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Image-guided Adaptive Radiotherapy for Bladder Cancer

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Abstract

Technological advancement has facilitated patient-specific radiotherapy in bladder cancer. This has been made possible by developments in image-guided radiotherapy (IGRT). Particularly transformative has been the integration of volumetric imaging into the workflow. The ability to visualise the bladder target using cone beam computed tomography and magnetic resonance imaging initially assisted with determining the magnitude of inter- and intra-fraction target change. It has led to greater confidence in ascertaining true anatomy at each fraction. The increased certainty of dose delivered to the bladder has permitted the safe reduction of planning target volume margins. IGRT has therefore improved target coverage with a reduction in integral dose to the surrounding tissue. Use of IGRT to feed back into plan and dose delivery optimisation according to the anatomy of the day has enabled adaptive radiotherapy bladder solutions. Here we undertake a review of the stepwise developments underpinning IGRT and adaptive radiotherapy strategies for external beam bladder cancer radiotherapy. We present the evidence in accordance with the framework for systematic clinical evaluation of technical innovations in radiation oncology (R-IDEAL).

Key words: Adaption; adaptive radiotherapy; bladder cancer; CBCT; image guidance; MRI

Introduction

The pace of technical innovation in radiation oncology is high. Ever increasingly complex solutions risk drift into clinical practice before robust evidence demonstrating improved patient outcomes has been acquired [1]. To guard against this, a framework for the assessment of technological innovation has been devised [2,3]. It was initially proposed to address the specific challenges of assessing technological developments in surgery [2]. This framework recognises that, unlike the phased approach adopted in drug trials, assessing complex new technologies necessitates evaluation of technique and procedure that covers aspects of Innovation, Development, Exploration, Assessment, as well as Long-term clinical outcomes (IDEAL) [2]. This five-stage process was subsequently adapted for the systematic evaluation of radiotherapy innovation (R-IDEAL) by an international consortium [3]. The different stages and proposed study design for evaluation at each stage of R-IDEAL is summarised in Table 1.

Radiotherapy for bladder cancer has a number of established clinical applications. It offers opportunity for cancer cure with organ preservation as part of a multimodality strategy in those with localised muscle-invasive disease [4–7]. In the palliative setting, bladder radiotherapy has an important role for local disease and symptom control [8]. More recently, the potential immunomodulatory effect of radiotherapy and its possible synergy when combined with immunotherapy drugs have been explored [9,10].

The precise and accurate delivery of bladder cancer radiotherapy has presented a longstanding challenge. The bladder is a relatively mobile target subject to largely stochastic variation in organ filling and deformation [11–13]. In the era preceding in-room volumetric imaging, large population-based planning target volume (PTV) margins were applied in an attempt to try to account for this motion. The consequence was excessive normal tissue irradiation that still could not successfully alleviate high rates of geographical target misses [14].

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Table 1
R-IDEAL stages of systematic evaluation of innovation in bladder radiotherapy

	Radiotherapy predicate studies	Idea	Development	Exploration	Assessment	Long-term evaluation
	Stage 0	Stage 1	Stage 2a	Stage 2b	Stage 3	Stage 4
Purpose	Work-up required prior to first use in human.	Proof of concept, first time new technique/ technology used either for standard treatment (stage 1a) or alternative dose/ fractionation/target etc. (stage 1b)	Technical optimisation	Proof of early effectiveness	Formal comparison against standard treatment	Long-term outcome, post-marketing and surveillance
Study design	Phantom/planning studies	Structured case report	Prospective case series	Prospective study, preferably with randomised component	Randomised control trial	Prospective registries
Area of investigation in bladder radiotherapy	Determining bladder motion Contouring variation Verification Modelled outcomes/ planning studies Quality assurance Training	Use of fiducial markers Feasibility of bladder IGRT Feasibility of ART	Clinical implementation of ART strategies	Early effectiveness based on reported disease control and toxicity outcomes of ART strategies	Randomised control trial of ART versus standard whole bladder radiotherapy (36 Gy in 6 fractions) Randomised control trial of dose-escalated tumour boost ART versus standard dose ART versus whole bladder radiotherapy	Infrastructure for future reporting of MR-guided radiotherapy
Number of publications	48	7	6	9	2	1

ART, adaptive radiotherapy; IGRT, image-guided radiotherapy; MR, magnetic resonance.

Image-guided radiotherapy (IGRT) enabled by both kilovoltage and megavoltage cone beam computed tomography (CBCT) and more latterly with magnetic resonance imaging (MRI) has permitted visualisation of the bladder target at the time of radiation delivery [15–17]. It has led to improved target coverage and enabled the development of a number of adaptive radiotherapy (ART) solutions, whereby knowledge of patient-specific anatomical variation can now be fed back into the plan and dose delivery optimisation during the treatment course [18].

Here we present a systemic review supporting IGRT and ART developments in bladder cancer radiotherapy. We present this evidence in accordance with the R-IDEAL framework for clinical evaluation of technical innovations in radiation oncology to illustrate the research pipeline to clinical implementation.

Methods

A literature search was carried out in December 2020 using PubMed and Google Scholar. The search was conducted using the following keywords: 'bladder cancer', 'radiotherapy', 'image guidance', 'CBCT', 'MRI', 'adaptive radiotherapy' and 'adaptation'. The reference sections of the articles were then manually searched to identify publications that were not extracted in the initial search. A citation search of the identified articles was then also carried out. We searched for full-length articles as well as conference abstracts. Only those publications evaluating external beam radiation therapy were included; bladder cancer brachytherapy studies were excluded. Details of the study described in each article were extracted and categorised according to the R-IDEAL framework in order to aid discussion of the developmental stages of bladder IGRT and ART.

Findings

In total, 73 articles describing the development, feasibility, validation, implementation and clinical effectiveness of bladder IGRT and ART were identified. Forty-eight studies were categorised into R-IDEAL stage 0. Thematically, these preparatory studies covered a number of areas, including target visualisation with CBCT or MRI, quantifying magnitude of whole bladder (clinical target volume) and tumour (gross tumour volume; GTV) motion, verification, training, quality assurance and the modelled dosimetric impact of bladder ART in planning studies.

Seven articles were categorised into R-IDEAL stage 1 and describe first-time use and proof of concept of bladder IGRT and ART in bladder cancer patients. Fifteen articles were categorised as R-IDEAL stage 2 and describe clinical implementation of IGRT and ART with dose advantage or early effectiveness based on toxicity and disease control outcomes reported. Two studies were categorised as R-IDEAL stage 3 and describe multicentre randomised control trials of bladder ART versus non-ART approaches. One article met R-IDEAL stage 4 criteria but is yet to report clinical outcomes [19]. Tables 2 and 3 summarises the main outcomes of these trials as grouped by R-IDEAL stage.

Discussion

Target Visualisation with Online Imaging

Online image quality has been assessed broadly using two methods. The first is the ability to use the image for target contouring, the second is the ability to use the image for position verification [15,25,26].

