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Adjuvant treatment following radical cystectomy for muscle-invasive urothelial carcinoma and variant histologies: Is there a role for radiotherapy?

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ABSTRACT

Comprehensive molecular characterisation of muscle-invasive urothelial carcinoma and variant histological subtypes has led to the identification of recurrent driver mutations that are distinct in these aggressive subgroups of bladder cancer. While distant metastasis dominates as a pattern of relapse following radical cystectomy or chemoradiotherapy, loco-regional control rates are also suboptimal with single modality local treatment, and likewise, harbour equivocal implications on the long-term prognosis of patients. The role of adjuvant radiotherapy for optimising disease control within the pelvis is controversial, with limited evidence to support its efficacy. Herein, we present a stepwise review on adjuvant radiotherapy post-cystectomy; first, discussing the evidence to date supporting the concept that adjuvant radiotherapy is effective in targeting occult metastases within the pelvis, and adds to the benefits of adjuvant chemotherapy. Next, we outlined the principles underlying the definition of radiotherapy target volumes. To conclude, we addressed the need for appropriate patient stratification for treatment intensification, based on existing clinical models and novel molecular indices of aggression in muscle-invasive urothelial cancers and variant histological subtypes.

INTRODUCTION

While most localised bladder cancers are adequately treated with transurethral resection of the bladder tumour (TURBT) or radical cystectomy (RC) with favourable outcomes, muscle-invasive bladder cancer (MIBC) represents an aggressive phenotype with an evident need for treatment intensification. At the same time, about 10%–25% of MIBCs are urothelial carcinomas with divergent differentiation resulting in variant histological subtypes, including squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma, micropapillary, sarcomatoid, plasmacytoid, small cell, and other neuroendocrine variants.[1–4] These variant histological subtype bladder cancers are perceived to represent aggressive disease, over and above the unfavourable natural history of MIBC. Overall, these tumours have a high propensity for relapse following definitive local treatment, with the primary risk of recurrence being systemic metastasis.[5 6] However, comparable rates of loco-regional recurrence have also been observed in these subgroups, ranging from 10% to 50% depending on pathological grade, T-category, and other clinical indices. In fact, it is likely that the reported rates of pelvic relapses are grossly underestimated, since the majority of studies report on disease-free survival, which often leads to censoring of a patient at the time of distant metastasis, without having to report on concomitant or subsequent local recurrence. It is based on these arguments that investigators had chosen to examine the role of adjuvant radiotherapy in targeting loco-regional occult metastasis, but significant toxicities with historical radiotherapy techniques had inadvertently precluded its routine use. With the advent of intensity-modulated radiotherapy (IMRT) and image guidance, along with less toxic chemotherapy regimes, we propose that adjuvant radiotherapy is feasible post-RC. Here, we review existing evidence on the efficacy of adjuvant radiotherapy post-RC, including the target volumes, and suggest potential strategies for patient selection.

SEARCH STRATEGIES AND OUTCOME

We searched the PubMed and MEDLINE databases for articles published in English from 1 January, 2000, to 30 June, 2016, with the keywords ‘bladder’, ‘urothelial carcinoma’, ‘muscle-invasive’, ‘variant histology’, ‘cystectomy’, ‘adjuvant’, ‘chemotherapy’, ‘radiotherapy’, ‘clinical trials’, ‘pelvic nodes’,

'lymph node dissection', 'biomarkers', and 'genomics'. Priority was accorded to randomised clinical trials or studies in human beings. Selected references were judged on relevance, and included widely referenced and highly regarded older seminal work. Abstracts of main medical conferences were also included if survival and toxicity end points were reported.

Specific to the topic of adjuvant radiotherapy post-cystectomy, we identified seven clinical studies that fulfilled the above criteria, which comprised four randomised clinical trials and three single-institution retrospective series.

