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Mapping Local Failure Following Bladder Radiotherapy According to Dose

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Abstract

Aims: To determine the relationship between local relapse following radical radiotherapy for muscle-invasive bladder cancer (MIBC) and radiation dose.
Materials and methods: Patients with T2-4N0-3M0 MIBC were recruited to a phase II study assessing the feasibility of intensity-modulated radiotherapy to the bladder and pelvic lymph nodes. Patients were planned to receive 64 Gy/32 fractions to the bladder tumour, 60 Gy/32 fractions to the involved pelvic nodes and 52 Gy/32 fractions to the uninvolved bladder and pelvic nodes. Pre-treatment set-up was informed by cone-beam CT. For patients who experienced local relapse, cystoscopy and imaging (CT/MRI) was used to reconstruct the relapse gross tumour volume ($GTV_{relapse}$) on the original planning CT . $GTV_{relapse}$ D98% and D95% was determined by co-registering the relapse image to the planning CT utilising deformable image registration (DIR) and rigid image registration (RIR). Failure was classified into five types based on spatial and dosimetric criteria as follows: A (central high-dose failure), B (peripheral high-dose failure), C (central elective dose failure), D (peripheral elective dose failure) and E (extraneous dose failure).
Results: Between June 2009 and November 2012, 38 patients were recruited. Following treatment, 18/38 (47%) patients experienced local relapse within the bladder. The median time to local relapse was 9.0 months (95% confidence interval 6.3–11.7). Seventeen of 18 patients were evaluable based on the availability of cross-sectional relapse imaging. A significant difference between DIR and RIR methods was seen. With the DIR approach, the median $GTV_{relapse}$ D98% and D95% was 97% and 98% of prescribed dose, respectively. Eleven of 17 (65%) patients experienced type A failure and 6/17 (35%) patients type B failure. No patients had type C, D or E failure. MIBC failure occurred in 10/17 (59%) relapsed patients; of those, 7/11 (64%) had type A failure and 3/6 (50%) had type B failure. Non-MIBC failure occurred in 7/17 (41%) patients; 4/11 (36%) with type A failure and 3/6 (50%) with type B failure.
Conclusion: Relapse following radiotherapy occurred within close proximity to the original bladder tumour volume and within the planned high-dose region, suggesting possible biological causes for failure. We advise caution when considering margin reduction for future reduced high-dose radiation volume or partial bladder radiotherapy protocols.

Keywords: Bladder cancer radiotherapy; deformable registration; IMRT; patterns of local failure

Introduction

Radical radiotherapy is an accepted alternative to surgery (cystectomy) in selected patients with localised muscle-invasive bladder cancer (MIBC) [1,2]. Contemporary evidence indicates that radiotherapy when delivered with radiosensitisation has equivalent survival outcomes to cystectomy [3–7]. A choice between the two modalities should therefore be offered to patients where appropriate [2,8].

The bladder presents a number of technical challenges for radiotherapy [9]. It is a highly mobile target that changes size and shape. Traditionally, to compensate for this inter- and intra-fraction variation, bladder radiotherapy was delivered on an empty bladder with application of large population-based planning target volume (PTV) margins.

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Image-guided radiotherapy (IGRT), informed by soft-tissue visualisation, has led to greater confidence in ascertaining true bladder position at each fraction. This increased certainty of delivered dose to the target has led to PTV margin reduction [9]. For example, a 1.5 cm isotropic PTV margin utilising cone-beam computed tomography (CBCT) soft-tissue set-up achieves bladder target coverage in >90% of fractions [10]. IGRT has also enabled the development of adaptive radiotherapy solutions in bladder cancer to further reduce the risk of geographical miss and integral dose to surrounding normal tissue [9,11–13].

The possibility of further reducing dose to normal tissue arises with bladder tumour-focused reduced high-dose volume irradiation. Conventionally the whole bladder has been taken as the target for radiotherapy, even in the presence of unifocal disease. However, treating the tumour and sparing the normal bladder is attractive as it opens opportunity to reduce toxicity and facilitate dose escalation [14,15].

