Review Article

A practical approach to bladder preservation with hypofractionated radiotherapy for localised muscle-invasive bladder cancer

R. Portner [a,*], A. Bajaj [b], T. Elumalai [a], R. Huddart [c,d], V. Murthy [e], H. Nightingale [a], K. Patel [a], P. Sargos [f], Y. Song [a], P. Hoskin [g,h], A. Choudhury [a,h]

[a] The Christie NHS Foundation Trust, Manchester, UK
[b] Department of Radiation Oncology, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA
[c] Royal Marsden NHS Foundation Trust, London, UK
[d] Institute of Cancer Research, UK
[e] Department of Radiation Oncology, ACTREC and Tata Memorial Hospital, Homi Bhabha National University, Mumbai, India
[f] Department of Radiation Oncology, Institut Bergonié, F-33076 Bordeaux Cedex, France
[g] Mount Vernon Cancer Centre, Northwood, UK
[h] Division of Cancer Sciences, University of Manchester, Manchester, UK

ABSTRACT

Bladder preservation with trimodality treatment (TMT) is an alternative strategy to radical cystectomy (RC) for the management of localised muscle invasive bladder cancer (MIBC). TMT comprises of transurethral resection of the bladder tumour (TURBT) followed by radiotherapy with concurrent radiosensitisation. TMT studies have shown neo-adjuvant chemotherapy with cisplatin-based regimens is often given to further improve survival outcomes. A hypofractionated radiotherapy regimen is preferable due to its non-inferiority in local control and late toxicities. Radiosensitisation can comprise concurrent chemotherapy (with gemcitabine, cisplatin or combination fluorouracil and mitomycin), CON (carbogen and nicotinomide) or hyperthermic treatment.

Radiotherapy techniques are continuously improving and becoming more personalised. As the bladder is a mobile structure subject to volumetric changes from filling, an adaptive approach can optimise bladder coverage and reduce dose to normal tissue. Adaptive radiotherapy (ART) is an evolving field that aims to overcome this. Improved knowledge of tumour biology and advances in imaging techniques aims to further optimise and personalise treatment.

Introduction

Urothelial bladder cancer is the 10th most common cancer with over 500,000 new cases and 210,000 deaths worldwide in 2020 [1]. Approximately 70% of patients are >65 years of age and it is also more common in males [2]. Nearly half of cases are associated with a history of smoking, with patients frequently presenting with multiple co-morbidities and frailty [3]. Approximately 30% of patients will present with muscle-invasive bladder cancer (MIBC). Surgical management with radical cystectomy (RC) and extended pelvic lymph-node dissection was historically considered to be the gold standard management option. However, this can be associated with morbidity, high post-operative complication rates and often requires a permanent stoma which can affect the patient's quality of life [4].

Bladder preservation or tri-modality therapy (TMT) (Fig. 1) is an alternative curative treatment for MIBC. Whilst previously offered only to elderly or frail patients, international guidelines now recommend it as a viable option to all suitable patients. It consists of maximal TURBT followed by radiotherapy administered concurrently with radio-sensitisers. In some cases, neo-adjuvant chemotherapy is offered to improve outcomes [5,6]. Previous pelvic radiotherapy is the only real contraindication to TMT, although patients with poor bladder function may best be served by RC rather than TMT. Multi-focal disease, carcinoma-in-situ and presence of hydronephrosis were considered contraindications for TMT, although inclusion of these patients in the BC2001 [7] and BCON [8] trials [9] was permitted.

There are no Phase III trials directly comparing surgery and radiotherapy, with the SPARE trial (NCT00867347) finding randomisation

difficult due to strong pre-conceived clinician and patient preference [10]. Outcomes from matched cohorts, population data and a meta-analysis do however give similar results. A meta-analysis comparing outcomes for RC and TMT showed no difference in overall survival, disease-specific survival or progression-free survival with slightly higher early complications in the surgical group. 5-year OS was estimated at 56.2% with RC and 55.0% with TMT [11]. Of note, patients tended to be older in the radiotherapy groups. Propensity score analysis from two studies confirmed equivalent disease-specific survival rates [12,13].