LOCO-REGIONAL RELAPSE POST-RC IS ASSOCIATED WITH ADVANCED DISEASE AND VARIANT HISTOLOGIES

As mentioned earlier, distant metastasis dominates as the pattern of relapse in the majority of urothelial carcinomas and variant histological subtype MIBCs following RC, thus supporting the role of adjuvant chemotherapy for the targeting of occult metastases. Among patients with high-risk features identified on histopathology, individuals with pathological node involvement (pN+) are often recommended for systemic treatment post-RC. Nonetheless, the risk of relapse may not be limited to systemic progression alone in this high-risk subgroup, and the likelihood of loco-regional disease recurrence within the pelvis is further determined by other clinical indices, such as pathological T (pT)- and margin-status. In particular, pT-status has been consistently shown to correlate with risk of pelvic failures based on a number of studies.[7–9] As with the SWOG 8710 randomised controlled trial, pelvic failure rates were 32% compared with 8% (p<0.0001) in the pT3-4 and pT1-2 subgroups, respectively, with the increased risk being 3.8-fold, even after adjusting for significant covariates (neoadjuvant chemotherapy, number of nodes removed, and margin status).[8] Intuitively, margin positivity would be linked to an increased risk of local recurrence, and in this regard, the serosa, ureters, and urethra represent at-risk resection regions (>10% risk of involvement).[9]

Although nodal involvement has been shown to be a strong predictor of loco-regional and distant relapses, as judged by the 29% compared with 12% local relapse rates in patients with pN+ and pN0 disease, respectively, from SWOG 8710,[8] the optimal management of pelvic nodes remains debatable to date. Of note, variant subtype MIBCs are also thought to be at risk of nodal metastasis, with reported rates of as high as 40% in some series.[4 10–14] Taken together, it would suggest that extended lymphadenectomy, which is linked to a higher detection sensitivity of pN+ disease,[15 16] features as a key determinant of outcomes post-RC. However, an improved disease control within the pelvis was not always observed with an extended procedure,[7–9] and it is possible that variations in node retrieval and analysis of pathological specimens represent significant confounders. Regardless of the ongoing controversy, it is generally agreed that patients with advanced pT- and pN- status represent a high-risk subset, since 30%–40% of individuals still suffer from pelvic relapses post-RC, despite having undergone RC at high-volume surgical centres.[7–9]

PROGNOSTIC IMPLICATIONS OF PELVIC DISEASE CONTROL

The prognostic significance of loco-regional relapse is primarily linked to the increased likelihood of concomitant or subsequent systemic progression.[17] Moreover, it is observed that patients who present with pelvic recurrence post-RC are hardly ever salvaged.[18] Such dismal natural history of pelvic recurrences may be partly explained by the high propensity for stepwise occult metastasis seeding along the para-aortic nodal chain, which would argue against the idea of oligo-recurrence within the pelvis. Collectively, these arguments highlight the critical importance of eradicating occult tumour clones from the outset.

In variant bladder cancers, the implications of improved pelvic control are harder to discern, given the subtle differences in modes of tumour dissemination between the different variant histologies. Micropapillary urothelial carcinoma has a propensity for nodal metastasis, while plasmacytoid variants tend to spread via the peritoneum.[13 15] For small cell carcinoma and neuroendocrine variants, it is often perceived that odds of systemic metastasis outweigh that of local relapse, since the majority of patients (>80%) present with locally advanced or extensive metastatic disease.[19] Nonetheless, it has been reported that patients with isolated nodal disease still enjoy superior outcomes compared to patients with extensive-stage small cell carcinoma of the bladder, which would suggest an advantage of optimising local control in this variant subtype.[19] Loco-regional control is also, if not more, critical in other variant histological subtypes such as sarcomatoid carcinoma, squamous cell carcinoma, and adenocarcinoma.