In the partial 2 × 2 factorial design of BC2001, patients were randomised to either conventional whole bladder radiotherapy or a reduced high-dose radiation volume to the bladder tumour [16]. Consistent with earlier data, it successfully showed that tumour-focused partial bladder radiotherapy could be utilised with no adverse effect on local control [17]. However, factors such as the isotropic expansion of 1.5 cm around the bladder tumour to create the PTV_{tumour}, three-dimensional conformal planning and set-up to skin or bone would invariably have left little normal bladder sparing compared with whole bladder treatment [16–18].

Intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) improves radiation conformity relative to three-dimensional conformal bladder radiotherapy techniques [10,19]. They also enable delivery of a simultaneous integrated boost [12]. Therefore, alongside IGRT and adaptive techniques, IMRT and VMAT may offer the opportunity for normal tissue sparing in tumour-focused bladder irradiation [14,15].

It remains critical to know that PTV margin reduction and highly conformal contemporary treatments do not beget an unintended decrease in tumour control. Evidence of how local failure relates to the planned and delivered bladder radiotherapy dose is lacking. In this study, we analysed the spatial and dosimetric characteristics of local failure in a high-risk bladder cancer patient population receiving tumour-focused reduced high-dose volume partial bladder radiotherapy with IMRT and IGRT to inform future protocol development in this setting.

Materials and Methods

Study Population

Patients who consented to a single-centre clinical research and ethics committee-approved phase II study assessing the feasibility of IMRT to the bladder and pelvic lymph nodes conducted in accordance with Good Clinical Practice guidelines were evaluated [20]. Eligible patients had histologically proven MIBC, with evidence of nodal involvement (N1-3) or at high risk of nodal involvement because of the presence of T3b/T4 disease or adverse high-risk pathological features. All suitable patients received neoadjuvant chemotherapy prior to radiotherapy. Radiotherapy was delivered with concomitant chemotherapy wherever possible, following reporting of the BC2001 trial [3].

Radiotherapy planning computed tomography (CT) was acquired with an empty bladder. Target structures included the bladder tumour (GTV), whole bladder ($CTV_{bladder}$), pelvic nodes ($CTV_{pelvic\ LN}$), and involved nodes ($CTV_{involved\ LN}$). The expansion margins applied and planned dose levels are summarised in Table 1.

Treatment was delivered with an empty bladder using CBCT verification. CBCT was registered to the planning CT initially using bony anatomy, a soft-tissue match was then applied if necessary. A systematic correction was carried out after the first three fractions. Weekly images were acquired thereafter and were reviewed with a tolerance of 3 mm. Full details of planning and delivery techniques are provided in the main study paper [20].

Study follow-up following the completion of radiotherapy included repeat cystoscopy at 3, 6, 12, 18, 24, 36, 48 and 60 months, and then annually thereafter as clinically appropriate. A chest X-ray was carried out at 6, 18, 30, 36, 48 and 60 months. Cross-sectional imaging (CT chest, abdomen, and pelvis ± magnetic resonance imaging [MRI] pelvis) was carried out at 12 and 24 months. Additional follow-up visits, including cross-sectional imaging, was permitted at the physician's discretion and as clinically indicated.

The site of relapse as determined by imaging and the surgical bladder map/cystoscopy report were collected. Only those patients with evidence of local relapse or local disease progression as determined on cross-sectional

Table 1
Applied expansion margins to create the planning target volume (PTV)

Structure	Applied expansion to create corresponding PTV (cm)					PTV	Planned dose (Gy)
	Cranial	Caudal	Lateral	Anterior	Posterior		
GTV	1.0	1.0	1.0	1.0	1.0	PTV_{tumour}	64
$CTV_{bladder}$	1.5	0.5	0.5	1.5	1.0	$PTV_{bladder}$	52
$CTV_{involved\ LN}$	0.5	0.5	0.5	0.5	0.5	$PTV_{involved\ LN}$	60
$CTV_{pelvic\ LN}$	0.5	0.5	0.5	0.5	0.5	$PTV_{pelvic\ LN}$	52

CTV, clinical target volume; GTV, gross tumour volume; LN, lymph node.

imaging (CT and/or T2-weighted MRI sequences) were included in this analysis. Baseline patient and tumour characteristics, and treatment received were recorded.