Segmentation of most targets on CBCT can be challenging due to poor tissue contrast and increased susceptibility to reconstruction artefacts [26]. The soft-tissue contrast between the outer bladder wall and neighbouring pelvic contents usually enables delineation of the whole bladder target on CBCT. Comparable contouring variation to planning computed tomography (CT) can be achieved [25–27]. The image quality of CBCT is also sufficient that automatic bladder segmentation tools can be successfully applied with similar performance to manual bladder delineation [23,24].

The high spatial resolution of MRI, particularly using multiparametric MRI, allows the bladder muscle layer integrity to be evaluated, which improves local tumour (T) staging accuracy [86–88]. Incorporating online MRI into the radiotherapy workflow has the potential to improve delineation and reduce inter-observer contouring variation [30]. Online MRI, even with low field strength (0.35T) provides better bladder visualisation than CBCT [89]. Although CBCT allows reasonable discrimination of the bladder wall, visualisation of the tumour itself is challenging [27,80]. The superior soft-tissue contrast of MRI may therefore enable more reliable tumour-focused partial bladder radiotherapy.

Randomised control trials of tumour-focused partial bladder external beam radiotherapy versus whole bladder radiotherapy have successfully shown no adverse effect on local control [90,91]. However, bladder tumour visualisation is impeded after transuretheral resection of the bladder tumour and good response to neoadjuvant chemotherapy [92]. To overcome this, many groups have explored cystoscopic insertion of fiducial markers at the borders of visible tumour (GTV) or tumour bed [36–43].

Fiducial markers that have been used for this purpose in the era of volumetric imaging include gold seeds, surgical titanium clips, and Lipiodol® [36–43]. Gold seeds and surgical clips are prone to migration and are vulnerable to loss following implantation [93,94]. Diathermy and microtines improve retention rates but marker loss still occurs in up to one-fifth of patients [42,95]. Metallic fiducials are visible on CBCT but produce signal void on MRI [96].

Lipiodol® is an iodised oil contrast injected subepithelially into the bladder wall. Its liquid nature means it can easily leak into intra- and extravesical spaces, which in high concentration leads to streak artefacts on CBCT [37,40,97,98]. Lipiodol is not visible on MRI.

An alternative novel radiographic marker, BioXmark®, has also been investigated in radical bladder radiotherapy. It is liquid at the time of injection but then transforms into a

Table 2
Summary of predicate work categorised according to R-IDEAL stage

Stage	Theme	References	Findings
0	IGRT	Wright et al, 2008 [20]	CBCT improves target covered, with margin reduction, and reduced normal tissue irradiation
		Kron et al, 2010 [21]	
		Foroudi et al, 2012 [22]	
		Foroudi et al, 2014 [14]	
0	Segmentation	Van de Schoot et al, 2014 [23]	Automatic bladder segmentation on CBCT is accurate
		Rosewall et al, 2016 [24]	
		Foroudi et al, 2009 [25]	
		Weiss et al, 2010 [26]	
		Nishioka et al, 2013 [27]	
		Chai et al, 2012 [28]	Semi-automatic and automatic bladder segmentation on CBCT using patient-specific model can aid plan selection
		Chai et al, 2012 [29]	
		Hunt et al, 2019 [30]*	MR-based delineation, demonstrates high agreement for whole bladder, lower for GTV
0	Bladder motion	Mangar et al, 2007 [31]	Cine-MR intra-fractional motion predominantly superior and anterior direction
		McBain et al, 2009 [32]	Cine-MR motion up 57 mm identified over 28 min
		Gronborg et al, 2015 [33]	Intra-fractional motion over 10 min captured by 5 mm
		Nishioka et al, 2017 [34]	Motion predominantly superior and anterior direction; Intra-fractional motion over 10 min captured by 5 mm
		Dees-Ribbers et al, 2014 [13]	Motion between a full bladder and an empty bladder protocol does not differ
		Yee et al, 2010 [35]	Inter-fraction motion predominantly anterior direction
0	Fiducial marker	Chai et al, 2010 [36]	GTV deformation and motion assessed using lipiodol
		Sondergaard et al, 2010 [37]	
		Van Rooijen et al, 2010 [38]	Feasibility of using lipiodol for IGRT (CBCT);
		Kong et al, 2016 [39]	PTV derivation for partial bladder irradiation
		Pos et al, 2009 [40]	
		Kong et al, 2014 [41]	
1a		Garcia et al., 2014 [42]	Feasibility of micro-tined gold fiducial markers for IGRT (CBCT)
		De Ridder et al., 2020 [43]	Feasibility of BioXmark for IGRT (CBCT)
0	Quality assurance	Kong et al, 2019 [44]	Inter-observer CBCT registration variability reduced with use of lipiodol
		Krishnan et al, 2019 [45]	Retrospective audit of plan selection demonstrating adequate target coverage achieved based on post-treatment CBCT
0	Training	Foroudi et al., 2010 [46]	Description of radiographer training programme requirements to achieve and maintain competency for plan selection
		Foroudi et al, 2013 [47]	
		McNair et al, 2015 [48]	
		Boejen et al, 2015 [49]	
		Hales et al, 2020 [50]	Development training for radiographer led MR-guided ART workflow
0	Resource implication	Chen et al, 2018 [51]	Composite volume using planning CT and CBCTs days 1–5 balances resource and efficacy of target coverage
		Kong et al, 2018 [52]	Resource burden for 3 ART strategies compared
1a	Feasibility of CBCT for IGRT	Henry et al, 2006 [15]	First report of CBCT use in bladder patients

ART, adaptive radiotherapy; CBCT, cone beam computed tomography; CT, computed tomography; GTV, gross tumour volume; IGRT, image-guided radiotherapy; MR, magnetic resonance; PTV, planning target volume.
* Published as an abstract at the time of the literature search.

three-dimensional gel-like shape [43]. Although visible on CBCT, signal void is expected on MRI [99].

Determining Magnitude of Target Motion

The bladder varies in size and position between fractions (inter-fraction change) and during treatment delivery (intra-fraction change) [11–13]. No patient or tumour characteristics reliably predict those who may be more likely to exhibit greatest motion [100,101]. Interventions, such as drinking protocols, catheterisation for both bladder emptying and instilling identical fluid volume, dietary modifications or laxatives, do not minimise this variation sufficiently that PTV margin reduction in isolation could be undertaken without compromising target coverage [13,102–104].

