. Five studies found a high concordance of plan selection among RTTs [13,14,19,23,31], with five studies concluding that a plan library is clinically feasible to treat bladder cancer [13,14,16,23,25]. The importance of education programmes in limiting variation, ensuring competency and confidence in evaluating CBCT pelvic scans in a reasonable amount of time has been highlighted. Studies report that upon completion, inter-observer variability is reduced [49] and a high concordance of plan selection reported between RTTs and clinicians is observed [14,27]. Plan concordance becomes even more important when using IMRT and a hypofractionated schedule.

Studies have reported plan agreement of 70–80%, with a larger plan used in the remaining 20–30% of treatment fractions [14,19]. McDonald et al. [13] report plan concordance of 91%, while Burrige et al. [19] found that intra-subject variability on PTV choice was the same 73% of the time. Lalondrelle et al. [14] found plan concordance of 76% among users.

Conversely, Kuyumcian et al. [46] found a large inter-observer variability for plan choice post education between RTTs, suggesting a plan library may add more uncertainty to the process and this was particularly evident if treating partial bladder [23,28]. The time needed for education is perceived by some as having a negative impact on departmental workflow efficiency [39].

Technology required, workflow and new paradigms

CBCT has become more frequently available in RT departments as soft tissue matching has become the standard image verification method for several anatomical sites [50]. Therefore, the majority of centres will already have the technology required to create and select plan libraries for bladder cancer.

However, software that is not designed with plan libraries in mind can lead to a cumbersome process and confusion yielding a geographic miss [35]. Therefore, while CBCT modality may be available, the process of plan selection is complex if the software is not plan library specific. Development of an integrated decision support system to decide which patients would benefit from plan library re-optimisation would aid in reducing confusion and increasing efficiency [24]. Three studies found the availability of technology may hinder plan library implementation [23,33,35] and that additional training was required, which costs time and money [13,14,35,39].

It has been reported that use of a plan library results in increased treatment time [13,19,28,35] hence has an effect on daily workflow [19,27,34,39,47]. On average, 5–12 additional minutes are required [16,21,25,26,29,33,37] (see Table 1). Burrige et al. [19] found a 'PTV of the day', which was defined in this study as a library of plans based on one CTV with different PTV margins, to be impractical time-wise for a busy centre if more than three plans were included in the library. However, a library of three plans was found to be safe and uncomplicated to use.

The number of plans developed for each patient needs to be balanced between optimum plan availability versus the resources needed to create and verify 3–6 plans [13,19,23,34]. Furthermore, more plans to select from will make timely decisions on the optimal plan more difficult [24]. A plan library consisting of three plans was the most commonly cited (Table 1). Murthy et al. [33] reported that geographic misses can occur as result of confusion due to numerous plans from which to make a selection.

The majority of studies on ART for bladder cancer published to date have focused on a plan library approach using CT or CBCT. Another form of ART is online re-planning, where images are acquired daily for re-optimisation of the treatment plan prior to each fraction as first described by Yan et al. [51]. Due to advancements in treatment planning algorithms and the development of the MRI linear accelerator [52–54], online re-planning may now be a clinically feasible option [55]. MRI-guided ART (MRIGART) has been investigated by Vestergaard et al. [55] as a method of online re-planning. MRI allows for an online review of both inter- and intra-fractional motion [56–60], but the optimal method to overcome intra-fractional motion has yet to be concluded.

To date, the majority of MRIGART studies have focused on prostate and gynaecological cancer [59,61], with few studies published on bladder cancer. Vestergaard et al. [55] compared bladder target coverage between online MRI-guided adaptive re-optimisation using three different margins (isotropic, anisotropic, population-based) against the plan library approach. It was found that all three MRIGART strategies resulted in a large reduction in treatment course-averaged PTVs compared to a plan library approach. The anisotropic margin achieved the largest reduction of median 304 cm³ [55].

However, MRIGART has some reported limitations for bladder cancer. Target under-dosage, due to translational bladder shifts of >1 cm³ was found in 20% of the fractions for MRIGART isotropic, 15% for MRIGART anisotropic and 4% for MRIGART population-based margins [55]. The additional time

required to carry out online re-planning is not yet established with an estimated requirement of 10 minutes additional time post MRI and pre-treatment.

While there is a growing body of evidence in support of plan libraries for bladder cancer, each study included in this review differs in their approach towards implementation, with some conflicting results. Ten studies reported improvement in CTV/PTV coverage and 17 saw reductions in dose to OARs. Until definitive evidence of improved accuracy in conjunction with clarification on the optimal route to clinical feasibility, widespread use of plan libraries will remain challenging in many RT departments. The advent and mainstreaming of MRI technology in RT treatment is likely to improve the potential for daily adaption of bladder RT plans.


