

EDITORIAL

# A Tailored Radiation Therapy Strategy for Older Patients With Localized Bladder Cancer Not Eligible for Curative Treatment

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Neoadjuvant platin-based polychemotherapy followed by radical cystectomy (RC) with pelvic lymph nodes dissection is considered a standard treatment for nonmetastatic muscle-invasive bladder cancer (MIBC). Trimodality therapy (TMT), consisting of maximal transurethral resection of the bladder followed by concomitant chemotherapy and radiation therapy, is an alternative to RC for carefully selected patients, with comparable outcomes.<sup>1</sup>

Because of an increase in overall life expectancy, there has been a rise in the incidence of cancers, particularly those with a long latency period such as MIBC, which has a peak incidence observed after 80 years of age.<sup>2</sup> Older patients are often underrepresented in clinical trials resulting in limited prospective evidence regarding treatment feasibility, efficacy, and safety. It is therefore challenging to extrapolate the best treatment strategies for this population. In a systematic review evaluating the outcome and complication rate of surgery in older patients with localized MIBC, overall and cancer-specific survival significantly decreased and perioperative mortality significantly increased with age. Most of the included studies involved a proportion of older patients (>70 years old) who were well-selected, healthier patients and not representative of the

entire older bladder cancer population. Frail patients often receive suboptimal therapy, including omission of perioperative platinum-based chemotherapy and limited node dissection, and they are more likely to develop perioperative complications with a relatively high risk of post-RC mortality.<sup>2</sup> To illustrate this point, patients older than 80 years saw their odds ratios for 90-day mortality rise further to 2.4 to 7.9.<sup>2</sup>

Similar concerns exist with TMT, considered the best alternative curative approach for older and frail patients with localized MIBC. Indeed, the tolerance and efficacy of a course of TMT can be compromised by transportation issues during normofractionated radiation therapy and ineligibility to associated chemotherapy regimens, thus influencing physicians toward less aggressive, less effective treatment approaches. An evaluation of a population-based cancer registry indicated that the percentage of patients who receive curative treatment, including RC or TMT, drops from 52% to 12% for patients age <60 years versus >80 years.<sup>3</sup> Gray et al<sup>4</sup> reported that only 35% of patients age 81 to 90 years underwent treatment with curative intent, whereas less than 15% of patients age >90 years received a similar approach. Disappointingly, the proportion of

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patients treated with RC decreased with increasing age, but the percentage of patients treated with TMT did not increase proportionally.<sup>4</sup>

Considering these observations, there is clearly a need for an “in-between” curative and palliative treatment approach dedicated to the older population. The main goals of this strategy should be to (1) select the right patient population; (2) develop a treatment that is feasible and well tolerated without significant adverse events or reduced quality of life (QOL), and convenient for the patient; (3) palliate tumor-related symptoms; and (4) improve local control and oncologic outcomes.

In the current issue of the *International Journal of Radiation Oncology Biology Physics*, Huddart et al<sup>5</sup> reported the results from a multicenter phase 2 trial including patients with localized MIBC receiving radiation therapy (36 Gy in 6 weekly fractions) and randomized between a standard planning (SP) and an adaptive planning (AP) approach consisting of a plan-of-the-day strategy based on a library of 3 plans. The group proposed a strategy mixing curative and palliative objectives in a population of patients who were ineligible for conventional radical treatments. Indeed, these patients would be candidates for curative treatment intent based on their disease status, but they would not tolerate RC or more conventional daily fractionated radiation therapy; they had an expected survival >6 months and World Health Organization performance status score of 0 to 3. These inclusion criteria represent the real-life population of frail and older patients, often considered borderline to receive curative treatment, but for whom palliation would be suboptimal management. As such, the authors must be congratulated for conducting such a pragmatic and well-designed multicenter study in this often-neglected population.

In this study, 63 patients were enrolled with a median age of 85 years (interquartile range, 81-89 years), and most with significant comorbidities. In comparison, in a multicenter phase 3 trial, James et al<sup>6</sup> demonstrated a significant improvement in 2-year locoregional disease-free survival that favored curative radio-chemotherapy over radiation therapy alone, including well-selected patients with a median age of 72 years.<sup>6</sup> Giacalone et al reported the long-term results from the Massachusetts General Hospital TMT experience, in patients whose median age was 67 years.<sup>7</sup> The MRC-BA09 multicenter randomized trial comparing the efficacy and toxicity of 2 palliative radiation therapy schedules (35 Gy in 10 fractions and 21 Gy in 3 fractions) for symptomatic improvement in patients unsuitable for curative treatment had a median age of 6 years less than in the Huddart et al trial.<sup>8</sup>

A limitation is that ineligibility for curative therapy was based solely on the local investigator's judgment, without quantitative determinants, thus creating an opportunity for bias in patient selection. Systematic geriatric assessment is independently associated with changes in cancer treatment,<sup>2</sup> reducing the potential for undertreatment or

overtreatment, either of which could result in decreased health-related QOL. In addition, there is a lack of consensus in the literature on the definitions of “frail” and “elderly.” There is a need for a dedicated geriatric assessment to identify vulnerabilities not routinely captured in oncology assessments, the necessity of and estimation of the toxicities related to specific forms of chemotherapy by using specific scales, an estimation of life expectancy in the absence of cancer, and communication of all of these data to patients and caregivers in an effort to optimize treatment decisions.<sup>9</sup> Huddart et al<sup>5</sup> lack such an initial assessment, mitigating the patient selection relevance and potentially explaining why 11% of patients did not receive the whole course of radiation therapy.