Consensus drawn from studies assessing inter-fraction change is that bladder motion occurs predominantly in the cranial direction (as a result of bladder filling) and

Table 3
Bladder adaptive radiotherapy (ART) studies categorised according to R-IDEAL stage

Stage	Reference (No. patients)	Target	Technique and dose	ART strategies	PTVs	Findings
0	Burridge et al., 2006 [53] ($n = 20$)	Bladder	CRT 55 Gy/20 fractions	PoD − single CT	Non-ART: Bladder +15 mm 2 PoD PTVs: Bladder +15 mm (A,P,R,L,I) and 5 mm (S) Bladder +15 mm (A,P,R,L,I) and 10 mm (S)	Irradiated small bowel volume reduced by 31 cm^3 73% agreement in plan selection
0	Foroudi et al., 2009 [54] ($n = 5$)	Bladder	CRT 60 Gy/30 fractions	PoD − CT and CBCTs days 1–5	Non-ART: Bladder +15 mm 3 PoD PTVs: Small: smallest bladder (as seen on CT/CBCTs) + 5 mm Medium: mid between small and large +5 mm Large: PTVcomp CT & CBCTs +5 mm	ART reduced irradiated volume with improved target coverage
0	Vestergaard et al., 2010 [55] ($n = 10$)	Bladder and PLN	IMRT 60 Gy/30 fractions	PoD − CT and 3–4 CBCTs	Non-ART: CTV +25 mm (A), 20 mm (P), 15 mm (R,L), 28 mm (S), 18 mm (I) 3 PoD-PTV method 1: Small, medium and large expanded by margin that covers 50, 70, 90% of population +3 mm 3 PoD-PTV method 2: Small = bladder +8 mm Medium = bladder + margin scaled according to the location frequency of CTV in the first 5 CBCTs Large = bladder +23 mm (A,S), 18 mm (P), 13 mm (R,L,I) 3 PoD-PTV method 3: Small = PTVcomp of 2 smallest bladder (as seen on planning CT/CBCTs) + 3 mm Medium = PTVcomp of planning CT + CBCTs +3 mm Large = bladder +23 mm (A,S), 18 mm (P) 13 mm (R,L,I)	Reduction in irradiated volume by 30–40% PoD-PTV method 1 recommended
0	Lalondrelle et al., 2011 [56] ($n = 25$)	Bladder	CRT 30–36 Gy/5–6 fractions	PoD − 3 CTs	Non-ART: Bladder +15 mm 3 POD-PTVs: Bladder at t0 + 15 mm Bladder at 15 min +15 mm Bladder at 30 min +15 mm	Improved target coverage from 51% to 96% with PoD-PTVs Anisotropic margins of 0–25 mm recommended
0	Tolan et al., 2011 [57] ($n = 11$)	Bladder + PLN	CRT 46 Gy/23 fractions to PLN + bladder Sequential 14–20 Gy/7–10 fractions	PTVcomp- CT and CBCT days 1–15	Non-ART: Bladder +20 mm 3 PTVcomp assessed (i) OV = CBCT days 1–15 (ii) OV + 5 mm	Reduction in irradiated volume with OV + 5 mm

Table 3 (*continued*)

Stage	Reference (No. patients)	Target	Technique and dose	ART strategies	PTVs	Findings
			bladder/partial bladder		(iii) Measurement-based PTV (mPS-PTV) = planning CTV + OV	
0	Kuyumcian et al., 2012 [58] ($n = 27$)	Bladder	CRT 64 Gy/32 fractions	PoD − CT and CBCT days 1−5	Non-ART PTV: CTV +15 mm PoD-PTVs: Small = smallest bladder (as seen on planning CT/CBCTs) + 5 mm Medium = halfway between small and large Large = PTVcomp of CT and CBCTs +5 mm Alternative method PoD-PTVs: Small = PTVcomp of 2 smallest bladder (as seen on planning CT/CBCTs) + 5 mm Medium and large as above	Small PoD-PTV generated using 2 smallest volumes as seen on planning and CBCT days 1−5 was selected more frequently than initial method
0	Hutton et al., 2013 [59] ($n = 10$)	Bladder	CRT 55 Gy/20 fractions	PoD − single CT	PoD-PTVs: Small = bladder +5 mm Medium/standard = bladder +15 mm Large = bladder +7.5 mm (R,L,I) 12 mm (P), 25 mm (S,A)	Non-standard PTV used 42% Additional 4 min per fraction to workflow
0	Webster et al., 2013 [60] ($n = 20$)	Bladder	CRT 52.5 Gy/20 fractions	PoD − single CT PTVcomp − CT and CBCT days 1−3	Non-ART: Bladder +15 mm 4 PoD-PTVs: Bladder +15 mm (R,L,A,P,I), 5 mm (S) Bladder +15 mm (R,L,A,P,I), 10 mm (S) Bladder +15 mm (R,L,A,P,I), 15 mm (S) Bladder +15 mm (R,L,A,P,I), 20 mm (S) PTVcomp = bladder CBCT days 1−3 + 5 mm; PTVcomp= bladder CBCT days 1−3 + 10 mm	PoD improved target coverage and improved normal tissue sparing by 17% relative to non-ART
0	Vestergaard et al., 2013 [61] ($n = 7$)	Bladder + PLN	VMAT 60 Gy/30 fractions	PoD − CT and CBCT days 1−4 Re-optimisation	Non-ART: Bladder +25 mm (A), 20 mm (P), 15 mm (R,L), 28 mm (S), 18 mm (I) 3 PoD-PTVs: Small = PTVcomp of 2 smallest bladder (as seen on CBCTs) + 3 mm Medium = PTVcomb CBCT days 1−4 + 3 mm Large = non-ART PTV Re-optimisation: Daily bladder on CBCT +5 mm	PoD and re-optimisation reduced irradiated volume compared with non-ART Re-optimisation reduced normal tissue V_{45Gy} by 40% compared with PoD
0	Kong et al., 2014 [41] ($n = 12$)	Bladder, PLN, sequential partial bladder boost	IMRT 46 Gy/23 fractions to bladder + PLN, sequential 14−20 Gy/10 fractions	PTVcomp CT and CBCT days 1−5	Non-ART: Partial bladder +20 mm PTVcomp = CT + CBCTs days 1−15 registered using lipiodol +3 mm	Reduction in irradiated volume by 66% compared with non-ART Median distance between CTV and PTVcomp up to 11 mm

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Table 3 (*continued*)