ADJUVANT STRATEGIES FOR REDUCING LOCO-REGIONAL RELAPSE

A competing strategy to adjuvant chemotherapy or radiotherapy in patients with MIBC and variant histologies would be the use of neoadjuvant cisplatin-based chemotherapy.[20] It is estimated that neoadjuvant chemotherapy confers a 5% overall survival and 9% disease-free survival benefit at 5 years, consistent across all pathological subtypes.[21] Apart from targeting occult metastatic tumour clones, upfront systemic treatment also appears to improve loco-regional disease control by a magnitude of 5% (95% CI 1% to 9%, p=0.012).[20] The effect of chemotherapy on the primary tumour is not surprising, considering that 20%–40% of tumours develop a pathological complete response following MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) or GC (gemcitabine, cisplatin) chemotherapy.[5 22–24] However, it has to be cautioned that reduction of local relapse by neoadjuvant chemotherapy has not been uniformly observed in all trials. For example, the International Collaboration of Trialists reported no difference in local relapses or salvage

cystectomy rates between patients who received neoadjuvant CMV (cisplatin, methotrexate, vinblastine) and those who did not.[6] Consequently, there is the prevailing fear that adoption of systemic treatment upfront could lead to a delay in definitive treatment for non-responders. On this note, biomarkers such as mutations in *ERCC1* and other DNA repair genes have been reported to predict for sensitivity to cisplatin-based chemotherapy, and thus would be useful tools to identify patients suitable for neoadjuvant chemotherapy *a priori*.[25–27] Nonetheless, even with substantial rates of pathological complete response, gains in overall survival have been modest at best (approximately 5%), thus arguing the need for treatment intensification in the adjuvant setting, perhaps in the form of radiotherapy.

While it is reasonable to expect that adjuvant chemotherapy would exert the same effects as neoadjuvant chemotherapy, a recurring theme in this setting points to the reality that many MIBC patients suffer from severe complications after RC, which in turn hinders the delivery of adjuvant chemotherapy. It is partly for the same reason that several studies investigating the role of adjuvant chemotherapy have suffered from poor accrual and premature closure. Consistent with these observations, the meta-analysis of adjuvant chemotherapy trials failed to draw any conclusive evidence regarding its efficacy.[28] Therefore, we are presented with the conundrum of rethinking adjuvant strategies that harbour equipoise in efficacy, but perhaps present better tolerability than adjuvant chemotherapy.

IS ADJUVANT RADIOTHERAPY EFFECTIVE IN OPTIMISING LOCO-REGIONAL CONTROL?

Arguably, there is limited evidence on the efficacy of adjuvant pelvic radiotherapy, but based on the findings of few randomised trials and retrospective series, it would seem that the primary advantage of adjuvant radiotherapy relates to improved local control, and possibly disease-free survival (table 1).[29–36]Notably, Zaghloul *et al* investigated the role of adjuvant radiotherapy to the cystectomy bed and nodal basins, albeit using a variety of fractionation schedules, in patients with pT3-T4 MIBC, and observed substantial gains in local control rates amounting to 37%–43% compared with patients who underwent RC alone. Benefits of adjuvant radiotherapy were observed across all histological subtypes.[34 35] More recently, the same group demonstrated that the addition of adjuvant radiotherapy to chemotherapy, delivered in a sandwich fashion, led to significantly improved pelvic control rates than adjuvant chemotherapy alone. Employing a hyperfractionation scheme of 45 Gy in 30 twice-daily fractions, the authors reported 3-year loco-regional failure-free rates of 87% for radiotherapy alone and 96% for chemoradiotherapy compared with 69% for chemotherapy alone.[33 36] To add, there is also supportive evidence for a dose response in this setting. As observed by Cozzarini *et al*, adjuvant radiotherapy doses of ≥50.4 Gy (range of 50.4–66 Gy) led to a higher local control rate of 88.4% compared with 77.8% in patients treated with RC alone, and this covariate was significant even on multivariable analysis.[30]