Radiotherapy practice in the UK was reviewed during the COVID-19 pandemic. Whilst radiotherapy across all tumour sites had fallen there has been an increase in bladder radiotherapy by 64.2% [14]. It remains to be seen if this trend is maintained as the pandemic is controlled. This review aims to outline current practical aspects of radical radiotherapy and areas of future development.

Methods

Studies were identified from the Pubmed electronic databases from inception to June 2021. The search strategy involved keywords including 'muscle invasive bladder cancer', ' bladder preservation', 'tri-modality', 'radiotherapy', 'chemotherapy', 'radiosensitiser', 'nodal irradiation', 'partial bladder', 'radiotherapy boost', 'adaptive radio-therapy', 'biomarkers'.

Current approach to bladder preservation

Role of neo-adjuvant chemotherapy

Platinum-based combination chemotherapy provides an absolute overall survival benefit of 5% and disease-free survival benefit of 9% at 5 years [5,15]. It treats micro-metastatic disease and allows for potential of downsizing tumour volume, especially for patients with large tumours where TURBT is difficult or completeness is not possible. Although most studies involved neoadjuvant chemotherapy prior to surgery, the UK Medical Research Council BA06 trial permitted either surgery or radiotherapy after cisplatin, methotrexate and vinblastine (CMV). They observed a 16% reduction in the risk of death, corresponding to an increase in 3-year survival from 50% to 56% among all patients in favour of neo-adjuvant chemotherapy. In the modern era, the commonest platinum-based schedules used are gemcitabine and cisplatin (GC) or

dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) [16,17]. These regimens are not without risk of toxicities and require careful patient selection, with a 44% risk of Grade 3–4 toxicities [18,19].

The Vesper trial (NCT00808639) sets out to compare dd-MVAC to GC prior to cystectomy. Provisional data showed although manageable dd-MVAC had higher rates of gastrointestinal toxicity and asthenia. Higher local control rates with dd-MVAC were however observed, with non-muscle invasive status of 63% compared to 49% for GC (p = 0.007) [20]. Until survival data is available three cycles of GC remains a reasonable choice for neo-adjuvant chemotherapy. In the UK, the NICE guidelines stipulate that neoadjuvant chemotherapy should form part of the clinical pathway in appropriate patients, for patients having radical treatment including those receiving bladder preservation [21].

Radiotherapy technique

Radiotherapy techniques have evolved over decades from a four-field fixed box technique, to 3D-conformal radiotherapy (3D-RT) techniques using multi-leaf collimators (MLC). In the modern era, there is a widespread use of intensity modulated radiotherapy (IMRT) in a further attempt to limit dose to critical organs at risk. When compared to 3D-RT, IMRT or volumetric-modulated arc therapy (VMAT) technique is considered dosimetrically superior, maintaining target coverage with considerably reduced rectal and small bowel dose [22,23]. VMAT would generally be preferred to IMRT in view of shorter delivery which mini-mises the impact of bladder filling.

The bladder is subject to significant day to day variation in size and shape that can result in target misses. Using Cone beam CTs (CBCT) to provide three-dimensional soft-tissue images ('image guided radio-therapy') obtained immediately prior to treatment allows adjustments in machine set-up or patient position to ensure optimal coverage and avoid [24,25].