Stage	Reference (No. patients)	Target	Technique and dose	ART strategies	PTVs	Findings
			bladder/partial bladder			
0	Vestergaard et al., 2014 [62] ($n = 13$)	Bladder	IMRT	PoD − CT and CBCT days 1–4	Non-ART: Bladder +25 mm (A), 20 mm (P), 15 mm (R,L), 28 mm (S), 18 mm (I) 3 PoD-PTVs method 1: Small = PTVcomp smallest 2 bladders (as seen on planning CT/CBCTs) + 8 mm Medium = PTVcomp (planning CT and CBCTs) + 8 mm Large = Non-ART PTV 3 PoD-PTVs method 2 (DVF) Small, medium and large = planning CT + 8 mm margin covering 33%, 67% and 99% of bladder target	Both ART approaches reduced PTV compared with non-ART DVF-based POD had greater normal tissue sparing
0	Tuomikoski et al., 2015 [63] ($n = 10$)	Bladder	60 Gy/20 fractions	PoD − 4 CTs and CBCTs days 1–4	Non-ART: Bladder +28 mm (S), 25 mm (A), 20 mm (P), 18 mm (I), 15 mm (R,L) 4 CT-based PoD PTVs: Bladder on CT acquired every 15 min +8 mm CT and CBCT based PoD PTVs: Small = PTVcomp smallest 2 bladders (as seen on initial empty planning CT/CBCTs) + 8 mm Medium = PTVcomp (initial planning CT and CBCT days 1–4) + 8 mm Large = bladder +28 mm (S), 25 mm (A), 20 mm (P), 18 mm (I), 15 mm (R,L)	Both ART approaches reduced PTV compared with non-adaptive approach Greater volume reduction seen with CT-based POD than CT and CBCT based POD (46% versus 36% compared with non-ART)
0	Canlas et al., 2016 [64] ($n = 10$)	Bladder	VMAT 64 Gy/32 fractions	PoD − single CT	5 PoD PTVs: Bladder +10 mm Bladder +15 mm (A,S), 10 mm (R,L,I,P) Bladder +15 mm Bladder +20 mm (A,S), 15 mm (R,L,I,P) Bladder +20 mm	V95% $\geq$ 98% achieved for 100% ART reduced bowel V45Gy, V50Gy and normal tissue V95% by >24% and 43% compared with PTV 15 mm and 20 mm
0	Lutkenhaus et al., 2016 [65] ($n = 10$)	Bladder, SIB-partial bladder, PLN	VMAT 55 Gy/20 fractions partial bladder, 40 Gy/20 fractions to PLN and bladder versus 70 Gy/35 fractions partial bladder 60 Gy/30 fractions bladder, 48 Gy PLN	PoD − 2 CTs ($t = 0$ min and $t = 15$ min) and CBCTs days 1–4	Non-ART: Bladder +13 mm (S,I), 7 mm (A,P,R,L) 5 PoD PTVs − CT based to deliver 55 Gy Volume derived by scaling DVF generated from full bladder CT–empty bladder CT to represent 0, 33%, 67%, 100% and 133% bladder filling states; + 7 mm for bladder +9 mm GTV PTV PLN = PLN +7 mm 3 PoD-PTVs − CBCT based to deliver 70 Gy Small = PTVcomp smallest 2 bladders (as seen planning CT/CBCTs) + 5 mm Medium = PTVcomp (planning CT and	Both PoDs approaches reduced irradiated volume compared with non-ART; lower bowel doses were achieved with CT-based PoD Modelled tumour control probability due to prescription differences

Table 3 (*continued*)

Stage	Reference (No. patients)	Target	Technique and dose	ART strategies	PTVs	Findings
					CBCTs) + 5 mm Large = bladder +28 mm (S,A), 20 mm (P), 15 mm (R,L,I) PTV for GTV = PTVcomp GTV planning CT t = 0 and t = 15 min +6 mm PTV PLN = PLN +8 mm (S,I) and 5 mm (R,L,A,P)	
0	Vestergaard et al., 2016 [66] (n = 10)	Bladder	VMAT 36 Gy/6 fractions	Re-optimisation − MR	Online re-optimisation using PTV; Iso: bladder +5 mm Aniso: bladder +7 mm (S), 5 mm (A,R,L,I,P) Pop: bladder +14 mm (A,S), 9 mm (P), 5 mm (R,L,I)	Target underdosed (1 cm^3 below 95%) of fractional dose was seen 20%, 15% and 4% fractions using Iso, Aniso and Pop PTV, respectively, as assessed on 10 min MR
0	Adil et al., 2019[67] (n = 10)	Bladder + PLN	50 Gy/20 fractions to bladder, 40 Gy/20 fractions to PLN	PoD − single CT	Non-ART: Bladder +15 mm; PLN +7 mm 3 PoD PTVs: Iso 10: bladder +10 mm Iso 15: bladder +15 mm Aniso: bladder +15 mm (A,S), 10 mm (R,L,I,P)	Bladder +1.5 mm (A,S), 1 cm (R,L,I,P) with daily CBCT reduced risk of geographical miss (5 cm^3 bladder falling outside of PTV) to 0.5%
0	Kong et al., 2019 [68] (n = 10)	Bladder + PLN	IMRT 46 Gy/23 fractions to bladder + PLN, sequential 20 Gy/10 fractions partial bladder boost	PoD − single CT PTVcomp− CT + CBCT days 1 −5 Re-optimisation	Non-ART: Bladder +20 mm 4 PoD-PTVs: Bladder + iso 0 mm, 5 mm, 10 mm, 15 mm PTVcomp = planning CT and CBCTs bladder +5 mm Re-optimisation Bladder +5 mm (PLN PTV = PLN +5 mm)	PoD, CV and re-optimisation reduced irradiated V95 by 12%, 16% and 25% respectively compared with non-ART
1a	Heneke et al., 2008 [16]	Bladder	-	Re-optimisation	-	First clinical report of MR IGRT use in bladder patients
1a	Silbot et al., 2020 [69]* (n = 10)	Bladder	64 Gy/32 fractions	Re-optimisation (CBCT based)	Re-optimisation: patient-specific intra-fraction margin determined from pre-post treatment CBCT days 1−3	First report of CBCT-based and artificial intelligence driven system use in bladder patients. Adaptive process 12.1 min Median reduction in PTV 47% compared (standard)
2a	Tuomikoski et al., 2011 [70] (n = 5)	Bladder + partial bladder boost	IMRT 45−50.4 Gy/25−28 fractions to bladder, sequential 10−20 Gy/5−10 fractions partial bladder boost	PoD − 3-4 CTs (serially acquired t = 15−30 min intervals)	Non-ART: Bladder and GTV +20 mm 3-4 POD-PTVs: Bladder: 15 mm (R,L,I,P), 10 mm (A,S); GTV: 15 mm (R,L,I,P) and 10 mm (A,S) applied to various CTs	Target coverage V95<100% in 3% of fractions Bowel V45Gy improved by 155 cm^3 (46%) compared to non-ART

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Table 3 (*continued*)