Limitations

One of the limitations of this review was the lack of long-term follow-up data reported in included studies thereby limiting data on correlation between improved accuracy of treatment and clinical outcome. The majority of included studies described improvement in accuracy in qualitative rather than quantitative terms, making comparison between studies difficult.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Michelle M. Leech  <http://orcid.org/0000-0002-6510-1633>

References

- [1] Pos F, Remeijer P. Adaptive management of bladder cancer radiotherapy. *Semin Radiat Oncol.* 2010;20:116–120.
- [2] Ploussard G, Daneshmand S, Efstathiou JA, et al. Critical analysis of bladder sparing with trimodal therapy in muscle-invasive bladder cancer: a systematic review. *Eur Urol.* 2014;66:120–137.
- [3] Arcangeli G, Strigari L, Arcangeli S. Radical cystectomy versus organ-sparing trimodality treatment in muscle-invasive bladder cancer: a systematic review of clinical trials. *Crit Rev Oncol Hematol.* 2015;95:387–396.
- [4] Zhang S, Yu YH, Zhang Y, et al. Radiotherapy in muscle-invasive bladder cancer: the latest research progress and clinical application. *Am J Cancer Res.* 2015;5:854–868.
- [5] Turner SL, Swindell R, Bowl N, et al. Bladder movement during radiation therapy for bladder cancer: implications for treatment planning. *Int J Radiat Oncol Biol Phys.* 1997;39:355–360.
- [6] Harris SJ, Buchanan RB. An audit and evaluation of bladder movements during radical radiotherapy. *Clin Oncol (R Coll Radiol).* 1998;10:262–264.
- [7] Pos FJ, Koedooder K, Hulshof MC, et al. Influence of bladder and rectal volume on spatial variability of a bladder tumor during radical radiotherapy. *Int J Radiat Oncol Biol Phys.* 2003;55:835–841.
- [8] Meijer GJ, Rasch C, Remeijer P, et al. Three-dimensional analysis of delineation errors, setup errors, and organ motion during radiotherapy of bladder cancer. *Int J Radiat Oncol Biol Phys.* 2003;55:1277–1287.
- [9] Muren LP, Smaaland R, Dahl O. Organ motion, set-up variation and treatment margins in radical radiotherapy of urinary bladder cancer. *Radiother Oncol.* 2003;69:291–304.
- [10] Fokdal L, Honore H, Hoyer M, et al. Impact of changes in bladder and rectal filling volume on organ motion and dose distribution of the bladder in radiotherapy for urinary bladder cancer. *Int J Radiat Oncol Biol Phys.* 2004;59:436–444.
- [11] Pos FJ, Hulshof M, Lebesque J, et al. Adaptive radiotherapy for invasive bladder cancer: a feasibility study. *Int J Radiat Oncol Biol Phys.* 2006;64:862–868.
- [12] Lotz HT, Pos FJ, Hulshof MC, et al. Tumor motion and deformation during external radiotherapy of bladder cancer. *Int J Radiat Oncol Biol Phys.* 2006;64:1551–1558.
- [13] McDonald F, Lalondrelle S, Taylor H, et al. Clinical implementation of adaptive hypofractionated bladder radiotherapy for improvement in normal tissue irradiation. *Clin Oncol (R Coll Radiol).* 2013;25:549–556.
- [14] Lalondrelle S, Huddart R, Warren-Oseni K, et al. Adaptive-predictive organ localization using cone-beam computed tomography for improved accuracy in external beam radiotherapy for bladder cancer. *Int J Radiat Oncol Biol Phys.* 2011;79:705–712.
- [15] Wright P, Redpath AT, Hoyer M, et al. The normal tissue sparing potential of adaptive strategies in radiotherapy of bladder cancer. *Acta Oncol.* 2008;47:1382–1389.
- [16] Foroudi F, Wong J, Kron T, et al. Online adaptive radiotherapy for muscle-invasive bladder cancer: results of a pilot study. *Int J Radiat Oncol Biol Phys.* 2011;81:765–771.
- [17] Tanyi JA, Fuss MH. Volumetric image-guidance: does routine usage prompt adaptive re-planning? An institutional review. *Acta Oncol.* 2008;47:1444–1453.
- [18] Thörnqvist S, Hysing L, Tuomikoski L, et al. Adaptive radiotherapy strategies for pelvic tumors—a systematic review of clinical implementations. *Acta Oncol.* 2016;55:943–958.
- [19] Burrige N, Amer A, Marchant T, et al. Online adaptive radiotherapy of the bladder: small bowel irradiated-volume reduction. *Int J Radiat Oncol Biol Phys.* 2006;66:892–897.
- [20] Kron T, Wong J, Rolfo A, et al. Adaptive radiotherapy for bladder cancer reduces integral dose despite daily volumetric imaging. *Radiother Oncol.* 2010;97:485–487.
- [21] Lotz HT, van Herk M, Betgen A, et al. Reproducibility of the bladder shape and bladder shape changes during filling. *Med Phys.* 2005;32:2590–2597.
- [22] Murphy MJ, Balter J, Balter S, et al. The management of imaging dose during image-guided radiotherapy: report of the AAPM Task Group 75. *Med Phys.* 2007;34:4041–4063.
- [23] Hutton D, Leadbetter J, Jain P, et al. Does one size fit all? Adaptive radiotherapy for bladder cancer: a feasibility study. *Radiography.* 2013;19:17–22.
- [24] Vestergaard A, Muren LP, Sondergaard J, et al. Adaptive plan selection vs. re-optimisation in radiotherapy for bladder cancer: a dose accumulation comparison. *Radiother Oncol.* 2013;109:457–462.
- [25] Vestergaard A, Muren LP, Lindberg H, et al. Normal tissue sparing in a phase II trial on daily adaptive plan selection in radiotherapy for urinary bladder cancer. *Acta Oncol.* 2014;53:997–1004.
- [26] Vestergaard A, Sondergaard J, Petersen JB, et al. A comparison of three different adaptive strategies in image-guided radiotherapy of bladder cancer. *Acta Oncol.* 2010;49:1069–1076.
- [27] Foroudi F, Wong J, Haworth A, et al. Offline adaptive radiotherapy for bladder cancer using cone beam computed tomography. *J Med Imaging Radiat Oncol.* 2009;53:226–233.
- [28] Tuomikoski L, Collan J, Keyrilainen J, et al. Adaptive radiotherapy in muscle invasive urinary bladder cancer—an effective method to reduce the irradiated bowel volume. *Radiother Oncol.* 2011;99:61–66.
- [29] Foroudi F, Pham D, Rolfo A, et al. The outcome of a multi-centre feasibility study of online adaptive radiotherapy for muscle-invasive bladder cancer TROG 10.01 BOLART. *Radiother Oncol.* 2014;111:316–320.