RT set-up

Current radiotherapy techniques follow a common workflow. Most patients are scanned and treated supine with arms positioned across the chest away from the beams using simple immobilisation. The patient is aligned using anterior tattoos on the symphysis pubis and singular lateral tattoos. Patients are asked to void immediately prior to planning
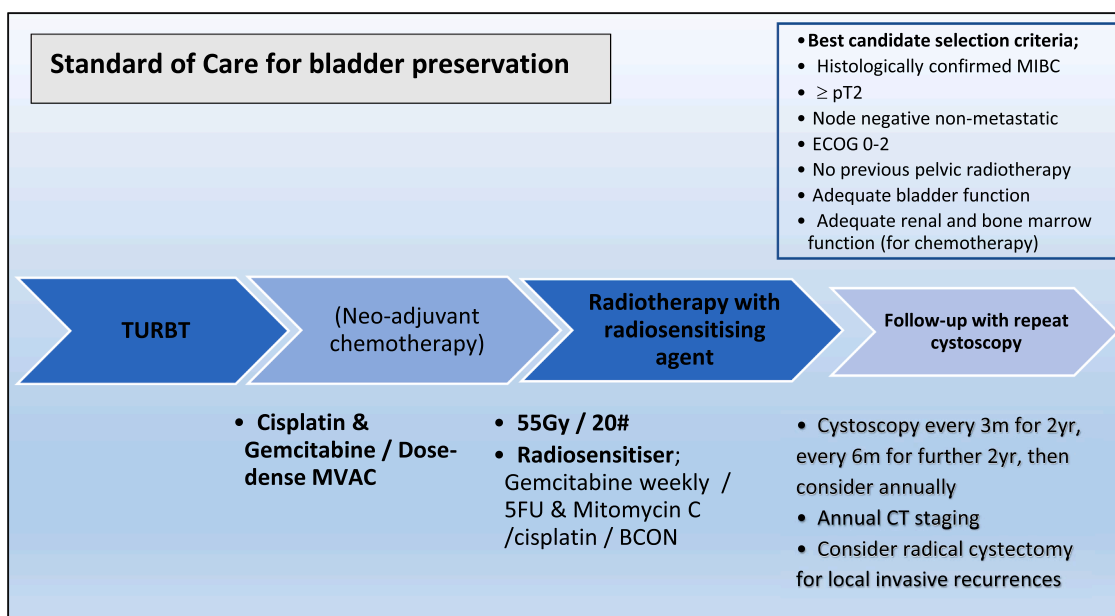

Fig. 1. Schematic of tri-modality treatment.

CT to ensure an empty bladder. Whilst dose escalation or partial bladder boost are not standard practice these are best planned with a comfortably full bladder (200–300 cc) using a bladder filling protocol [26]. An empty rectum is preferable to avoid bladder deformation, so patients are encouraged to clear their bowels prior to planning scan. Laxatives or micro-enemas may be required if rectal volume remains enlarged. CT scans with slices taken at 3 mm intervals extend from bottom of ischial tuberosities to 3 cm above the dome of the bladder or bottom of L5. Intravenous contrast is not routinely used [27,28].

Radiotherapy planning volumes

Radiotherapy planning involves initially contouring a clinical target volume (CTV) to include potential macroscopic residual disease (post-TURBT) and areas at risk of microscopic disease. This encompasses the whole bladder with any extravesical extension. Prostatic or vaginal tissue is not usually included unless there is direct invasion. If tumour is present in the bladder neck or there is extensive carcinoma in situ an additional 1.5 cm of prostatic urethra and 1 cm female urethra can also be included. Gross tumour volume (GTV) contouring can be challenging post-TURBT. Whilst surgical bladder mapping at TURBT, surgical clips with markers, radio-opaque contrast agents like lipiodol and imaging from the diagnostic MRI can help, contouring the GTV or tumour bed is not standard procedure unless a concomitant boost or partial bladder technique is employed.

The CTV is expanded to a planning target volume (PTV) to account for changes in anatomy and set-up. Previous studies of bladder motion show there is more movement in anterior and superior directions [29]. This can range from 0.85 to 1.4 cm anteriorly and 1.19–1.50 cm superiorly, compared to 0.5–1.3 cm in other directions [30–32]. Regardless of the variability in bladder motion a uniform expansion of CTV is currently used most commonly. In both the BCON trial [8] and the whole-bladder radiotherapy arm in the BC2001 trial [7] a 1.5 cm isotropic expansion was used from CTV to PTV. Anisotropic expansion remains under investigation. Adaptive radiotherapy techniques, discussed below, aim to personalise radiotherapy plans based on the individual patient's bladder motion [25].

As conventional contours cover the whole bladder volume this may over-treat normal bladder and surrounding tissue. Previous studies of partial bladder (defined as GTV with isotropic expansion) compared to whole bladder radiotherapy were unable to demonstrate non-inferiority and showed no significant improvement in late toxicity [7]. At present reducing dose to the uninvolved bladder regions is not recommended.