Stage	Reference (No. patients)	Target	Technique and dose	ART strategies	PTVs	Findings
2a	McDonald et al., 2013 [71] ($n = 25$)	Bladder	CRT 36 Gy/6 fractions or 30 Gy/5 fractions	PoD − 2 CTs ($t = 0$ and $t = 30$ min)	Non-ART: Bladder +15 mm 3 PoD-PTVs: Small = bladder +5 mm Medium = bladder + 15 mm (A,S), 10 mm (P), 5 mm (R,L,I) Large = bladder +20 mm (A), 25 mm (S), 12 mm (P) 7.5 mm (R,L,I) or if >50 cm^3 bladder filling between CTs Large = bladder $t = 30$ min CT +15 mm (A,S), 10 mm (P), 5 mm (R,L,I)	Target coverage V95>95% 219 cm^3 volume reduction in tissue receiving 95% dose compared with non-ART
2a	Tuomikoski et al., 2013 [72] ($n = 5$)	Partial bladder boost or bladder followed by sequential boost	VMAT 52.5 Gy/2 fractions to partial bladder or 44 Gy/22 fractions to bladder followed by 20 Gy/10 fractions to GTV	PoD − 3-4 CTs (serially acquired at t -15 min)	Non-ART: Bladder/GTV +20 mm 3-4 POD-PTVs for bladder boost = GTV defined by lipiodol on CT $t = 0$, 15, 30 and 45 min +10 mm or 3-4 POD-PTVs for bladder: 15 mm (R,L,I,P) and 10 mm (A,S) applied to various CTs 3-4 POD-PTVs for boost: GTV defined by lipiodol on CT $t = 0$, 15, 30 and 45 min +10 mm	Feasibility of partial bladder boost delivery with ART
2a	Vestergaard et al., 2014 [73] ($n = 20$)	Bladder and PLN	VMAT 60 Gy/30 fractions to bladder, 48 Gy/30 fractions to PLN	PoD − CT + CBCT days 1–4	Non-ART: Bladder +28 mm (A,S), 20 mm (P), 15 mm (R,L,I) and PLN +12 mm 3 PoD-PTVs: Small = PTVcomp smallest 2 bladders (as seen planning CT/CBCTs) + 8 mm Medium = PTVcomp (planning CT and CBCTs) + 8 mm Large = bladder +28 mm (S,A), 20 mm (P), 15 mm (R,L,I)	30% (183 cm^3) reduction in adaptive PTV, bowel V45Gy improved by 100 cm^3 and rectal V30 improved by 10% compared with non-ART Less sparing when PLN was included in treatment volume
2a	Lutkenhaus et al., 2015 [74] ($n = 10$)	Partial bladder boost, bladder and PLN	VMAT 55 Gy/20 fractions partial bladder, 40 Gy/20 fractions to PLN and bladder	PoD − 2 CTs (empty and full)	Non-ART: Bladder +13 mm (A,S), 7 mm (R,L,P,I); GTV +9 mm 5 PoD PTVs: Volume derived by scaling DVF generated from full bladder CT-empty bladder CT to represent 0, 33%, 67%, 100% and 133% bladder filling states; + 7 mm for bladder, + 9 mm GTV PTV PLN = PLN +7 mm	Bowel V30Gy and V40Gy improved with ART
2a	Hunt et al., 2020 [17] ($n = 5$)	Bladder	IMRT 36 Gy/6 fractions or 30 Gy/5 fractions	Re-optimisation − MR	Bladder +15 mm (A,S), 10 mm (P), 5 mm (R,L,I)	Target coverage V95≥95% achieved for 28/29 fractions (as assessed on post-treatment scan) Median time on couch (workflow), 39 min, median intra-fraction volume change, 30 cm^3

Table 3 (*continued*)

Stage	Reference (No. patients)	Target	Technique and dose	ART strategies	PTVs	Findings
2b	Foroudi et al., 2011 [75] ($n = 27$)	Bladder	CRT 64 Gy/32 fractions	PoD − CT and CBCT days 1−5	Non-ART: Bladder +15 mm 3 PoD PTVs: Small: smallest bladder (as seen on CT/CBCTs) + 5 mm Medium: mid between small and large +5 mm Large: PTVcomp CT and CBCTs +5 mm	Target coverage V95<99% in 2.7% 29% reduction in tissue receiving >45 Gy compared with non-ART CTCAE acute ≥grade 3, 15%
2b	Murthy et al., 2011 [76] (n =10)	Partial bladder boost, bladder and PLN	Tomotherapy 68 Gy/32 fractions to SIB, 64 Gy/32 fractions to bladder	PoD − single CT	6 POD-PTV: CTV + isotropic margin from 5 to 30 mm in 5 mm increments SIB PTV: GTV +10 mm	Dose escalation to 68 Gy feasible with ART with significant acute toxicity Geographical miss (bladder wall outside the selected PTV) was observed in 14% of superior bladder wall and 10% anterior bladder wall at the end of treatment
2b	Meijer et al., 2012 [77] ($n = 20$)	Bladder + partial bladder boost (lipiodol)	IMRT 46 Gy/23 fractions to bladder, 59.8 Gy/23 fractions to SIB	PoD − 2 CTs	6 POD-PTVs: Generated from interpolation of target as seen on both CT scans with GTV +10 mm and bladder +6 mm	≥95% appropriate fractions covered No CTCAE ≥grade 3 genitourinary or gastrointestinal 10% (2/20) local recurrence after median follow-up of 28 months
2b	Foroudi et al., 2014 [78] ($n = 50$)	Bladder	CRT 6 Gy/32 fractions	PoD − CT and CBCT days 1−5	Non-ART PTV: Bladder +15 mm 3 PoD PTVs: Small: summation of 2 smallest bladder (as seen on CT/CBCTs) + 7 mm Medium: mid between small and large +7 mm Large: PTVcomp CT and CBCTs +7 mm	Non-ART PTV/plan assessed in 16% patients (as bladder was larger than any adaptive PTVs) 18.4% patients bladder extended outside PTV as assessed on post-radiotherapy CBCT CTCAE acute ≥grade 3, 18%
2b	Murthy et al., 2016 [79] ($n = 44$)	Partial bladder boost, bladder and PLN	Tomotherapy 68 Gy/32 fractions to partial bladder, 64 Gy/32 fractions to bladder	PoD − single CT	Initial 10 patients 6 POD-PTVs [76] 3 PoD-PTVs: Small: bladder +20 mm (S), 15 mm (A), 10 mm (R,L,I,P) Medium: bladder +25 mm, 20 mm (A), 15 mm (R,L), 10 mm (I,P) Large: bladder +25 mm (S,A), 20 mm (R), 16.5 mm (L), 15 mm (P), 10 mm (I) PTV for SIB = GTV +10 mm PTV for PLN = PLN +5 mm	RTOG acute ≥grade 3, 11% genitourinary and 0% gastrointestinal; RTOG late ≥grade 3, 4% genitourinary and 0% gastrointestinal 12% local recurrence (7% MIBC, 5% non-MIBC) after median follow-up of 30 months
2b	Hafeez et al., 2016 [80] ($n = 20$)	Bladder + partial bladder boost	IMRT 52 Gy to bladder, 70 Gy to SIB	PoD − 2 CTs ($t = 30$ min and $t = 60$ min)	3 PoD-PTVs for Bladder: Small: bladder +5 mm Medium: bladder +15 mm (S,A), 10 mm (P), 5 mm (R,L,I) Large: bladder +25 mm (S), 20 mm (A), 12 mm (P), 7.5 mm (R,L,I) 3 PoD-PTVs for GTV: Small: GTV +5 mm Medium: GTV +5 mm	Mean D98 on post-treatment CBCT ≥97% Median follow-up of 19 months no muscle invasive recurrences No late ≥grade 3 gastrointestinal toxicity; 2 patients grade 3 genitourinary (cystitis) manged medically with resolution

(*continued on next page*)

Table 3 (*continued*)