- [30] Tuomikoski L, Korhonen J, Collan J, et al. Implementation of adaptive radiation therapy for urinary bladder carcinoma: imaging, planning and image guidance. *Acta Oncol.* 2013;52:1451–1457.
- [31] Canlas R, McVicar N, Nakano S, et al. Assessment of adaptive margins using a single planning computed tomography scan for bladder radiotherapy. *J Med Imaging Radiat Sci.* 2016;47:227–234.
- [32] Gronborg C, Vestergaard A, Hoyer M, et al. Intra-fractional bladder motion and margins in adaptive radiotherapy for urinary bladder cancer. *Acta Oncol.* 2015;54:1–6.
- [33] Murthy V, Master Z, Adurkar P, et al. 'Plan of the day' adaptive radiotherapy for bladder cancer using helical tomotherapy. *Radiother Oncol.* 2011;99:55–60.
- [34] Murthy V, Masodkar R, Kalyani N, et al. Clinical outcomes with dose-escalated adaptive radiation therapy for urinary bladder cancer: a prospective study. *Int J Radiat Oncol Biol Phys.* 2016;94:60–66.
- [35] Meijer GJ, van der Toorn PP, Bal M, et al. High precision bladder cancer irradiation by integrating a library planning procedure of 6 prospectively generated SIB IMRT plans with image guidance using lipiodol markers. *Radiother Oncol.* 2012;105:174–179.
- [36] Mangar SA, Scurr E, Huddart RA, et al. Assessing intra-fractional bladder motion using cine-MRI as initial methodology for Predictive Organ Localization (POLO) in radiotherapy for bladder cancer. *Radiother Oncol.* 2007;85:207–214.
- [37] Lutkenhaus LJ, Visser J, de Jong R, et al. Evaluation of delivered dose for a clinical daily adaptive plan selection strategy for bladder cancer radiotherapy. *Radiother Oncol.* 2015;116:51–56.
- [38] Vestergaard A, Kallehauge JF, Petersen JB, et al. An adaptive radiotherapy planning strategy for bladder cancer using deformation vector fields. *Radiother Oncol.* 2014;112:371–375.
- [39] Webster GJ, Stratford J, Rodgers J, et al. Comparison of adaptive radiotherapy techniques for the treatment of bladder cancer. *Br J Radiol.* 2013;86:20120433.
- [40] Sengelov L, von der Maase H. Radiotherapy in bladder cancer. *Radiother Oncol.* 1999;52:1–14.
- [41] Pos FJ, Hart G, Schneider C, et al. Radical radiotherapy for invasive bladder cancer: what dose and fractionation schedule to choose? *Int J Radiat Oncol Biol Phys.* 2006;64:1168–1173.
- [42] Colquhoun AJ, Jones GD, Moneef MA, et al. Improving and predicting radiosensitivity in muscle invasive bladder cancer. *J Urol.* 2003;169:1983–1992.
- [43] Sondergaard J, Hoyer M, Petersen JB, et al. The normal tissue sparing obtained with simultaneous treatment of pelvic lymph nodes and bladder using intensity-modulated radiotherapy. *Acta Oncol.* 2009;48:238–244.
- [44] Wright P, Muren LP, Hoyer M, et al. Evaluation of adaptive radiotherapy of bladder cancer by image-based tumour control probability modelling. *Acta Oncol.* 2010;49:1045–1051.