Relapse Volume ($GTV_{relapse}$) Reconstruction on Planning Computed Tomography

CT and/or T2-weighted MRI sequences identifying local relapse ($GTV_{relapse}$) were imported into the treatment planning system (Research RayStation version 9B, RaySearch Laboratories, Stockholm, Sweden) using both rigid image registration (RIR) and deformable image registration (DIR) techniques. For the RIR, relapse diagnostic images were co-registered to the planning CT scan. Manual translation of the registered images was carried out to match at the bladder base. For the DIR, hybrid-intensity and structure-based registration was carried out using the anatomically constrained deformation (ANACONDA) algorithm of the treatment planning system [21]. The hybrid-intensity DIR algorithm used image similarities (i.e. intensities) and anatomical information as provided in both image sets to control the deformation. Quality assurance of the DIR method was carried out by visual inspection. The whole bladder was selected as the controlling region of interest. To determine the dose received by the $GTV_{relapse}$ (D98% and D95%), the $GTV_{relapse}$ was reconstructed on the co-registered planning CT for both RIR and DIR approaches.

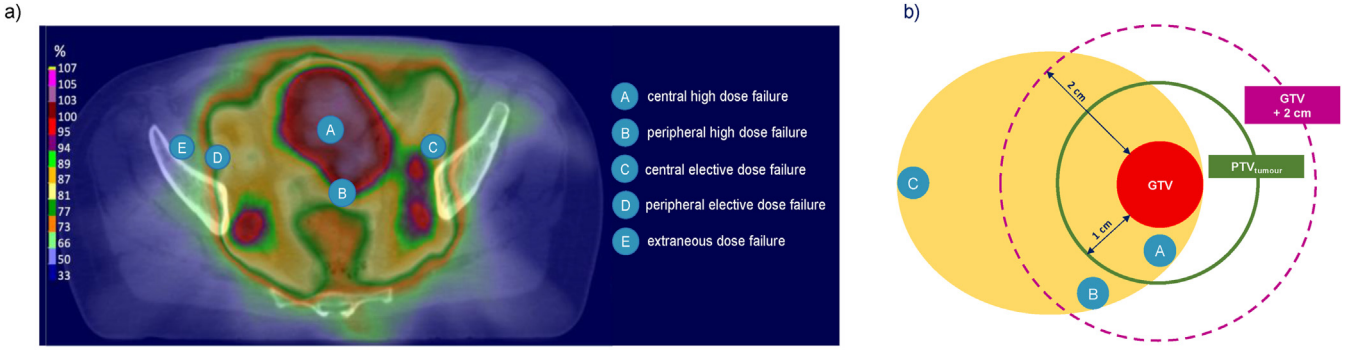
Classification of Patterns of Failure

The treatment planning system was used to identify the geometric centre of the $GTV_{relapse}$ on the co-registered (DIR) planning CT and a centroid was created at this site. The dose to the centroid was then ascertained. Failure classification type was then determined based on centroid position and dose received. Patterns of failure were classified using predefined established criteria [22]. Figure 1 summarises the pattern of failure classification.

Additional subclassification of high-dose failure within the bladder using DIR was determined a priori based on consideration of the proximity of the relapse volume to the PTV_{tumour} (Figure 1b). $GTV_{relapse}$ $\leq$1 cm of the original bladder tumour (GTV) (i.e. within PTV_{tumour}) was considered type A failure. $GTV_{relapse}$ >1 cm $\leq$2 cm of the GTV was considered type B failure. $GTV_{relaspe}$ >2 cm of the GTV, occurring in the uninvolved bladder, was considered type C failure.