That said, the community is also cognisant that adjuvant pelvic radiotherapy following RC is not without risks of severe normal tissue complications. The historical radiotherapy techniques of large anterior-posterior or anterior-parallel opposed fields resulted in severe late gastrointestinal effects, including ileal and rectal stenosis and obstruction in 10%–30% of patients.[34] Intestinal fistula was infrequent, but fatal. However, complication rates with RC alone were also substantial. As reported by Madersbacher *et al* in 417 patients with an ileal conduit post-RC, bowel and stomal complication rates occurred in 24% of patients, with a median onset of 36 months and 54 months, respectively.[37] Hence, like with modern surgical techniques (eg, laparoscopic cystectomy and neo-bladder creation), it is reasonable to expect that with the advent of IMRT and image guidance, radiation oncologists are now enabled to deliver doses of at least 50 Gy to high-risk target volumes within the pelvis, while avoiding excessive doses to normal tissue organs. Inferring from the results of pelvic IMRT in the treatment of other tumours, rates of severe late gastrointestinal or genitourinary toxicities are exceedingly low.[38–40] Rightfully so, pelvic IMRT has led to renewed interest in adjuvant radiotherapy for high-risk individuals with MIBC or variant histologies.

RADIOTHERAPY TARGET VOLUMES BASED ON RELAPSE PATTERNS

Robust radiotherapy quality assurance is necessary in order to achieve the best clinical outcomes, both in terms of tumour control and normal tissue complications. Measures relating to this aspect include ensuring accuracy in target contouring. Defining the at-risk clinical target volumes (CTVs) is wholly dependent on the observed patterns of relapse in the pelvis, along with consideration of the immediate echelons of nodal drainage against the likelihood of skipped nodal metastases. Patterns of pelvic recurrences in high-risk individuals post-RC have been remarkably consistent across studies[9 18 41] (figure 1). The predominant sites of relapse are localised to the pelvic nodal stations, which is not unexpected, given the rich vascular and lymphatic supply to the bladder. In patients with negative margins, iliac and obturator lymph nodes represent the most frequently involved sites[9 18] (figure 1). Failures in the cystectomy bed and recto-sigmoid nodal station were infrequent, except in the instance of positive serosal margin[9 18] (figure 1).

On this note, a panel of international experts comprising of urologists and radiation oncologists agreed on a consensus guideline for volume delineation, which considers surgical margin status. For the coverage of at-risk nodal regions, while a CTV encompassing the iliac (common, external, and internal iliac) and obturator lymph nodes would sufficiently treat 76% of patients