Prophylactic nodal irradiation for MIBC is a controversial area. In other pelvic cancers such as cervical and endometrial cancers, nodal relapses are common and prophylactic nodal irradiation has proven benefit [33]. Radiotherapy to the bladder alone already results in significant doses to nearby lymph nodal regions. When giving 64 Gy in 32 fractions the obturator nodes, external iliac and internal iliac nodes received 59 Gy, 45 Gy and 36 Gy respectively [34]. Tunio et al showed no benefit with the inclusion of elective pelvic lymph nodes compared to bladder-only radiotherapy [35]. Extended pelvic fields have also been shown to be associated with higher acute gastrointestinal toxicities [36].

With IMRT and image-guided radiotherapy, many groups are reducing the margins used for CTV to PTV expansion for the bladder. Although toxicity may be reduced, we do need to be wary of the reduced incidental dose to the nodes.

Brachytherapy alone has shown to be an effective bladder-preserving modality in patients with high-grade T1 or T2 disease. When compared to RC it showed equivalent survival benefit but with significantly lower high grade complications [37].

Fractionation and schedule

Throughout much of the world, bladder radiotherapy has been delivered with conventional fractionation of 1.8–2 Gy per fraction.

However, in the UK two radiotherapy schedules have commonly been employed, namely 64 Gy in 32# over 6.5 weeks and the hypofractionated regimen of 55 Gy in 20# over 4 weeks. Recently a published meta-analysis comparing the two regimens by combining two large Phase III trials, BC2001 [7] and BCON [8], the hypofractionated regimen is expected to be adopted as standard of care [38]. Hypofractionated radiotherapy was found to be superior to 64 Gy in 32 fractions in relation to invasive locoregional control, and non-inferior for overall survival and late bladder and rectum toxicity regardless of choice of radiosensitisers. Although bladder cancer is considered to be rapidly proliferating, it was also thought to hypothetically have a high α/β ratio with a concern that moderate hypofractionation would be less effective and be associated with increased late toxicity. As such the observation that moderate hypofractionation is more effective than conventional fractionation with no additional toxicity was unexpected. This would suggest that the α/β ratio is lower and/or the effect of repopulation more important than predicted. Radiotherapy effectiveness may be reduced after approximately 5 weeks due to tumour repopulation. Shorter fractionations are also more convenient for patients and more cost-effective [39] so the hypofractionated regimen should be adopted as standard of care. Dose constraints for organs at risk using hypofractionated are included in Table 1.

A split course radiotherapy regimen is used in some countries [36] incorporating induction radiotherapy with re-assessment cystoscopy, followed by completion radiotherapy if there has been response [36,40]. This however leads to much longer overall treatment times with risk of tumour repopulation. Evidence for this protocol is also less robust compared to hypofractionation [41].

In patients not suitable for curative treatment (due to disease stage or comorbidities) ultra-hypofractionated radiotherapy can provide both symptom improvement and local control. The use of 21 Gy in 3 fractions on alternate days has been shown to provide equivalent symptomatic improvement with no difference in efficacy or toxicity compared to 35 Gy in 10 fractions [42]. More recently a weekly treatment of 30–36 Gy in 6 fractions for elderly patients with locally advanced disease has reported local disease control rates of over 70% of patients , with modest acute and low levels of late toxicities [43].

Radiosensitisers

Radiosensitisation comes in the form of chemotherapy, hypoxia modification, hyperthermia or novel agents such as immunotherapy. The two largest randomised control trials comparing radiotherapy alone with radiosensitisation are the BC2001 and BCON trials.

There is historical evidence for the use of cisplatin as a radiosensitiser [44]. Although it is still used in some centres, patients with renal dysfunction are unsuitable for its use.

The BC2001 trial investigated benefit of 5-flourouracil and mitomycin C added to radiotherapy [7]. Compared to RT alone locoregional disease-free survival was significantly better with 2-year recurrence-free rates of 67% versus 54% and improved bladder cancer specific survival on long term follow up. Whilst there were significantly higher rates of acute grade 3–4 gastrointestinal toxicities there was no difference in late side-affects.

The BCON trial investigated the benefit of hypoxic modification to radiotherapy outcomes. Patients were randomised to radiotherapy with

Table 1
Recommended dose constraints for a hypofractionated schedule.

