Bladder Radiotherapy: is Cinderella ready for the Ball?

Management of locally advanced muscle invasive bladder cancer (MIBC) has been dominated by Radical Cysto-prostectomy. In comparison, the use of radiotherapy has been a Cinderella; little used, often neglected, outside a few isolated pockets. Bladder radiotherapy, over recent years, has made much progress. In this special edition we pull together expertise from across the globe to examine the current status of bladder radiotherapy. This should lead us to ask; is Cinderella ready for the ball?

As discussed by Choudhury et al (1) and Ballas et al (2) in this special edition; a key stimulus to the awakening of radiotherapy has been two key UK based randomised trial that showed that radio sensitisation with either chemotherapy (5FU and Mitomycin C) (3) or hypoxic modification (Carbogen/Nicotinamide) (4) significantly improved local control and survival. These results rivalled those reported in surgical series despite being performed in older, less fit patients. More recently a meta-analysis of these two trials has shown that there may be additional benefit to using hypo-fractionated radiotherapy(5) and could thus result in a further improvement in results if adopted. This is a seemingly counter-intuitive finding is most likely due to reduced repopulation in the shorter hypo-fractionated regime given the assumed high ∝/ß ratio of bladder cancer (unless the assumptions are wrong) but is very welcome given this results in shorter treatment time, reduced resource use with no cost in increased toxicity. This win-win result has been particularly welcome during the COVID pandemic with evidence of rapid implementation at least within the UK. (6)

There is no doubt bladder radiotherapy is challenging needing precision in technique and dosing as outlined by Fontayne and colleagues (7) in their review. Much data exists of significant day to day variation in bladder size, shape and volume. In previous years this has likely led, despite the use of large CTV to PTV margins to high rates of marginal misses. Indeed, it is perhaps surprising given current knowledge of these issues that older radiotherapy techniques achieved the results that they had. The advent of daily soft tissue imaging has been a major step ward in addressing these issues and improving treatment accuracy. In 2009, I speculated that such technical innovations could leap frog bladder from a technical backwater into the forefront of technical developments. (8) The recent delivery of randomised multicentre daily adaptive ‘plan of the day’ radiotherapy trials that this, at least in part, been the case. As described by Hafeez, (9), we await with the interest to see if using this technology to undertaking dose escalated tumour boosting as used in the recent RAIDER trial will deliver further improvement in results. The field is unlikely to stand still with use of MR guided functional treatment and real time MR guided radiotherapy being especially exciting (10). (11)

The acid question is how does radiotherapy compare to Radical cystectomy in the management of MIBC?

This is a very difficult question to answer with multiple selection, stage migration and other biases between series of radiotherapy and surgery patients. It is regrettable that the one recent randomised trial failed to recruit even though the limited data shows little difference in outcomes. (12)

Radiotherapy has much to commend it; avoidance of a major operation, retention of the native bladder and likely preservation of erectile function though treatment delivery can lead to decline in health related quality of life (HRQoL) and does requiring continued careful follow up of the bladder. As reviewed by Nikapota and Appleyard, (13) the majority of bladder radiotherapy survivors maintain or improve their quality of life. The limited comparative date seems to point to this being better than after cystectomy.

Due to the biases described above comparing oncological outcomes from retrospective studies, case series and population based studies are fraught with difficulties and yield mixed results. Though some appear to favour surgery when biases are taken into account overall data shows little difference between the two modalities which is interesting as much of radiotherapy data comes from a pre chemo radiotherapy/ image guided era. Indeed, one recent meta-analysis of published series of reported studies comparing 'trimodality therapy' and surgery suggested superior outcomes from TMT. (14). An intriguing comparison can be made with the management of anal cancer (fig 1). As a result of a number of studies of chemo-radiotherapy in 1990's including the 'ACT' trials; (15) this treatment has largely replaced surgery. Chemo-radiotherapy with the same chemotherapy schedule achieves similar results in bladder cancer; so asking why the chemo-radiotherapy has not had the same influence?

The assumption of the primacy of radical cystectomy in the management of muscle invasive bladder cancer is entrenched within many both urologists and oncologists managing bladder cancer and frequently not questioned. But, as outlined by Lydia Makaroff (16) from Fight Bladder Cancer, we need to listen to our patients. Recognise this is a complex decision, ensure they have full information of the options, and support them with a multidisciplinary team. In the end, if eligible for both treatments, the ultimate decision should be left to the individual as this is most likely to lead to a satisfied patient.

The question regarding the choice of surgery or radiotherapy could be rationally answered if we had biomarkers predictive biomarkers of good or poor outcomes from surgery or radiotherapy. At one stage the use of MRE11 looked promising is this context but hasn't stood up to more detailed scrutiny (17). In this special edition Efasthiou and colleagues (18) look critically at this issue with the conclusion that though there are interesting avenues to explore we are not there yet and need to make progress in this area.

Much focus has been on either radiotherapy (or trimodality therapy) or cystectomy. However for a proportion of patients with locally advanced tumours, Murthy et al (19) ask the question as to whether, on the basis of a ground breaking Egyptian trial, the choice should be both modalities acting in tandem. This raises a series question as to how best to select such patients

One area that there is a clear role for radiotherapy is the often-neglected area of those hard to treat elderly and/or frail patients that are not fit enough for the rigours of conventional treatment. As reviewed by Henry (20) and colleagues there needs may be met by ultra- hypo fractionated radiotherapy especially, as suggested in the recent HYBRID trial, if combined with adaptive treatment

Overall, the future looks bright for radiotherapy. There is scope for further technical improvements with the advent of MR guided daily adaptive radiotherapy being particularly exciting. There is promise of further refinement of hypoxia manipulation (1) and as discussed by Wilkins and colleague's (21) great potential for immunotherapy to improve results.

A key for thus brighter future is to ensure that evidence based improvements are translated into routine clinical practice. As discuss by Varughese and (22) colleagues it remains disappointing that despite the solid evidence patients even today patients aren't being offered neoadjuvant chemotherapy and radiosensitiser treatment. Closing this gap has to be a priority for now.

If we can achieve this, we can say Cinderella is dressed and yes, she can go to the ball.

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Figure 1

Comparison of outcomes of Anal and Bladder cancer with chemo-radiotherapy

	Anal cancer	**Bladder cancer**
Key study	ACT 1	BC2001
Treatment	5-Fluorouracil and Mitomycin C Radiotherapy 60Gy/31f	5-Fluorouracil and Mitomycin C Radiotherapy 64Gy/32f
Loco regional failure	~29%	33% (any recurrence) 18% (invasive recurrence)
Overall survival	58%	50%
Salvage/alternative treatment	Abdomino-perineal resection/colostomy	Cysto/prostatectomy Ileostomy
Ref	Northover et al 2010 ()	James et al 2012 (3)