Table 1 Adjuvant RT studies in bladder cancer

Study	Sample size	Patient characteristics	Histology	Cohorts	RT fractionation scheme	Median follow-up duration (mo)	OS	DFS	LCR/LRFS	DMR/DMFS	Acute GI toxicity ≥G3	Late GI toxicity ≥G3	Late GU toxicity ≥G3
Randomised controlled trials													
Zaghloul *et al*.[35] (1986)	106	pT3a-4a pN0-2	UC and variants	Observation *vs* Adjuvant RT (with or without misonidazole)	37.5 Gy/30fr (TID)	34	*NR*	2-y=33% *vs* 65%; p<0.0001	(LCR) 2-y=54% *vs* 93%; p = *NR*	(DMR) 2-y=6.6% *vs* 5.5%; p = *NR*	*NR vs* 5% (vomiting); *NR vs* 29% (diarrhoea)	*NR vs* 0%	‡No difference at 2y
Zaghloul *et al*.[34] (1992)	236	pT3a-4a pN0-2	UC and variants	Observation *vs* Adjuvant TID RT *vs* Adjuvant OD RT	37.5 Gy/30fr (TID); 50 Gy/25fr (OD)	69	*NR*	5-y=25% *vs* 49% *vs* 44%; p<0.0001	(LCR) 5-y=50% *vs* 87% *vs* 93%; p<0.0001	*NR*	*NR vs* 5% *vs* 3% (vomiting); *NR vs* 19% *vs* 19% (diarrhoea)	*NR vs* 10% *vs* 4% (late enteritis to intestinal fistulae)	‡2-y=5% *vs* 4% *vs* 12% (upper obstructive uropathy); 3.5% *vs* 2% *vs* 12% (renal impairment)
El-Monim *et al*.[31] (2013)	100	cT2-4a	UC & variants	Neoadjuvant RT *vs* Adjuvant RT	50 Gy/25fr	32	3-y=53.4% *vs* 51.8%; p = NS	3-y=47.4% *vs* 34.1%; p = NS	(LRFS) 3-y=89.3% *vs* 80.6%; p = NS	(DMFS) 3-y=61.5% *vs* 55.7%; p = NS	*NR*	2% *vs* 4.5%	*NR*
Zaghloul *et al*.[33 36] (2016)	198	pT3-4 pN0-2	UC & variants	Adjuvant RT *vs* Adjuvant chemotherapy† *vs* Adjuvant chemo#-RT	45 Gy/30fr (BID)	19	3-y = *NR vs* 51% *vs* 64%; p = NS	3-y=63% *vs* 56% *vs* 68%; p = NS	(LRFS) 3-y=87% *vs* 69% *vs* 96%; p<0.01	(DMFS) 3-y = *NR vs* 79% *vs* 73%; p = NS	*NR*	8% *vs* 2% *vs* 7%	*NR*
Retrospective													
Reisinger *et al*.[32] (1992)	78	pT2 G3-4 or pT3-4a or pN+	*NR*	Neoadjuvant RT *vs* Neoadjuvant RT + Adjuvant RT	(Neoadjuvant) 5 Gy/1fr; (Adjuvant) 45 Gy/25fr	52	5-y=57% (pT2 G3-4), 56% (pT3a), 39% (pT3b), 50% (pT4/pN+)	*NR*	(LCR) 5-y=92.5% (overall)	*NR*	*NR*	8% *vs* 37% (bowel obstruction)	13% *vs* 10% (urethral stricture/stoma stenosis)
Cozzarini *et al*.[30] (1999)	165	pT2-T4a pN0-2	UC	Observation *vs* Adjuvant RT	45–66 Gy	36	*NR*	5-y=35% *vs* 36.2% (<50.4 Gy) *vs* 44.6% (≥50.4 Gy)	(LCR) 5-y=77.8% *vs* 83.5% (<50.4 Gy) *vs* 88.4% (≥50.4 Gy)	*NR*	*NR vs* 2%	*NR*	*NR*
Bayoumi *et al*.[29] (2014)	170	pT3-4 pN0-1	UC and variants	Observation *vs* Adjuvant RT	50 Gy/25fr ±10 Gy/5fr boost (positive margin)	47	5y=38% *vs* 52%; p = NS	5-y=40% *vs* 65%; p=0.04	(LCR) 5-y=45% *vs* 67%; p<0.001	(DMR) 5-y=38% *vs* 39%; p = NS	*NR vs* 19% (diarrhoea); *NR vs* 13% (proctitis)	*NR vs* 8% (small bowel obstruction)	*NR*

BID, twice daily; DFS, disease-free survival; DMFS, distant metastasis-free survival; DMR, distant metastasis rate; GI, gastrointestinal; GU, genitourinary; LCR, local control rate; LRFS, loco-regional failure-free survival; NR, not reported; NS, not statistically significant; OD, once daily; OS, overall survival; RT, radiotherapy; TID, thrice daily; UC, urothelial carcinoma.
#2 cycles of gemcitabine/cisplatin given before and after RT.
†4 cycles of gemcitabine/cisplatin
‡RTOG toxicity grading was not used in this study.