Statistical Consideration

If the $GTV_{relapse}$ D98% is >95% of the prescription dose in 30% of patients, it would be assumed that failure is occurring within the high-dose treatment volume. Patient characteristics were reported using descriptive statistics. The median time to local failure was calculated using the



c)

Type of failure	A	B	C	D	E
Centroid location	High dose TV	High dose TV	Intermediate/ low dose TV	Intermediate/ low dose TV	Outside TV
Dose to 95% failure volume (D95%)	≥95% of dose prescribed to TV	<95% of dose prescribed to TV	≥95% of dose prescribed to TV	<95% of dose prescribed to TV	N/A
Possible cause	Biological	Delineation error Dosimetric failure Rapidly progressing disease	Improper risk assessment	Delineation error Dosimetric failure Rapidly progressing disease	Improper risk assessment
Possible intervention	Increase dose/sensitivity Non-technical/ Non-operator dependent	Increase CTV margin QA target delineation QA dose delivery	Increase dose/sensitivity	Increase CTV margin QA target delineation QA dose delivery	Non-technical/ Non-operator dependent

Abbreviations CTV clinical target volume; GTV gross tumour volume; PTV planning target volume; TV target volume; QA quality assurance

Fig 1. Classification of failure pattern as applied to the study cohort: (a) axial slice through pelvis showing example dose map and corresponding sites of failure, (b) subclassification of failure types A, B and C in relation to distance from original gross tumour volume (GTV), (c) description of failure type and cause (adapted from [11,22]).

Kaplan–Meier method. Comparison of the median D98% and D95% for the RIR and DIR methods was carried out using the non-parametric Wilcoxon's signed ranks significant test (with a significant level of 0.05). Analyses were carried out using SPSS v.27 (IBM, Chicago, IL, USA).

Results

Between June 2009 and November 2012, 38 patients completed radical radiotherapy as per protocol. Twenty-seven of 38 (71%) patients had evidence of disease recurrence. Eighteen (67%) patients experienced local relapse, seven (18%) patients had metastatic relapse and two patients (5%) had nodal relapse only. Seventeen of 18 patients with local relapse were evaluable based on the availability of planning scans and cross-sectional imaging. Patient demographics, tumour characteristics and relapse characteristics of these 17 patients are summarised in Table 2. The median time to local failure was 9.0 months (95% confidence interval 6.3–11.7 months). At the time of analysis, 12/17 (71%) patients had died; 9/12 (75%) patients died of metastatic bladder cancer and 3/12 (25%) patients died of other causes. Of the 5/17 (29%) patients alive, three patients were disease free.

The median volume of the $GTV_{relapse}$, contoured on the imported relapse imaging, was 18.2 cm^3 (range 4.7–215.8 cm^3).

Using the RIR approach, the median $GTV_{relapse}$ D98% was 54.3 Gy (range 34.5–64.0 Gy), 84.9% (range 54.0–99.9%) of the prescribed dose; the mean $GTV_{relapse}$ D98% was 54.8 Gy (±8.0 Gy standard deviation), 85.6% of the prescribed dose. The median $GTV_{relapse}$ D95% was 55.15 Gy (range 38.3–64.2 Gy), 86.0% (range 60.0–100.2%) of the prescribed dose; the

Table 2
Patient and tumour characteristics at baseline and relapse

Baseline characteristic		**N (%)**
Median age (range)	68 years (51–87 years)	
Gender	Male	14 (82)
	Female	3 (18)
Histological differentiation	Poor	17 (100)
	Moderate	0
	Well	0
Clinical T stage	T2	6 (35)
	T3	9 (53)
	T4	2 (12)
Clinical N stage	N0	8 (47)
	N1	4 (23)
	N2	3 (18)
	N3	2 (12)
Chemotherapy	Neoadjuvant	14 (82)
	Concurrent	9 (53)
	Neoadjuvant and concurrent	6 (35)
	None	0
Residual mass prior to radiotherapy*	Yes	12 (71)
	No	5 (29)
Relapse characteristics		**N (%)**
Relapse clinical T stage	CIS only	3 (18)
	Ta-T1	4 (23)
	T2	8 (47)
	T3	1 (6)
	T4	1 (6)
CIS adjacent to relapse MIBC/non-MIBC	Yes	5 (29)
	No	9 (53)
	N/A	3 (18)
Relapse imaging modality	CT	13 (76)
	MRI	2 (12)
	Both CT and MRI	2 (12)
Management of disease relapse	Salvage radical cystectomy	4 (23)
	Palliative systemic chemotherapy	3 (18)
	Intravesical BCG	3 (18)
	Best supportive case	7 (41)

