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From a Storm to Sunshine: The Future of Bladder-sparing Therapy is Bright

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Trimodal therapy (TMT), which combines optimal transurethral resection of bladder tumor (TURBT) and concurrent chemoradiotherapy, has attracted much interest for the management of patients with muscle-invasive bladder cancer (MIBC), as it allows bladder preservation while ensuring similar oncological outcomes to radical cystectomy [1]. To achieve such oncological results, local control is of utmost importance, and may include salvage cystectomy in cases of invasive local recurrence. Salvage cystectomy rates as high as 10–40% have been reported for contemporary, often heterogeneous, TMT series [2], with local relapse frequently occurring at the initial site of disease, which could be defined as the index lesion by analogy with other solid malignancies including prostate cancer [3]. Consideration of the radiotherapy (RT) dose-response effect as suggested in several series [4] provides a rationale for increasing the focal radiation dose to the index tumor when delivering RT. The main challenge in dose escalation for focal radiation during bladder RT is related to internal motions in the bladder that lead to changes in the position, volume, and shape of the organ between each fraction (inter-fraction) and within a fraction (intra-fraction). Image-guided adaptive RT has been developed to address such variation and involves modification of the dose distribution before and even during each RT fraction. One of the most robust adaptive strategies is the "plan of the day" (PoD) approach, in which two planning computed tomography scans are performed to build a library of treatment plans with varying planning target volumes created to cover the range of expected filling and positional variations in the bladder.

In this issue of *European Urology*, Huddart et al [5] report results from RAIDER, a phase 2 noncomparative randomized controlled trial assessing the feasibility (stage I) and safety (stage II) of focused dose escalation to the index tumor and a reduced dose to the uninvolved bladder using image-guided adaptive RT via a PoD approach for patients with T2–4a N0 M0 MIBC. Patients were randomized to standard whole-bladder RT, standard-dose adaptive RT, or dose-escalated adaptive RT (DART) with the possibility of two radiation schedules in either 20 fractions or 32 fractions. The primary outcome for stage I was the proportion of DART patients for whom the RT plan could adhere to the radiation dose constraints according to the protocol. For stage II of the trial, the primary outcome was the RT-related Common Terminology Criteria for Adverse Events (CTCAE) grade $\geq$3 late toxicity rate at 6–18 mo after RT. A total of 345 patients were included, most of whom had a cT2 tumor (81%); most of the patients (70%) received concurrent radiosensitizing therapy, while 49% received neoadjuvant chemotherapy. Results for stage I of the study demonstrated that DART could be delivered successfully in more than 80% of patients, independent of the radiation schedule. This result is in line with other prospective DART series, in which the vast majority of patients successfully received such a regimen [6,7]. In stage II, radiation-related grade $\geq$3 CTCAE toxicity following DART was <1% (90% confidence interval [CI] 0.1–7.9%) for both fraction schedules, confirming that

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>20% toxicity with DART could be ruled out according to the upper 90% CI bound. In the DART arm, the 2-yr cumulative incidence of RTOG grade ≥3 toxicity was 2.4% (95% CI 0.8–7.4%) for 20 fractions and 1.0% (95% CI 0.1–6.7%) for 32 fractions. These data compare favorably with the BC2001 results (2-yr cumulative incidence of RTOG grade ≥3 toxicity 5%) [8] and the RTOG pooled analysis (7% of patients experienced late grade ≥3 pelvic toxicity at median follow-up of 5.4 yr) [9]. However, it is worth mentioning that the median time to late grade ≥3 toxicity was 18.4 mo (range 9.4–98.8) for genitourinary toxicity and 25.8 mo (range 8.0–57.8) for gastrointestinal toxicity in the RTOG pooled analysis [9], while the primary outcome in the present study was late toxicity occurring 6–18 mo after RT, underlining the need for longer follow-up. In terms of efficacy, DART provided a promising 2-yr locoregional control rate of 84%, which compares favorably to the 67% in the BC2001 trial [8].

Although preliminary, these results are noteworthy as they suggest an improvement in clinical outcome following TMT solely because of advances in radiation delivery. To the best of our knowledge, moderate hypofractionation with doses of ≥2 Gy per fraction is the only other example of an oncological benefit related to RT advances [10]. However, while implementation is relatively straightforward for hypofractionation, it is challenging for tumor-focused DART for several reasons. First, the latter requires intensity-modulated RT via an image-guided approach, which is still not available for this indication in many low- and middle-income countries. Second, the PoD adaptive strategy requires daily plan selection, which requires implementation of a training program for physicians and radiotherapists. The use of online replanning instead of PoD in the future, possibly via magnetic resonance imaging (MRI)-guided RT, could avoid this issue and is a promising technical approach. Finally, identification of the index tumor remains complex in most cases and requires integration of robust imaging and pathological data. To better identify the index lesion and increase the accuracy for detection of local relapses, the use of MRI for delineation and treatment follow-up must be assessed in clinical trials. Current advances for index tumor identification include the use of gold fiducial markers or suburothelial injection of lipiodol, which could also increase the precision of dose delivery in the future. The tumor-focused dose escalation approach should theoretically be limited to unifocal lesions outside the dome with an adequate index-tumor/whole-bladder ratio to allow significant sparing of the rest of the bladder for optimal bladder function and quality of life after treatment.

Because of such issues, and to avoid needless complexity in radiation delivery, selection of the best candidates to benefit from this RT approach is of interest. From this perspective, assessment of residual tumor via second TURBT after neoadjuvant treatment and testing for genomic alterations in the DNA repair–associated genes *ATM*, *RB1*, and *FANCC* that predict tumor response to chemotherapy [11] could help in selecting suitable candidates for tumor-focused DART.

Overall, the next generation of TMT will probably include new developments in RT delivery such as those used in the RAIDER trial [5], which hopefully will increase interest in bladder-sparing approaches for MIBC. Future TMT trials will have to include these radiation advances in order to offer optimal RT while testing new neoadjuvant, concurrent, and maintenance systemic strategies.

Conflicts of interest: The authors have nothing to disclose.

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