Stage	Reference (No. patients)	Target	Technique and dose	ART strategies	PTVs	Findings
					Large: GTV +25 mm (S), 20 mm (A), 12 mm (P), 7.5 mm (R,L,I) If > 50 cm^3 bladder filling between CTs Large: bladder and GTV on $t = 60$ CT +15 mm (A,S), 10 mm (P), 5 mm (R,L,I)	
2b	Hafeez et al., 2017 [81] ($n = 55$)	Bladder	CRT 36 Gy/6 fractions or 30 Gy/5 fractions	PoD − 2 CTs ($t = 0$ and $t = 30$ min)	[71]	CTCAE acute ≥ grade 3 genitourinary and gastrointestinal toxicity was 18% and 4%, respectively. No grade 4 genitourinary/gastrointestinal toxicity was seen Late RTOG ≥grade 3 (any) toxicity at 6 and 12 months was 6.5% and 4.3%, respectively Local control at 3 months was 92%
2b	Beulens et al., 2019 [82] ($n = 44$)	Bladder + partial bladder boost with Lipiodol	IMRT 46 Gy/23 fractions to bladder, 59.8 Gy/23 fractions to SIB	PoD − 2 CTs	[77]	RTOG acute ≥grade 3 genitourinary and gastrointestinal toxicity was 2.3% and 0%, respectively RTOG late ≥grade 3 (any) toxicity at 12 months was 3% At median follow-up of 38 months, local recurrence rate was 11.4%
2b	Murthy et al., 2019 [83] ($n = 106$)	Partial bladder boost, bladder and PLN	Tomotherapy 64 Gy/32 fractions to bladder, 68 Gy/32 fractions to GTV	PoD − single CT	[79]	RTOG acute ≥grade 3 genitourinary and gastrointestinal toxicity was 7.5% and 0%, respectively RTOG late ≥grade 3 genitourinary and gastrointestinal toxicity was 6.5% and 3.8%, respectively After median follow-up 26 months, 3 year local regional disease control was 74.3%
3	HYBRID Trial, [84] ($n = 65$)	Bladder	CRT 36 Gy/6 fractions	PoD − single CT	Non-ART PTV: Bladder +15 mm versus 3 POD-PTVs: Small: bladder +5 mm Medium: bladder +15 mm (S,A), 10 mm (P), 5 mm (R,L,I) Large: bladder +25 mm (S), 20 mm (A), 12 mm (P), 0.8 mm (R,L,I)	CTCAE ≥ grade 3, 6% in ART and 13% in non-ART Local control rate of 88% in ART and 74% in non-ART%
3	RAIDER Trial, [85]	Bladder + SIB	IMRT Bladder, 52 Gy/32 fractions (46 Gy/20 fractions); 64 or 70 Gy/32 fractions (55 or 60	PoD 2 CTs ($t = 0$ and $t = 30$ min)	Non-ART PTV: Bladder +15 mm versus 3 PoD-PTVs for bladder: Small: bladder +5 mm Medium: bladder +15 mm (S,A), 10 mm	Trial recruitment completed, outcomes awaited

Table 3 (*continued*)

Stage	Reference (No. patients)	Target	Technique and dose	ART strategies	PTVs	Findings
			Gy/20 fractions) to SIB		(P), 5 mm (R,LI) Large: bladder +25 mm (S), 20 mm (A), 12 mm (P), 7.5 mm (R,LI) 3 PoD-PTVs for GTV: Small: GTV +5 mm Medium: GTV +15 mm (S,A), 10 mm (P), 5 mm (R,LI) Large: GTV +25 mm (S), 20 mm (A), 12 mm (P), 8 mm (R,LI) If > 50 cm^3 bladder filling between CTs Large: bladder and GTV on $t = 60$ CT +15 mm (A,S), 10 mm (P), 5 mm (R,LI)	
4	MOMENTUM Study [19]	Bladder	IMRT 55 Gy/20 fractions 36 Gy/6 fractions	MR-guided online re-optimisation	[17]	Data collection in progress

A, anterior; Aniso, anisotropic; CBCT, cone beam computed tomography; CRT, conformal radiotherapy; CT, computed tomography; CTV, clinical target volume; DVF, deformation vector field; GTV, gross tumour volume; I, inferior; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; Iso, isotropic; L, left; MIBC, muscle-invasive bladder cancer; MR, magnetic resonance; OV, occupancy volume; P, posterior; PoD, plan of the day, library of plans; Pop, population; PLN, pelvic lymph node; PTV, planning target volume; PTVcomp, composite volume; R, right; S, superior; SIB, simultaneous integrated boost; VMAT, volumetric modulated arc therapy.

* Published as an abstract at the time of the literature search.

anterior direction (as a result of filling and variation in rectal contents) [13,35,56]. Based on this knowledge, anisotropic PTV margins have been used by some in an attempt to better capture this asymmetrical filling.

Inter-fraction GTV motion has also been assessed. This has usually been quantified by extrapolating motion of fiducial markers when inserted around the tumour or tumour bed [34,36,37,41,105–107]. Whether this is a reliable surrogate is unclear. Marker placement in the normal bladder at the boundary of the tumour may not always be representative of changes in GTV position, and so the further away from the GTV border, the less representative it becomes [36]. Different degrees of invasion could also vary tumour contractibility, as it can be presumed that bladder wall fixation and stretch may be different for T2 tumours compared with T4 tumours [35]. It remains unclear whether there is any correlation between GTV size change and bladder filling status. As the bladder tumour is relatively rigid and non-elastic compared with non-tumour-bearing bladder regions, it may be minimal [32,107]. One conclusion that can be drawn from this work is that despite these limitations when GTV is present on the superior and anterior regions of the bladder, larger positional variation should be expected than when GTV is present at other regions of the bladder [34,36,41,106,107].

Understanding and quantifying target motion between the time it takes to acquire the initial online image and to complete the delivery of dose is also an important consideration to minimise the risk of intra-fractional geographical miss. The most commonly used method to determine intra-fractional motion has been to acquire CBCT prior to and following bladder radiotherapy, but cine MRI and serial MRI acquired over time have also been used [53,56,61,66,70,71,75,108].

Changes occurring to the whole bladder over a period of up to 20 min may successfully be accommodated by an isotropic margin ranging from 2 to 7 mm [13,45,53,56,61,70,71,75]. However, target under-dosing of more than 1 cm^3 below 95% of the fractional dose was seen in 20% of fractions at 10 min when a 5 mm isotropic margin is used [66]. In this patient population, serial MRI scans were acquired at 2-min intervals for 10 min post-voiding. It appears that much larger anisotropic margins (14 mm cranially and anteriorly, 9 mm posteriorly and 5 mm in all other directions) would actually be necessary to successfully maintain target coverage by 10 min [66]. Over a time frame in the region of 30–40 min, an anisotropic margin of 15 mm applied cranially and anteriorly, 1 cm posteriorly and 5 mm in all other directions successfully maintains target coverage in 96.6% of fractions [17]. From these studies, there does not seem to be consensus on a preferred intra-fraction margin, but the longer the anticipated online adaptive workflow, the larger margins necessary.

Intra-fraction bladder volume change would also expected to be impacted by the rate of bladder filling. Mean rates of filling can vary between 0.9 and 4.0 ml/min [13,31,32,37,45,80,109,110]. More rapid filling would be anticipated when drinking protocols to achieve a partially filled or full bladder are used [80]. Rate of filling has been shown to change over the treatment course but there are conflicting data as to

whether it decreases or increases [31,32,80] but is independent of whether the bladder is full or empty [13,66].

Application of Image-guided Radiotherapy

Patient set-up based on skin tattoos or bone alone is not adequate to correct for the true bladder target displacement [14,20,22]. Feasibility of CBCT to inform bladder radiotherapy delivery was first reported in 2006 by Henry *et al.* [15]. Image quality was deemed adequate for visualising the bladder for treatment position verification and delineation.