BCG, Bacillus Calmette-Guerin;
CIS, carcinoma in situ;
CT, computed tomography; MIBC, muscle-invasive bladder cancer; MRI, magnetic resonance imaging.
* Maximal transurethral resection of the bladder tumour prior to radiotherapy was evident in 5/17 (29%) patients.

mean $GTV_{relapse}$ D95% was 55.9 Gy (±7.4 Gy standard deviation), 87.3% of the prescribed dose.

Using the DIR approach, the overall median $GTV_{relapse}$ D98% was 62.0 Gy (range 51.2–63.5 Gy), 97.0% (range 80.0–99.0%) of the prescribed dose; the mean $GTV_{relapse}$ D98% was 59.0 Gy (±4.9 Gy), 92.1% of the prescribed dose. The median $GTV_{relapse}$ D95% was 63.0 Gy (range 51.6–63.7 Gy), 98.4% (range 81.0–99.5%) of the prescribed dose; the mean $GTV_{relapse}$ D95% was 59.8 Gy (±4.7 Gy), 93.4% of the prescribed dose.

The difference in the mean $GTV_{relapse}$ D98% between the RIR and the DIR methods was statistically significant (54.8 Gy versus 59.0 Gy; $P = 0.005$). The difference in the mean $GTV_{relapse}$ D95% between the RIR and the DIR methods was also statistically significant (55.9 Gy versus 59.8 Gy; $P = 0.017$). Figure 2 summarises the D98% and D95% for all patients when applying each image registration method.

Patterns of Failure

With the RIR method, 7/17 (41%) patients demonstrated type A failure, 8/17 (47%) patients had type B failure and 2/17 (12%) patients had type C failure. No patients demonstrated type D or type E failures.

With the DIR method, 11/17 (65%) patients demonstrated type A failure and 6/17 (35%) patients had type B failure. No patients had type C, D or E failure. Of the 11 patients with type A failure, 7/11 (64%) patients had MIBC recurrences and 4/11 (36%) patients had non-MIBC recurrent disease. Of the six patients with type B failure, 3/6 (50%) patients had MIBC disease recurrence and the remaining 3/6 (50%) patients had non-MIBC disease recurrence. Figure 3 summarises the patterns of failure with each type of co-registration method.

Subclassification of high-dose failure within the bladder based on proximity of the relapse volume to the PTV_{tumour} identified 9/17 (53%) patients with type A failure, defined as relapse within ≤1 cm of the original GTV, 4/17 (23.5%) patients with type B failure, defined as relapse between 1 and 2 cm distance from the original GTV, and 4/17 (23.5%) patients with type C failure, defined as relapse >2 cm from the original GTV and within the uninvolved bladder. Of the nine patients with type A failure, 7/9 (78%) patients had MIBC recurrence and 2/9 (22%) patients had non-MIBC recurrence. Of the four patients with type B failure, 1/4 (25%) had MIBC recurrence and 3/4 (75%) patients had non-MIBC recurrences. Of the four patients with type C failure, 2/4 (50%) had MIBC recurrence.

