Failing to close the gap between evidence and clinical practice in radical bladder cancer radiotherapy

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Bladder cancer is the eleventh most common cancer diagnosis in the UK, accounting for 3% of all new cancer cases (2017) (1). It remains a major health issue with over 10,000 new cases and over 5,500 deaths a year (1, 2).

Localised muscle invasive bladder cancer (MIBC) in particular presents a large unmet clinical need. Globally radical treatment is underutilised with only 50% of eligible patients receiving curative treatment (3). One the reasons for this may be that radical cystectomy remains the perceived standard of care in MIBC, however aetiological association with smoking means pre-existing comorbidities often preclude major surgery (4). Radiotherapy was only reserved for patients deemed unfit for cystectomy. This meant historical comparisons of survival outcomes made on these unmatched cohorts were often incorrectly interpreted as favouring surgery (5, 6).

Radical radiotherapy with use of current radiosensitisers demonstrates it can achieve comparable oncological outcomes to surgery (7-12). This is supported by meta analyses and propensity matched analyses comparing radical cystectomy with radiotherapy when delivered following transuretheral resection of the bladder tumour and with concurrent radiosensitisers also known as tri-modality treatment (13, 14). Guidance on bladder cancer management published in 2015 by the UK's National Institute for Health and Care Excellence (NICE) recognises equipoise regarding definitive treatment and recommends that a choice of radical cystectomy or radiotherapy with a radiosensitiser is offered to patients for whom radical therapy is suitable (15, 16).

Overall survival even with radical treatment remains poor and has remained relatively unchanged for many years. This is due in part to the fact that evidence from large studies including randomised control trials have not translated into routine clinical practice (3, 17). The gap between clinical practice and trial evidence is unfortunately seen best in the slow uptake of neo-adjuvant chemotherapy into routine care, despite it being the only addition to radical treatment that has demonstrated clear survival benefit.

In 2003, the Advanced Bladder Cancer Meta-Analysis Collaboration established a 5% 5-year absolute survival benefit with cisplatin based neo-adjuvant chemotherapy across all stages of disease (18). The subsequent updated analysis published in 2005 confirmed these findings (18, 19), however evaluation of patient series outside the UK suggests use remains low internationally (2-20%) (3, 20, 21).

The recently published results of the audit led by the Royal College of Radiologists (RCR) benchmarking contemporary UK radiotherapy practice for the management MIBC against national guidance are similarly disappointing (22). Our survey of UK practice, reported here, also reflects slow translation of trial evidence in to clinical practice.

In 2013, The Clinical Trials and Statistics Unit at The Institute of Cancer Research (ICR-CTSU) carried out a national on-line survey of NHS consultants with specialist interest in urological malignancy. This evaluated UK radical radiotherapy practice for localised MIBC in the preceding calendar year (2012). The survey results went on to help inform the design of the RAIDER, randomised phase II trial of adaptive image guided standard or dose-escalated tumour boost tadiotherapy in the treatment of transitional cell carcinoma of the bladder (NCT02447549) (23).

26% (25/95) of invited individuals responded to the survey, reflecting response from 44% (21/48) UK radiotherapy centres. Respondents reported treating 585 patients with MIBC using radical radiotherapy in 2012.

In the table below we summarise the ICR-CTSU survey results alongside the same indices that were reported in the RCR audit which captured clinical practice during a 16-week period between 5 December 2016 and 27 March 2017 (113 days) (22).

Although response rates to our survey were lower than for the RCR audit, respondents treated more than double the number of patients. On the whole our survey results reflect a large and persistent gap between established evidence and routine UK clinical practice. Of particular concern is that, although the time frame between our survey and RCR audit spans the 2015 NICE bladder cancer management guidelines, compliance with level 1 evidence-based recommendation for the use neo-adjuvant chemotherapy and concurrent radiosensitisation remains low (15, 24).

Although it is accepted that a small proportion of patients may not be suitable for these interventions, the centre variation shown in Figure 1 illustrates treatment access inequality plays a role.