The modelled benefit of soft-tissue IGRT results in superior bladder target coverage, with smaller margins and a subsequent reduced integral dose to the surrounding tissues [14]. A PTV derived using a 1.5 cm isotropic margin would only be expected to cover 95% of bladder wall displacements in 56% and 63% of patients set up to skin and bone, respectively. However, matching using CBCT, target coverage is expected in 96% of patients. In order to successfully ensure that >95% target coverage is achieved using skin or bone set up, a 2.5 cm PTV margin would be required [22]. Arguably therefore, daily CBCT imaging should always be considered when bladder PTV margins ≤1.5 cm are being used. Despite this evidence, the recent UK audit of bladder radiotherapy conducted by the Royal College of Radiologists identified that CBCT was used for bladder cancer radiotherapy verification in about 80% of patients. For the remaining patients, it is assumed that two-dimensional portal imaging is still being used for set up [111].

The estimated dose of each CBCT is about 0.03 Gy; therefore, the additional radiation dose for a radical course of radiotherapy would be <1 Gy for each patient. The risk of harm from this contributory dose is low, and the likelihood of secondary malignancy is mitigated by the older age demographic and relatively poor long-term survival outcomes in bladder cancer compared with other cancers [112–116].

The MR-guided radiotherapy solution provides an alternative IGRT solution. This has been achieved in two ways. Although shuttle-based i.e. 'MR on rails' is available at some centres, its utility for bladder cancer IGRT is probably limited given expected intra-fractional changes [108,117,118]. Alternatively, hybrid systems incorporating both MRI and a linear accelerator (MR-Linac) in a single machine allows an in-room, real-time MRI scan to be obtained immediately before each fraction [108,119,120].

Real-time motion monitoring and tracking alone is unlikely to offer a solution for whole-bladder cancer radiotherapy given the target is increasing in volume over time [32,31]. However, the tumour itself has the potential to be tracked when considering partial bladder radiotherapy. The technical feasibility has been shown with the delivery of stereotactic bladder radiotherapy using the CyberKnife® system tracking gold fiducial markers [121].

Adaptive Radiotherapy Solutions

Compositive Volume (Offline Solution)

The composite volume as applied to bladder radiotherapy was first described by Pos *et al.* [106]. Daily imaging was acquired for the first 5 days of treatment in order to define a patient-specific volume that aims to capture the maximal excursions of the target (internal target volume). A smaller margin to account for remaining residual uncertainties was then applied to create the PTV. This study pre-dated routine CBCT use, and instead used repeated CT scans on the day of treatment to define the internal target volume [106]. Subsequent studies adopted a similar method but using the treatment verification CBCTs [57,60,101].

The composite volume approach has been shown to adequately maintain target coverage and reduce the PTV by about 40–50% compared with population-based standard PTV approaches [57,106]. A limitation of this approach is that it can only be implemented after sufficient CBCTs have been acquired. It does not, therefore, lend itself well to hypofractionated schedules [101]. Too few CBCTs risk not capturing all the potential excursions that would probably be encountered. Too many CBCTs and the opportunity to implement an adaptive strategy for the remaining fractions is lost. Three CBCTs is probably insufficient, as target coverage would only be successfully achieved in 50% of patients [60]. Although planning CT with 15 CBCTs improves target coverage to 95%, it would mean possibly the majority of fractions depending on fractionation would not benefit [57]. Inclusion of the planning CT and initial five CBCTs seems to achieve optimal balance of resources and efficacy [51].

Library of Plans (Online Solution)

An alternative method is to generate a library of patient-specific treatment plans using varying sizes of PTV from the start. CBCT acquired prior to each fraction means the most appropriate PTV and corresponding plan can be selected that covers the bladder target with minimal normal tissue exposure.

The library of plans can be generated using a number of different methods (summarised in Figure 1). The most simple is the application of increasing margins around the bladder to produce a series of PTVs of different sizes from a single planning CT scan [53,59,60,64,67,76,79,83,122,123].

The alternative is to use the patient's own bladder filling pattern as seen on serial planning CT scans acquired over a fixed time period (up to 60 min) or using the initial verification CBCTs to inform the library creation [53,56,70–75,77,78,80–82,122]. The margins reported to generate the library of PTVs and associated plans are variable. Some adopt incremental isotropic margins, whereas others adopt anisotropic margins to produce the PTVs (summarised in Table 3).

Despite the variation in library creation approaches, modelled dosimetric benefit suggests that the library of plan approach maintains target coverage, while reducing the PTV (by about 40%) with subsequent reduction in normal tissue irradiation compared with the single plan treatment delivery in all the reported modelling and feasibility studies [53,59,60,64,67,71,76,68].

The optimal number of plans making up the library is unclear. The balance between creating an extensive library of plans needs to be considered against the impact on resources and clinical usefulness. Murthy *et al.* [76] reported that of their

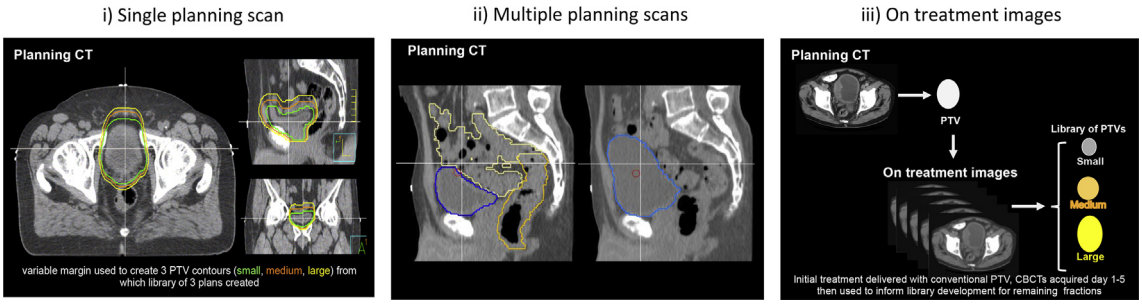

Fig 1. Library development strategies.

library of six intensity-modulated radiotherapy plans, the largest was not used at all and their second largest was used for <1% of treatments. Larger libraries are also associated with increased time for plan selection, which has an implication for intra-fraction filling and potentially greater risk of error [76,77]. It is possible that a library of three plans (small, medium and large) can be created to successfully cover up to 97% of inter-fraction changes depending on the PTV margins applied [80]. Too restrictive margins to create the PTVs can mean no plan appropriately encompasses the imaged target on a more frequent basis [78]. In these circumstances, the patient would be required to void their bladder with repeat of the set-up after review of the drinking protocol and time to CBCT acquisition [80,85].

Determining the 'best fit' of the most appropriate size PTV and corresponding plan for treatment delivery is also necessary. A guide contour that corresponds to the 95% isodose line to ensure that the macroscopic tumour is correctly covered for treatment has been suggested [75,77,78]. It is also acknowledged that intra-fraction filling should be accounted for at the time of plan selection. To achieve this, most groups are reliant on the operator judging by eye that the bladder edge as seen on CBCT is sufficiently encompassed by the smallest PTV with at least a 2–5 mm gap [56,70,71,76,80].