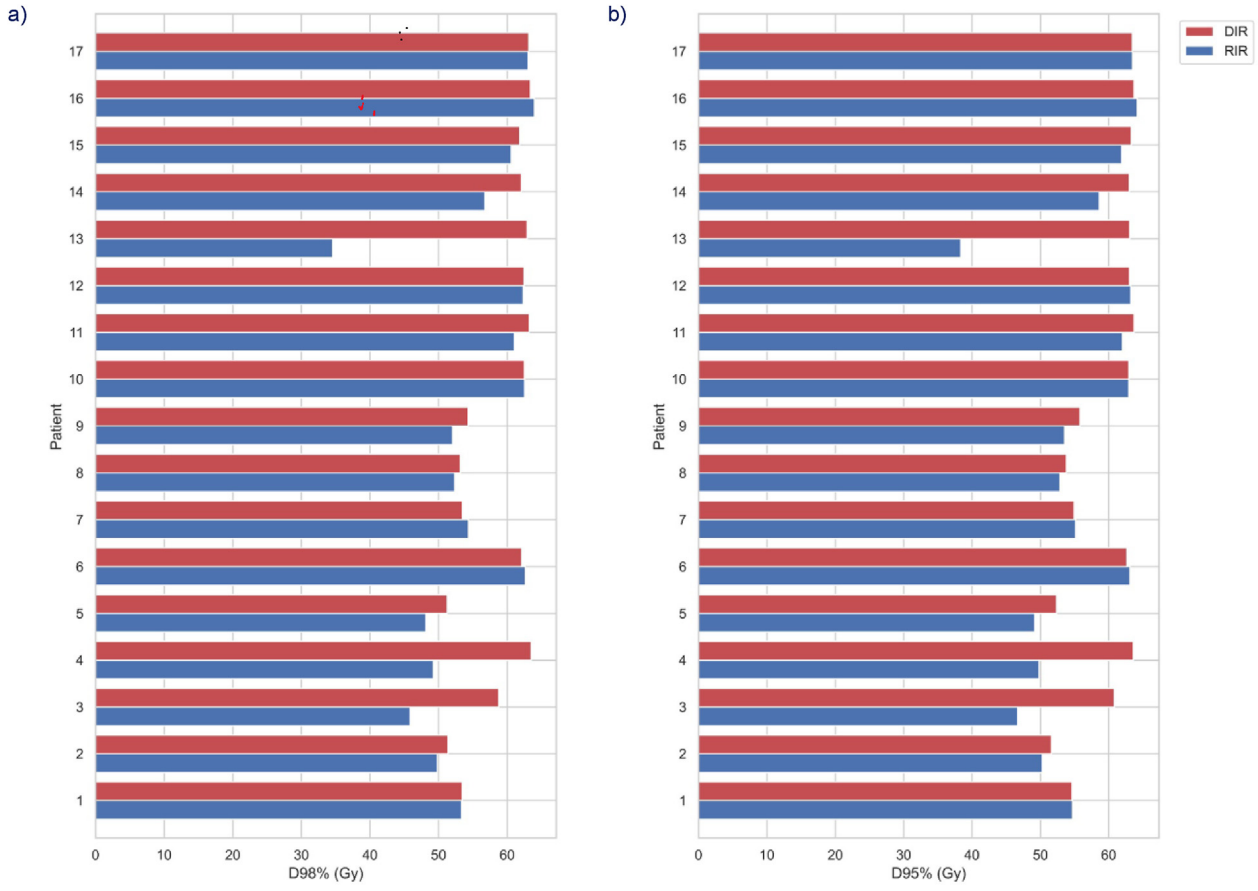


Fig 2. Individual patient $GTV_{relapse}$ (a) D98% and (b) D95% as determined by rigid image registration (RIR) and deformable image registration (DIR) methods.