One area where an increase in uptake as seen is the application of technological advances for radiotherapy delivery. The 2012 ICR-CTSU survey identified that

although 90% (19/20) of centres reported cone beam CT (CBCT) image guided radiotherapy (IGRT) capability, only 30% (6/20) used CBCT IGRT technique in their routine bladder cancer radiotherapy delivery. The 2016-2017 RCR audit identified that CBCT use for bladder cancer patient radiotherapy had increased and was being used for treatment verification in approximately 80% of patients. It is encouraging that the wider availability of CBCT from the beginning of the decade is finding application in bladder radiotherapy. We know evidence supports the use of IGRT to reduce geographical miss and normal tissue irradiation in bladder cancer radiotherapy but it is yet to be seen how it relates to improving clinical patient outcomes (25-27). The results of randomised studies of adaptive planning such as RAIDER and HYBRID (NCT01810757) will help inform effectiveness of this approach.

The question of how best we can close the gap between existing evidence-based intervention of proven benefit and the actual care delivered to MIBC patients across the UK remains. We propose wider adoption of bladder cancer specific specialised services as a potential solution.

We know that multi-disciplinary team (MDT) input is a powerful proven tool to improve cancer outcomes and improves equality of treatment access (24, 28). This approach has already been shown to improve access to neo-adjuvant chemotherapy in MIBC (28).

Centralisation of cancer surgery provides a model demonstrating improved patient outcome when patients are treated in a high output centre (29). The centralisation of radical cystectomies for bladder cancer has significantly reduced mortality and re-intervention rates (30). Whether the same benefit would be seen if applied to non-surgical aspects of bladder cancer care is not known. The relationship between centralisation and patient outcome is complex; and we recognise that volume alone is not a measure a quality of care (31).

(32)The implementation of national radiotherapy networks is a clear opportunity to ensure uniform approach to management of bladder cancer patients and to ensure best practice both in terms of radiotherapy delivery and use of concomitant therapies (32). Perhaps this will succeed, where the guidelines alone have failed.

One way forward, therefore would be that bladder cancer patients should be identified separately from the generic group of urological cancers with tumour specific specialist

MDTs' discussion, clinicians, and bladder cancer nurse specialist input. Without this we will continue to provide a *Cinderella (dis)service* for our bladder cancer patients and should not expect widespread improvement in patient outcomes.

Table of responses to 2012 ICR-CTSU survey and 2016-2017 RCR audit

	2012 practice ICR-CTSU survey	**2016-2017 practice** RCR audit (22)
UK radiotherapy centres responding	43% (21/48)	69% (41/59)
Number of MIBC patients treated with radical radiotherapy	585	275
Patients receiving neo-adjuvant chemotherapy	50% (294/585)	43% (119/275)
Fractionation		
60-64Gy in 32f, RCR recommended (33)	43% (9/21 centres)	24% (67/275 patients)
52.5-55Gy in 20f, RCR recommended (33)	57% (12/21 centres)	47% (131/275 patients)
Other (non RCR recommended)	0%	28% (77/275 patients)
Concomitant radiosensitisation	30% (168/585 patients)*	40% (109/275 patients)

* Mitomycin C and 5-fluorouracil was the most frequently used radiosensitiser and was used by 67% of centres (14/21). Other regimens reported were gemcitabine (5 centres), carbogen and nicotinamide (1 centre), Mitomycin C and capecitabine (1 centre), 5-fluorouracil alone (1 centre) and capecitabine alone (1 centre).