Structure	Dose constraint
Rectum	Mean dose < 40 Gy
	V50Gy < 50%
Small bowel	V50Gy < 98 cc
Femoral head	V50 < 50%
Body	Max dose (1 cc) < 105%

carbogen and nicotinomide (CON) or radiotherapy-alone. Carbogen (2% CO$_2$ and 98% O$_2$ at 15 L/min) was administered via a closed breathing system and face mask, commenced 5 min before and during each fraction. Nicotinamide was given orally at 40–60 mg/kg, given 1·5–2·0h before each fraction. 5-year OS was 50% in the CON arm compared to 39% with radiotherapy-alone [8].

Gemcitabine has shown activity in urothelial cancers in combination with platinum in the neo-adjuvant and metastatic setting. This can be also be given as a radiosensitisers as a weekly infusions at 100 mg/m^2 as in the Phase II GemX trial [45]. A meta-analysis of gemcitabine-based chemoradiotherapy showed complete responses was observed in 93% of patients and 5-year overall survival, disease-specific survival, and cystectomy-free survival rates were 59%, 80.9%, and 93.3%, respectively. The treatment was well tolerated [46].

Hyperthermia has been used as a radiosensitisers for decades. Hyperthermia has anti-cancer properties by increasing blood perfusion and increasing the availability of intra-tumoral oxygen. Various techniques exist including the use of external radiofrequency emitters and warm irrigation intravesicularly with bleomycin [47,48]. Although this is a long-established practice it is not common practice and only used in a small number of centres, especially as it is particularly resource intensive.

The use of immunotherapy agents in combination with radiotherapy remains experimental.

Their combination leads to immunogenic cell death which increases in immune markers and improved response to treatment [49]. Immunotherapy agents can also modulate the tumour microenvironment by normalising tumour vessels, which can potentially reduce hypoxia and increase radiosensitivity [50]. Phase I trials combining immunotherapy agents with hypofractionated radiotherapy have so far been unsuccessful. The Phase I trial combining atezolizumab to 50 Gy in 20 fractions with weekly gemcitabine was stopped early due to Grade 3 gastrointestinal toxicities despite dose reduction [51]. The PLUMMB trial (NCT02560636) was a dose-escalation study combining weekly pembrolizumab with 36 Gy in 6 weekly fractions in patients either not fit for radical radiotherapy or with symptomatic metastatic cancer. Recruitment was also stopped early due to dose-limiting toxicity [52].

Future horizons

Below we explore prospective advances for improving radiotherapy practice. Table 2 summarises recent trials on adaptive radiotherapy and dose escalation [6,43,53–58].

Adaptive radiotherapy

Adaptive radiotherapy (ART) aims to improve accuracy by using patient-specific anatomical information, often obtained prior to each fraction, for delivering dose to target whilst avoiding normal tissue, thus improving accuracy [59]. Two common methods of ART exist. The 'Composite method' uses an offline approach with information gathered from CBCTs from the first 3–5 fractions. This dictates the PTV margins for the remaining treatment rather than population-based PTV margins [57]. The 'Plan of the day' (POD) method is an online adaptive process whereby information from CBCTs are used to select the best plan from a library of patient-specific treatment plans of varying PTV expansions. This allows geometric corrections in response to variable position, size and shape of the bladder at each fraction and has potential to reduce margins [60]. The POD technique has been validated for bladder RT. A review by Collins and Leach concluded POD gives an improved CTV and PTV coverage, a reduced PTV volumes and a dose reduction to small bowel and rectum. Common problems identified were increased treatment times and variability in plan selection between observers, suggesting the need for additional resources and training [59].

MRI-guided radiotherapy (MR-RT) also has applications for ART. MRI provides improved soft-tissue contrast compared to standard CBCT-

Table 2
Studies of adaptive radiotherapy and dose escalation.