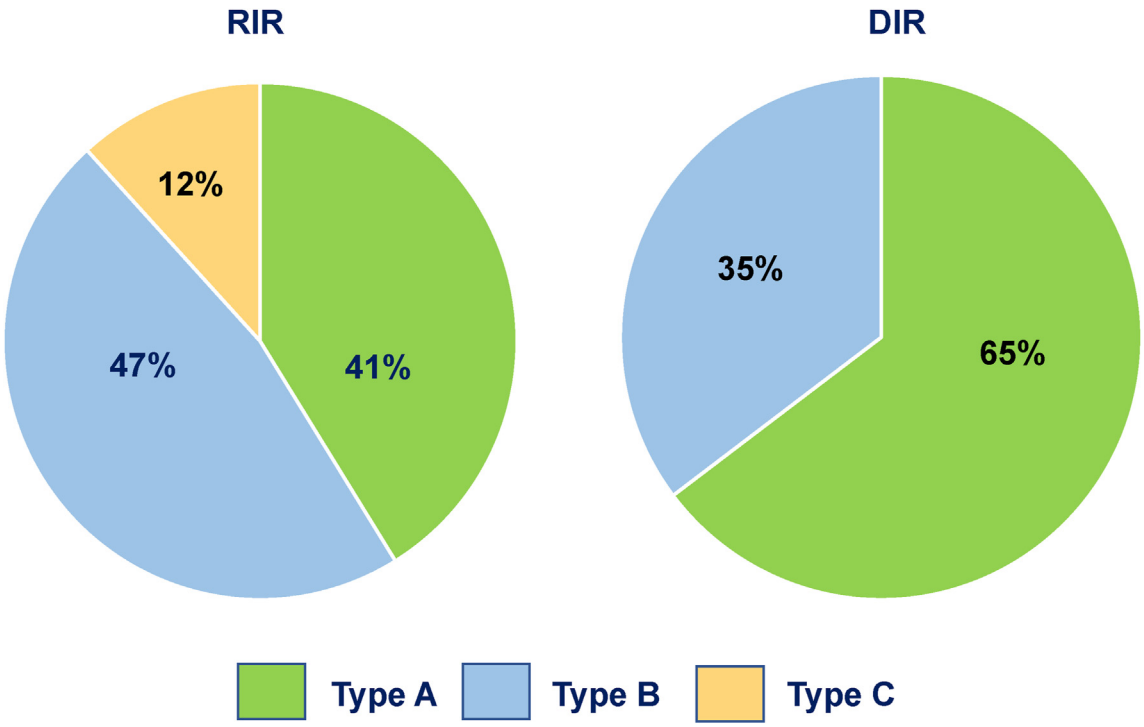


Fig 3. Failure pattern by co-registration method. RIR, rigid image registration; DIR, deformable image registration.

Discussion

To our knowledge this is the first report to determine the relationship of local failure in bladder radiotherapy with dose. Mapping patterns of local failure following radiotherapy have been reported in many tumours [22–26]. We sought to apply these methods to assess local failure in bladder cancer radiotherapy to help determine the success of a reduced high-dose volume partial bladder radiotherapy approach using reduced margins and IMRT delivery.

Our results show that almost all patients experience local recurrence within the high-dose region of the bladder. Despite the high-risk nature of our patient population, nodal relapses did not present a major cause of failure [20]. Depending on image registration method, local failure seems to occur predominantly within the original central high dose or at its periphery. This would be consistent with cystoscopic evaluation of local relapse, which identifies recurrences occurring within the same region of the bladder as the original muscle-invasive bladder tumour [27].

In this patient population, high rates of muscle-invasive bladder relapse were seen [20]. The reduced rate of invasive disease control probably reflects the high proportion of patients with locally advanced disease and radiotherapy delivered without concurrent chemotherapy prior to reporting of BC2001 [3].

We chose to apply both RIR and DIR to ascertain dose and failure type in order to quantify the potential differences likely to arise with each method. DIR has a known performance advantage over RIR and has been determined to be spatially more accurate [28]. Linking the geometries of the relapse image to the planning scan is complicated by a number of factors, including variation in patient position, image acquisition and gross anatomical changes. Despite this, DIR from CT to CT remains reliable with intensity-driven registration particularly in anatomical areas of high contrast [28]. The importance of selecting the correct method for reporting is highlighted by the fact that RIR seems to underestimate type A failures when compared with DIR.

Our subclassification scheme using DIR was devised to allow granular reporting of different high-dose failures for partial bladder irradiation with particular emphasis on being able to identify true type A failures, i.e. biological failures from type B and type C failures where technical or operator constituents may play a greater causal role. This was based on taking into consideration the distance of $GTV_{relapse}$ from the edge of the original GTV and PTV_{tumour} (Figure 1b). A 2 cm threshold was chosen to discriminate between type B and C failures because based on set-up technique adopted within the study, it is more likely to discriminate between the region of bladder receiving true elective dose rather than being marginal to the high-dose region [10,29].