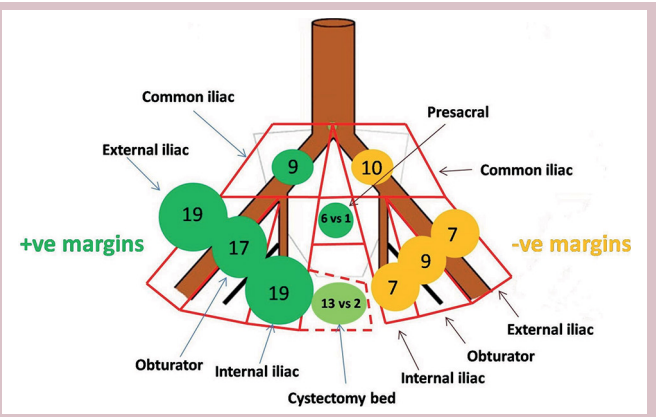

Figure 1 Illustration of common sites of pelvic relapse post-radical cystectomy in patients with ≥pT3 tumours,[9 18] stratified by margins status - (L) positive margin, (R) negative margin. Radiotherapy borders are superimposed, based on the consensus guidelines[42]. Inclusion of cystectomy bed is recommended in patients with positive margin. Values represent percentages.

with ≥pT3-status and negative margin disease, expansion of the CTV to include the presacral lymph nodes would increase the likelihood of pelvic control by a further 3%.[18] In the instance of positive serosal surgical margin, where risk of recurrence in the cystectomy bed could be up to 13%,[18] it is recommended to include the cystectomy bed in the CTV.[42] This contouring atlas is currently being prospectively validated in a phase II randomised trial (NRG-GU001, NCT02316548, Clinicaltrials.gov) of adjuvant pelvic IMRT versus observation alone in high-risk patients post-RC (defined as pT3-4pN0-2). Patients with mixed urothelial carcinoma and variant histologies are allowed in this study, which affirms the impression that variant histological subtype bladder cancers are more clinically aggressive. Patients with any neo-bladder creation are excluded, for fear of radiation effects to the small bowel and subsequent failure of the neo-bladder. Through this effort, it is hoped that homogenous, high-quality radiotherapy is ensured across all study centres participating in the trial.

NOVEL RISK STRATIFICATION INDICES FOR ADJUVANT RADIOTHERAPY

As aforementioned, the criteria for defining high-risk disease in NRG-GU-001 is largely based on observations from few prospective and retrospective series, suggesting that advanced pT- and pN-categories were strongly associated with loco-regional relapse. Others have also proposed novel prognostic models incorporating additional clinical indices such as lymph node yields and margin status. Perhaps, the most robust clinical model to date refers to the report by Christodouleas *et al*, in which the authors stratified patients into low-risk, intermediate-risk and high-risk categories based on the pT- and pN-status, and lymph node yields. Briefly, pT0-2 was considered low-risk disease, while pT3-4, pN0 and ≥10 nodes retrieved was classified as intermediate-risk, and pT3-4, pN+ or <10 nodes retrieved would constitute high-risk disease.[43] This model was subsequently validated across independent series from the USA, Europe, and Seoul, thus supporting its clinical utility.[9 44 45]