Study	Patient no.	Method	Findings	Ref
Cowan et al (2004)	149	Investigating partial bladder RT and dose escalation Unifocal T2-T3N0M0 MIBC randomised between; • Whole bladder conformal radiotherapy 52.5 Gy/20# • Partial bladder RT with 1.5 cm margin to 57.5 Gy/20# • Partial bladder RT with 1.5 cm margin to 55 Gy/16	No significant difference in complete response or local control rates between three arms. Reduction in treatment volume allowed delivery of an increased dose without a reduction in local tumour control or the development of excess toxicity. Dose-escalated partial bladder did not result in significantly improved overall survival	[53]
McDonald et al (2013)	25	ART with POD method using three conformal plans (small, intermediate and large PTV) Concordance between the on-line and off-line selections, frequency of plan usage, target coverage and normal tissue sparing were assessed.	55% of fractions delivered using small or large plans Mean coverage of CTV was 99% Mean reduction in normal tissue volume was 219 cm^3 compared with the previous standard approach. Overall good concordance in plan selection with ART	[54]
Foroudi et al (2014)	50	Multi-centred feasibility trial of ART with combined composite and POD method Three new CTVs (small, medium, large) generated prior to #10 based on first 5 consecutive CBCT Daily CBCT with selection of POD for #10 onwards Post-treatment CBCTs also obtained	All adaptive plans created by #10 84% patients completed adaptive phase using conventional plan < 3 times 5.5% post-treatment CBCTs showed bladder filling beyond PTV Overall online ART technically feasible across multiple centres. Bladder filling still problematic with small margins insufficient.	[55]
Tuomikoski et al (2015)	10	Two online ART methods compared; • RepeatCT using 4 different planning scans at 15 min intervals to create 4 PTVs • RepeatCBCT using planning scan and 4x daily CBCT combined to form 3x composite CTVs Plan selection rates and PTV volumes were evaluated	Both methods reduced PTV compared to non-ART PTVmean volume was smaller for RepeatCT than RepeatCBCT. Repeat CBCT produced a more adequate range of PTV volumes.	[56]
	106			[6]

Table 2 (*continued*)

Study	Patient no.	Method	Findings	Ref
Murthy et al (2019)		ART using POD method using three different PTVs generated around CTV from 0.5 – 2.5 cm Optional simultaneous integrated boost for solitary tumour	ART gave Acceptable toxicity rates from ART Simultaneous integrated boost did not provide additional benefit for OS, DFS, LRC but with no added toxicity	
Webster et al (2020)	20	Retrospective planning using 3 different 3D conformal RT strategies 1. Standard − 15 mm from CTV to PTV 2. Plan of day method using 4 plans 3. Composite method (CM) with CBCT from fractions 1–3 and selection of PTVs with 5 mm or 10 mm expansion	Plan of the day improved target coverage relative to conventional treatment Target coverage reduced with composite method with 5 mm expansion No benefit for composite method with 10 mm expansion Mean irradiated volume was reduced with all strategies – most for CM with 5 mm expansion	[57]
Hunt et al (2020)	5	Magnetic resonance image guided radiotherapy with online re-optimisation assessed Initial clinical feasibility of full online planning based on anatomical change seen at each fraction, within a time frame of<60 min	Turnaround times; Median time on treatment couch of 39 min, re-contouring time of 7 min, plan re-optimisation of 5 min, treatment delivery of 9 min Intra-fractional CTV volume changes on average were 30 cc with the majority of fractions achieving adequate CTV coverage. Concluding full online adaptation is technically and clinically feasible.	[58]
Huddart et al (2021)	65	Standard planning (SP) vs Adaptive planning (AP) for MIBC receiving 36 Gy in 6 weekly treatments AP using POD from 3 plans (small, medium, and large)	AP group, 85% received at least 1 fraction using a plan other than the medium plan 39% of treatments using either a small or large plan Most patients using either an adapted plan throughout or 2 or more of the 3 plans Overall POD adaptive radiation therapy was successfully implemented across multiple centres	[59]

guided imaging without exposure to additional ionising radiation. When combined with online adaptive re-planning it provides an important tool for ART [58]. An ART application involves an online 'Adapt to shape' workflow with MR imaging pre-treatment allowing daily re-contouring and plan re-optimisation whilst the patient is on the treatment couch. Using continuous MR imaging whilst the treatment is being delivered allows real-time motion monitoring, tracking and gating. The main drawback is that as treatment times can be longer this may lead to bladder filling. Although MR-radiotherapy has potential to reduce CTV to PTV margins by adapting to intra-fraction motion, it is currently only used in clinical trials.