The absence of CBCT data to verify the delivered dose to the original target is acknowledged to be a study limitation. It unfortunately was not possible to successfully retrieve archived CBCT data from decommissioned systems. However, extrapolating from work on whole bladder cancer radiotherapy margins, applying a 1 cm isotropic margin when treatment is delivered on an empty bladder with CBCT, whole bladder target coverage would be estimated to be 90% [10,29]. When set-up to bone is carried out, target

coverage falls to 40% [10,29]. It can be assumed therefore where CBCT soft-tissue set-up did not inform every fraction, a 1 cm margin to create the PTV_{tumour} may have incurred some element of geographical miss.

$GTV_{relapse}$ was identified and contoured on CT relapse imaging with information from the bladder map. Although CT provides high spatial resolution, it is not a reliable means of determining the extent of muscle involvement [30]. Evidence favours the use of multi-parametric MRI for local staging in bladder cancer [31–34]. The limited number of pelvic MRI scans carried out at relapse and reliance on CT delineation of $GTV_{relapse}$ may have introduced inaccuracy. The steep dose gradient of IMRT means that it could in turn result in inaccurate dose reporting to $GTV_{relapse}$.

The possibility of the $GTV_{relapse}$ delineation inaccuracies resulting in misclassification of failure type is mitigated by the centroid methodological approach described. The centroid method disregards dose to the whole volume of relapse, which has a tendency to incorrectly assign failure more peripherally. It has been shown to be superior than volumetric approaches [22,35].

The predominance of type A failures suggests that local failure is occurring because of biological reasons. It supports current strategies evaluating delivery of additional concomitant therapies or adjuvant therapies [36,37]. The possibility of overcoming potential radioresistance with tumour-focused dose-escalated partial bladder radiotherapy at conventional and moderately hypofractionated schedules is also being assessed [12,14,15,38]. Whether multi-parametric MRI could help identify this high-risk biological sub-volume for dose escalation is currently being investigated [18,31].

Type B and type C failures raise the question of a potential systematic error introduced in the radiotherapy process chain. Marginal high-dose recurrences consistent with type B failures suggest the original GTV delineation may have been underestimated or inter-fraction motion may not have been adequately accounted for, resulting in suboptimal dose delivery. It raises the question as to whether in this setting the application of a 1.0 cm isotropic margin around the original GTV was sufficient. We therefore advise caution when considering margin reduction. Type C failures may potentially represent those patients who may not be optimal candidates for a reduced high-dose volume partial bladder irradiation approach and for whom whole bladder radiotherapy may have been the preferred option. The small numbers of type C failures, however, suggest that the strategy of boosting tumour to a high dose is acceptable if geographical fidelity can be assured at planning and delivery.

The evolution of adaptive radiotherapy for bladder cancer to online techniques means that the risk of geographical miss becomes less likely [9,39]. But as these techniques use reducing margins, reporting failure in relation to spatially accurate dose information becomes even more critical if we are to move forward with our understanding of improving bladder cancer radiotherapy outcomes. Our study serves as a platform for future application in a more contemporary cohort of patients undergoing online adaptive bladder radiotherapy.

Conclusion

Most relapses following radiotherapy occurred within close proximity of the original bladder tumour volume within the planned high-dose region. This suggests that dose escalation may provide an opportunity to improve outcome. However, a significant proportion of patients seem to relapse within close proximity of the high-dose volume, suggesting target delineation inaccuracy, insufficient margin or geographical miss at treatment delivery. A combination of all these factors may play a part in contributing to local failure. Further work incorporating DIR of volumetric online imaging is planned to appreciate the impact of margin reduction with daily adaptive radiotherapy strategies.

Conflict of interest

The authors declare no conflict of interest.

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Contributions

All authors meet at least one of the criteria recommended by the IJCME. SH devised the study concept and methodological approach for analysis. HA, SBA, AD and SH carried out data interrogation and analysis. HA and SH wrote the first draft of the manuscript. All authors were involved in the review of the manuscript.

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