Figure 1a. Neoadjuvant chemotherapy use prior to radical radiotherapy in 2012

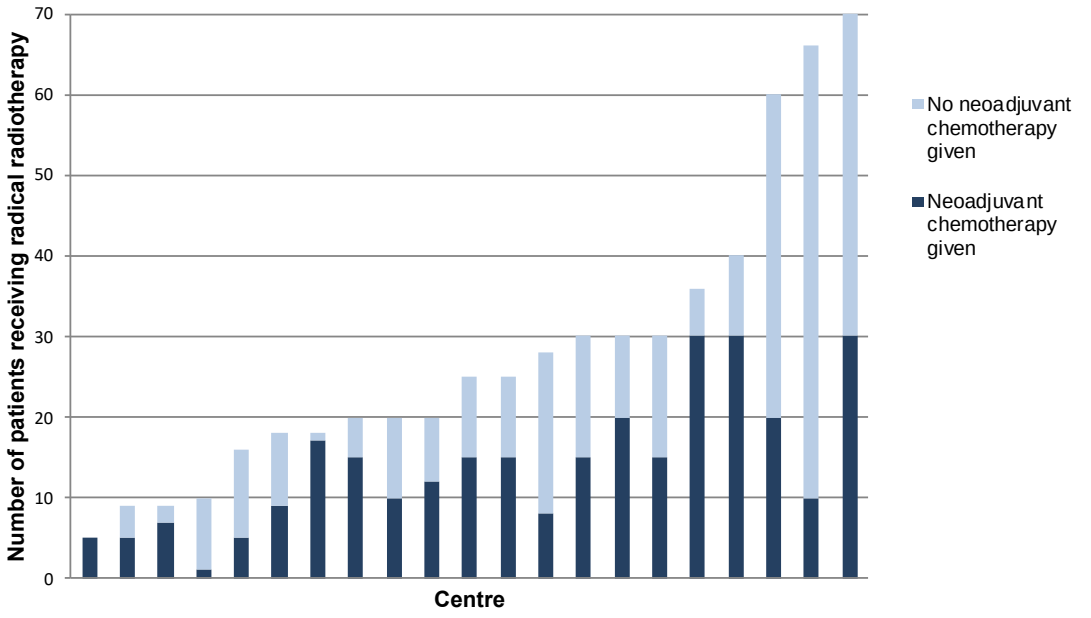
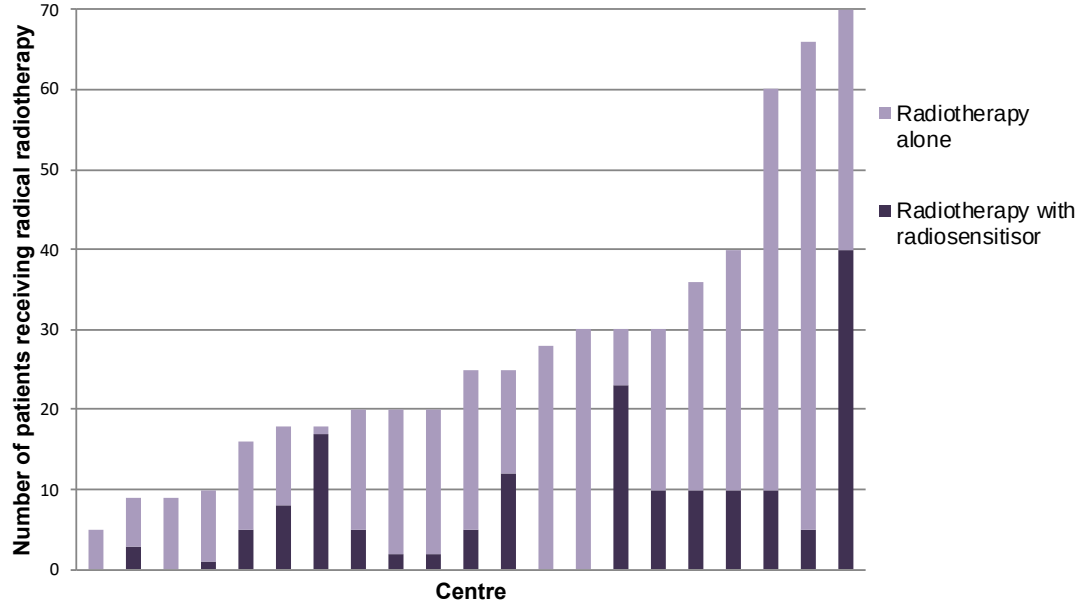


Figure 1b. Concurrent radiosensitiser use with radical radiotherapy in 2012



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