Dose escalation

Further dose escalation may result in better local disease control. Brachytherapy alongside radiotherapy is one established method of boosting tumour dose but this is not widely available and only suitable for highly selected cases. A systematic review by Mannion et al showed the addition of brachytherapy conferred a 5-year DSS of 75%, and a 5-year OS of 60% with an acceptable safety profile [61]. Previous adaptive and non-adaptive radiotherapy techniques have failed to demonstrate boosting dose to the tumour bed had better survival or local control [6,53]. The RAIDER trial (NCT02447549) compares whole bladder single-plan radiotherapy with standard-dose ART and a dose-escalated ART. This is expected to show whether dose escalation to the tumour improves outcomes [62].

MRI in radiotherapy

MRI has other applications in MIBC. Multiparametric MRI (mp-MRI) techniques, such as diffusion-weighted MRI and dynamic contrast enhanced MRI sequences can provide information on tumour biology such as tumour-cellularity, perfusion and hypoxia. This raises the prospect of biologically-adapted radiotherapy. Imaging biomarkers of dose–response could select patients for intensification or de-escalation of treatment. This has already shown clinical applications in head and neck cancers although is not standard of care [63].

T1 and T2-weighted MRI sequences improve tumour detection and staging. The Vesical Imaging Reporting and Data System (VI-RADS) scoring has been created as a standardized approach for imaging and reporting mp-MRI. When used in diagnostics it been validated in clinical applications to differentiating between MIBC and non-muscle invasive disease [64]. In the future the VI-RADS scoring have potential to improve radiotherapy planning by identifying the tumour bed better, especially for radiotherapy boosts.

MRI also has a role in diagnosis, especially when TURBT is not carried out. In the BCON trial only 40% of patients had maximal TURBT with over a quarter only undergoing biopsy [8]. The BladderPath study (ISRCTN 35296862) randomised patients to TURBT or to a diagnostic pathway with risk-stratified mp-MRI and aims to address whether mp-MRI can replace TURBT in MIBC staging. Early data has shown the mp-MRI approach is feasible [65].

Biomarkers

Predictive biomarkers identify patients who benefit from specific treatments. Tumour biology may guide who may benefit from radio-sensitisers, NAC or even radiotherapy over surgery. Whilst intrinsic radiosensitivity can be quantified by clonogenic survival assays studies, finding clinical applications of these are harder [66]. Tissue specimens from the BCON trial were analysed for tumour necrosis, a hypoxic 24-gene signature and basal and luminal tumour molecular subtypes. Although no long-term survival benefit was seen outcomes were significantly improved by hypoxic sensitisation in patients with marked tumour necrosis, high hypoxic gene scores and basal molecular subtype [67].

Low expression of the DNA damage response protein MRE11 was associated with worse cancer-specific survival compared to high expression. In a clinical application high MRE11 expression in the radiotherapy cohort had a significantly better cancer-specific survival compared with the high expression cystectomy cohort [68]. When tissue specimens from the BCON and BC2001 trials were re-examined they were unable to successfully validate MRE11 as a reproducible predictive biomarker of radiation-based bladder preservation success [69].

Conclusion

TMT for MIBC is an ever-evolving field. Current recommendations are for TURBT, neo-adjuvant chemotherapy with cisplatin and gemcitabine and hypofractionated radiotherapy with radiosensitisers. Recent developments in adaptive radiotherapy, dose escalation and the use of MRI-based imaging may improve tumour coverage and normal tissue sparing. We await the results of clinical trials that will answer these questions. Future developments in biological adaptive RT and the use of biomarkers is likely to further establish TMT as an effective and well-tolerated treatment for MIBC empowering patients with a real choice between surgery or preserving their bladders.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: R. Portner – No conflicts of interest. A. Bajaj – No conflicts of interest. T. Elumalai – No conflicts of interest. V. Murthy - No conflicts of interest. H. Nightinghale – No conflicts of interest. K. Patel – No conflicts of interest. P. Sargo - No conflicts of interest. R. Huddart was the principle investigator of the BC2001, RAIDER and HYBRID trials. Y. Song has received honorarium from Bayer and is on the advisory board for Merck. P. Hoskin was the principle investigator of the BCON trial but has no commercial conflicts of interest. A. Choudhury has the following declarations; Research funding from Elekta AB, CR-UK, NIHR, Prostate Cancer UK and MRC. Honoraria from ASCO, ASTRO, BMS, Astra Zeneca, Roche Editor in Chief Clinical Oncology.

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