MUTATIONAL LANDSCAPE OF MUSCLE-INVASIVE AND VARIANT SUBTYPE BLADDER CANCERS

Furthermore, through a number of comprehensive molecular profiling studies that have interrogated the genome, epigenome, and transcriptome, we now possess an adequate overview of the mutational landscape of urothelial and other variant carcinomas of the bladder.[46–49] Conventionally, urothelial carcinoma is thought to originate from the transitional epithelium. Epithelial cells that reside within this microenvironment are intrinsically slow-cycling, which could account in part for the progressive accumulation of mutational events in these cells following short-term exposure to known carcinogens.[50] The Cancer Genome Atlas (TCGA) consortium first reported in 131 chemotherapy-naïve bladder tumours, high frequencies of recurrent driver mutations (>10%), which included genes involved in cell cycle (eg, *CDKN1A*, *CDKN2A*, *RB1*), chromatin remodelling (*ARID1A*, *KDM6A*) and kinase signalling (*PIK3CA*, *EGFR*, *FGFR3*) pathways.[51] Transcriptomic profiling next identified distinct expression patterns that are linked to papillary or squamous differentiation. Crucially, more than two-thirds of the profiled mutations in the tumours could be matched to targeted therapeutics, thus justifying the clinical relevance of these molecular studies. In the same vein, two other translational studies that specifically focused on patients with advanced disease confirmed the findings of TCGA, but added observations of an enrichment of *ERBB2* mutations in micropapillary variants, and novel mutations in the gene *UNC5C*.[48 49] Moreover, Yap *et al* observed that somatic mutations in the DNA repair genes (*ATM*, *ERCC2*, *FANCD2*, *PALB2*, *BRCA1*, or *BRCA2*) also predicted for better relapse-free survival, which is in agreement with previous studies showing the link between mutated *ERCC2* and an enhanced response to cisplatin in urothelial carcinoma.[26 52] Pertaining to variant histologies, which were excluded from the TCGA study, a more recent report highlighted the high prevalence (>80%) of recurrent loss-of-function mutations in the *CDH1* gene in plasmacytoid tumours.[46] It is a renowned fact that plasmacytoid variants are associated with more advanced stages of disease, therapeutic resistance, and consequently, habour increased risks of local and systemic recurrences.[1 53 54] With these novel findings, we now have insights of the molecular pathways that potentially underpin the aggression of these tumours.

COMBINATORIAL CLINICO-MOLECULAR STRATIFICATION MODEL FOR ADJUVANT TREATMENT

In the background of molecular studies from TCGA and other consortiums, it is perhaps timely to advocate for an all-encompassing risk-stratification tool, which considers clinical, pathological, and molecular indices. While such