A discrete, predetermined library of plans to cover the spectrum of inter-fraction target variation means the individual conformity of the selected plan can be relatively poor [80]. Although the conformity improves with intra-fraction filling (by 8%), it remains poor, suggesting there is a large amount of redundancy in plan selection. The implication is that although target coverage is being attained, unnecessary non-target irradiation is still occurring [80].

Re-optimisation at Each Fraction (Online Solution)

An on couch ART strategy, based on the anatomy as seen at that fraction, has potential to significantly improve normal tissue sparing above that seen for composite and ART library of plan approaches [61,66,68]. In a planning study, Vestergaard *et al.* [61] found that the normal tissue volume receiving greater than 95% of the prescribed dose could be reduced from 66% with plan of the day to 41% using a CBCT re-optimisation technique when delivered on an empty bladder. Similar improvement was seen when pelvic lymph nodes and treatment was delivered on a full bladder protocol [68].

Technological solutions are now in place enabling online adaption for whole bladder radiotherapy on both CBCT and MRI using commercially available platforms [16,17,69,124]. The principal workflow components include generating an offline reference plan usually from a planning CT in order that density information can be acquired. At treatment, an online image is acquired. Target volume and organs at risk contours are reproduced, either by propagating them from the initial planning image using deformable registration or artificial intelligence algorithms [125]. The contours are reviewed and corrected if necessary. A new plan with full re-optimisation using the same constraints as the reference plan is generated. A quality assurance check is carried out. Treatment is delivered while motion monitoring occurs [16,17,69,124]. The median times to clinically deliver an online re-optimised bladder workflow with commercially available platforms is reported to be 12.1 min using CBCT and 39 min on the MR-Linac [17,69].

Practicalities of Clinical Implementation

The implementation of bladder IGRT and online ART has necessitated skill expansion, particularly for treatment radiographers. It requires iterative training, quality assurance and competency assessment. How this could be successfully achieved has been reviewed elsewhere [48,50,85,122,126,127].

In the single-centre setting with structured teaching, training, competency assessment and framework for maintaining acquired skills, concordance of online radiographer-led plan selection with offline clinician plan selection is >90% [48,71,80]. In these circumstances, non-concordant plan selection does not seem to adversely affect target coverage (mean D98 >95%) even when evaluated on the post-treatment CBCT scan [80]. In the multicentre setting, training for plan selection is effective but agreement seems to fall (78%), with discrepant cases reflecting treatment delivery with a larger PTV than that selected by the clinician offline [123]. This may not affect target coverage but has implications for a reduction in treatment-related toxicity. It supports the need for ongoing peer support and feedback following implementation of plan selection ART approaches [123,126].

Online re-optimisation workflows currently necessitate the presence of an oncologist, a medical physicist and a treatment radiographer [17]. Training to enable this work to be radiographer led are in development [50,128].

Clinical Effectiveness

Adaptive bladder radiotherapy strategies have been used in a number of different clinical settings. An overview of the clinical outcomes reported in these studies is presented in Table 3 and relate to R-IDEAL stages 2b and 3.

In a single-centre, non-randomised phase II study, whole (empty) bladder hypofractionated weekly treatment delivering 30–36 Gy in 5–6 weekly fractions using a library of three plans was evaluated in 50 patients who were unsuitable for radical treatment [81]. As each fraction represents about 17% of the prescription dose, the potential of a geographical miss has high potential to compromise tolerability and tumour control. Despite advancing age (median 86 years; range 68–97) and pre-existing multimorbidity, 87% of patients completed their treatment as prescribed. Treatment was well tolerated with acute ≥grade 3 genitourinary and gastrointestinal toxicity reported in 18% and 4% patients, respectively, and ≥grade 3 1-year late toxicity of less than 5%. Local control, 3 months after completing radiotherapy, was 92% [81]. Improved targeting would be expected to improve disease control. In an era pre-dating IGRT with CBCT, local control at 3 months with this fractionation in a similar patient population was 62% [129].

In a multicentre phase II trial (HYBRID NCT01810757), patients were randomised to receive 36 Gy in six fractions to the whole bladder using either a library of plans approach or a single plan (non-adaptive). Treatment was well tolerated, with ≥grade 3 non-genitourinary toxicity rates of 6% for the ART approach versus 13% for the non-adaptive group [122,123]. Local control was 88% in the ART group and 74% in the non-adaptive group. A trend favouring improved outcomes with ART seems apparent despite the limitation of the non-comparative trial design [123].

Daily radical whole bladder radiotherapy delivered using a library, plan of the day approach is technical feasible [78]. However, long-term clinical outcomes specific to this approach and patient group have not yet been reported.

Exploiting the dosimetric advantage of ART, a number of groups have shown the feasibility of delivering a higher dose to the bladder tumour as a simultaneous integrated boost [74,76,77,80,82]. In a large retrospective series escalating dose to the tumour up to 68 Gy there was a suggestion that outcomes are at least as favourable as those reported in BCON and BC2001 where routine pre-fraction soft-tissue imaging was not routinely used [4,7,83]. Murthy *et al.* [83] showed a 3-year local control rate of 74%. This compares with a 2-year local control of 67% in the BC2001 chemoradiotherapy arm [4]. Lower rates of late ≥grade 3 genitourinary (6.5%) and gastrointestinal (3.8%) toxicities were also seen as compared with BC2001 (8.3% ≥grade 3) [4,83]. In a subgroup analysis, no significant difference in disease control or toxicity was seen between those treated with simultaneous integrated boost ≤64 Gy and 68 Gy [83].

In a phase I study, dose escalation to 70 Gy in 32 fractions to simultaneous integrated boost with a library of plans is feasible with acceptable toxicity [80]. This dose level is being evaluated in a multicentre randomised control phase II trial of adaptive dose-escalated bladder radiotherapy (RAIDER NCT02447549) which completed recruitment earlier this year [85].

Conclusion

A single planning CT cannot reliably capture the expected inter-fractional bladder positional and volume changes expected during a course of treatment without the use of large margins. Set-up informed by volumetric soft-tissue image guidance minimises the risk of a geographical target miss. Using volumetric imaging, offline and online ART strategies have been developed. Technical solutions mean that commercial platforms now available allow full online CBCT- and MRI-informed re-optimisation to the actual anatomy of the day. Modelled benefit from a large number of planning studies illustrates that reliable margin reduction and a decrease in normal tissue irradiation is possible with ART when compared with single plan non-adaptive treatment delivery. The current evidence is weighted towards presumed clinical benefit based on these dosimetric gains. Whether these strategies will translate into improved clinical outcomes has yet to be determined in comparative randomised control trials.

Conflicts of interest

The Royal Marsden Hospital, The Institute of Cancer Research, Princess Margaret Cancer Centre and Odense University Hospital are members of the Elekta MR-linac Consortium, which aims to coordinate international collaborative research relating to the Elekta Unity (MR-linac). Elekta (Elekta AB, Stockholm, Sweden) and Philips (Philips, Best, the Netherlands) are commercial members of the MR-linac Consortium. Elekta financially supports consortium member institutions with research funding, education and travel costs for consortium meetings. S. Hafeez is bladder tumour site group lead within the MR-linac Consortium. No commercial financial support was received from any organisation for the submitted work.

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