- [45] Institute of Cancer Research, United Kingdom. A randomised phase II trial of adaptive image guided standard or dose escalated radiotherapy in the treatment of transitional cell carcinoma of the bladder. In: [ClinicalTrials.gov](https://clinicaltrials.gov) [Internet]. Bethesda (MD): National Library of Medicine (US); 2000; [Internet]; [cited 2016 Nov 28]. Available from: <https://clinicaltrials.gov/ct2/show/NCT02447549> NLM Identifier: NCT02447549.
- [46] Kuyumcian A, Pham D, Thomas JM, et al. Adaptive radiotherapy for muscle-invasive bladder cancer: optimisation of plan sizes. *J Med Imaging Radiat Oncol.* 2012;56:661–667.
- [47] Tuomikoski L, Valli A, Tenhunen M, et al. A comparison between two clinically applied plan library strategies in adaptive radiotherapy of bladder cancer. *Radiother Oncol.* 2015;117:448–452.
- [48] Kong VC, Taylor A, Rosewall T. Adaptive radiotherapy for bladder cancer—a systematic review. *J Med Imag Radiat Sci.* 2017;48:199–206.
- [49] White E, Kane G. Radiation medicine practice in the image-guided radiation therapy era: new roles and new opportunities. *Semin Radiat Oncol.* 2007;17:298–305.
- [50] National Radiotherapy Implementation Group. Image guided radiotherapy. Guidance for implementation and use. London: NHS; 2012.
- [51] Yan D, Vicini F, Wong J, et al. Adaptive radiation therapy. *Phys Med Biol.* 1997;42:123–132.
- [52] Jia X, Schümann J, Paganetti H, et al. GPU-based fast Monte Carlo dose calculation for proton therapy. *Phys Med Biol.* 2012;57:7783–7797.
- [53] Ziegenhein P, Kamerling CP, Oelfke U. Interactive dose shaping – efficient strategies for CPU-based real-time treatment planning. *J Phys: Conf Ser.* 2014;489:1–6.
- [54] Kamerling CP, Ziegenhein P, Heinrich H, et al. A 3D isodose manipulation tool for interactive dose shaping. *J Phys: Conf Ser.* 2014;489:1–6.
- [55] Vestergaard A, Hafeez S, Muren LP, et al. The potential of MRI-guided online adaptive re-optimisation in radiotherapy of urinary bladder cancer. *Radiother Oncol.* 2016;118:154–159.
- [56] Kupelian P, Sonke JJ. Magnetic resonance-guided adaptive radiotherapy: a solution to the future. *Semin Radiat Oncol.* 2014;24:227–232.
- [57] Jaffray DA, Carlone MC, Milosevic MF, et al. A facility for magnetic resonance-guided radiation therapy. *Semin Radiat Oncol.* 2014;24:193–195.
- [58] Bostel T, Nicolay NH, Grossmann JG, et al. MR-guidance – a clinical study to evaluate a shuttle-based MR-linac connection to provide MR-guided radiotherapy. *Radiat Oncol.* 2014;9:12.
- [59] Oh S, Stewart J, Moseley J, et al. Hybrid adaptive radiotherapy with on-line MRI in cervix cancer IMRT. *Radiother Oncol.* 2014;110:323–328.
- [60] Metcalfe P, Liney GP, Holloway L, et al. The potential for an enhanced role for MRI in radiation-therapy treatment planning. *Technol Cancer Res Treat.* 2013;12:429–446.
- [61] McPartlin AJ, Li XA, Kershaw LE, et al. MRI-guided prostate adaptive radiotherapy – a systematic review. *Radiother Oncol.* 2016;119:371–380.