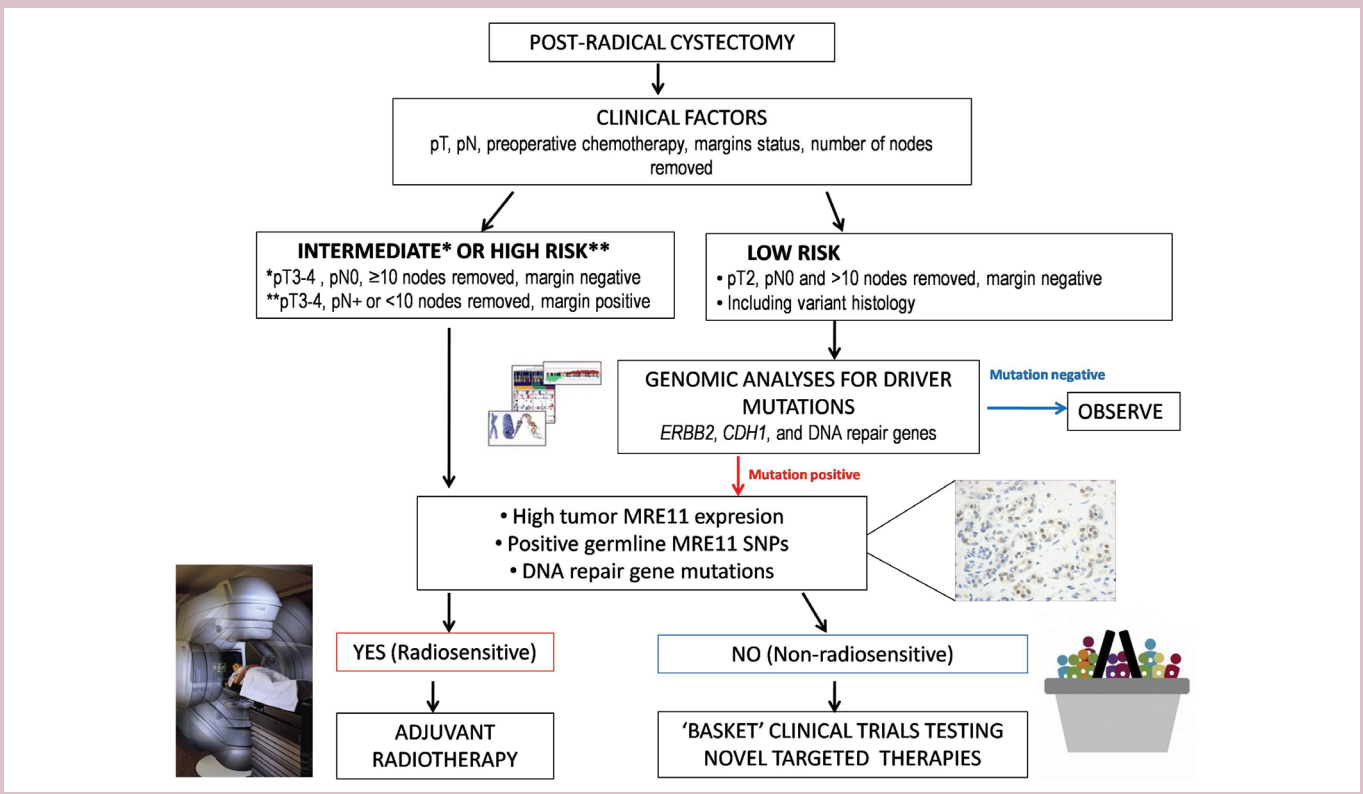

Figure 2 Proposed combinatorial risk-stratification model for the adjuvant treatment of post-radical cystectomy patients. SNPs, single-nucleotide polymorphisms.

a model is currently lacking, biomarkers such as *MRE11* tumour expression and germline variants have been proposed to predict for sensitivity to radiotherapy, but not outcomes following RC.[55 56] If validated, it is reasonable to assume that these predictive biomarkers are also applicable to select patients for adjuvant radiotherapy. An intuitive approach could be the following: foremost, identifying at-risk individuals based on the clinical model proposed by Christodouleas *et al*,[43] with an added layer of molecular stratification in patients with 'low-risk' urothelial carcinoma and variant histologies whose tumours are enriched for driver mutations in the *ERBB2*, *CDH1* and DNA repair genes; next, depending on their germline or tumour *MRE11* functional status, patients would be assigned to either adjuvant radiotherapy (radiosensitive) or basket novel targeted therapeutics trials (non-radiosensitive; figure 2).

FUTURE DIRECTIONS

The fervent embrace of immunotherapy by the oncology community in recent times is certainly palpable, as evidenced by the number of immune checkpoint inhibitor trials across numerous tumour sites.[57–63] In keeping with the efficacy of intravesical BCG in inducing an immunogenic response in the bladder post-TURBT, it would be plausible to think that anti-programmed death-1 (PD-1) or anti-programmed death ligand-1 (PD-L1) inhibitors are effective therapeutic agents in bladder cancers. On this note, nivolumab and atezolizumab have been approved in the management of treatment-refractory metastatic urothelial carcinoma.[64 65] Going forward, perhaps an approach worth considering could entail combination nivolumab or atezolizumab with adjuvant radiotherapy post-RC. Alternatively, genomic and transcriptomic profiling have also revealed novel molecular targets in advanced and variant bladder cancers, which could also pave the way for synergistic therapeutic combinations of small molecular inhibitors and radiotherapy.

CONCLUSION

There is a pressing need for treatment intensification in patients with advanced MIBC and variant histological subtype bladder cancers. However, it remains to be determined if adjuvant radiotherapy features as an integral component in the next phase of treatment regimens for these high-risk individuals. Understandably, there is widespread scepticism regarding its role, which is tied to the concern of significant toxicities with radiotherapy post-RC. Moreover, the favoured approach of neo-bladder creation post-RC only serves to hinder the reinvigoration of adjuvant radiotherapy. We await to see if this trend in surgical practice eventually affects the recruitment of patients onto NRG-GU-001. Perhaps, it is timely to remind all that optimising disease control in this high-risk subgroup is equally paramount to quality of life issues. Moreover, preliminary results of randomised controlled trials have been promising. Herein, we

presented arguments for better patient selection, and fewer toxicities with modern radiotherapy techniques, both of which ought to support the re-evaluation of this treatment modality in the adjuvant management of bladder cancer.

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