The primary endpoint in this study was nongenitourinary Common Terminology Criteria for Adverse Events grade  $\geq 3$  acute toxicity. Secondary endpoints included an evaluation of this adaptive strategy relevance, toxicity, control rate of presenting symptoms, patient-reported outcome measures, local disease control, and oncologic outcomes. Acute toxicity rates from prospective TMT studies classically range from 0% to 43%.<sup>6,7,10</sup> For older patients, acute toxicity is still a concern, as shown in a systematic review that analyzed hypofractionated radiation therapy outcomes.<sup>11</sup> Without radiosensitizer, as in Huddart et al,<sup>11</sup> significant grade  $\geq 3$  acute genitourinary (GU) and gastrointestinal toxicities were observed, ranging from 10% to 58% and from 4% to 62%, respectively. The toxicity results from the proposed ultra-hypofractionated therapy study are acceptable. There were no excessive Common Terminology Criteria for Adverse Events grade  $\geq 3$  toxicities, with grade  $\geq 3$  non-GU toxicities reported in 6% (95% confidence interval [CI], 0.7%-20.2%) of participants in the AP group and 13% (95% CI, 3.8%-30.7%) in the SP group. Overall grade  $\geq 3$  toxicity was observed in 19% (95% CI, 10.2%-30.9%) of patients, lower than the predefined threshold of 40%; grade  $\geq 3$  GU toxicities were more frequent than non-GU ones, affecting 9% (95% CI, 1.9%-24.3%) of participants in the AP group and 17% (95% CI, 5.8%-35.8%) in the SP group. Interestingly, these acute toxicities are associated with a small decline in patient-reported outcome measures at 3 months, but this improved over the following 6 months, returning to baseline in both groups, and confirming the safety and feasibility of a weekly ultra-hypofractionated therapy strategy in this population.

These QOL results agree with data from the recently published randomized BC2001 study, showing that immediately after (chemo)radiation therapy given with curative intent, a significant proportion of patients reported declines in health-related QOL, which then improved to baseline after 6 months.<sup>12</sup> In a multistudy analysis comparing 64 Gy in 32 fractions given over 6.5 weeks and 55 Gy in 20 fractions over 4 weeks, using individual patient data from 2 trials (BC2001 and BCON), health-related QOL from BC2001 suggested worse QOL after the moderately hypofractionated treatments. This did not result in excess

treatment interruptions, and no difference in health-related QOL was seen after 6 months. Overall, maintaining QOL with bladder preservation is an achievable goal, even in frail, older patients using hypofractionated or ultra-hypofractionated schedules depending on the eligibility criteria.<sup>13</sup> QOL deterioration can also be related to the local symptoms of bladder cancer, requiring frequent inpatient admissions. A variety of radiation therapy protocols have been developed for managing these symptoms; however, these protocols often cause adverse events. In the present study, however, for patients reporting symptoms at baseline, control of most of these symptoms was improved at 3 months in 50% and 75% of patients. Added to the low rate of acute toxicity observed, this ultra-hypofractionated schedule appears to be a relevant option to palliate symptoms and maintain or increase QOL. QOL can be affected by disease progression, this specific endpoint being one of the key objectives defined in this population. In the present study, at a median follow-up of 38.8 months, we must note an impressive level of local control (81%; 95% CI, 67.4%-91.1%); this suggests that 36 Gy in 6 fractions may be superior to the 21 Gy in 3 fractions used in MRCBA09, which reported 38% local control.<sup>8</sup>

Furthermore, promising oncologic results are presented. By extrapolating the curves from Huddart et al at 2 years, the proportion of patients free of invasive local recurrence is 65% to 70%, close to what was demonstrated by James et al<sup>6</sup> and the independent patient data meta-analysis including BCON and BC2001. The meta-analysis demonstrated that patients who received 55 Gy in 20 fractions had 29% lower risk of invasive isolated locoregional recurrence than those who received the 64 Gy schedule. Hypofractionation provided greater convenience, with comparable adverse events, particularly for older patients.<sup>13</sup> As for a moderate hypofractionated regimen, Amestoy et al<sup>11</sup> reported 2-year recurrence-free survival of 43% to 83%, but those patients do not correspond to the population discussed here. With a median survival of 18.9 months and more than 40% of patients surviving 2 years after treatment, Huddart et al suggest that 36 Gy in 6 fractions is effective at controlling disease. Oncologic results can be considered more than satisfactory in this borderline population that is ineligible for any curative approach; only 31% of patients underwent complete transurethral resection of the bladder, a factor known to be associated with improved local control. In the same way, 20% of patients had multifocal tumors, 31% had carcinoma in situ, and 30% had cT3-4 disease. These tumors' characteristics do not fit the well-known optimal criteria for TMT, which makes the results more impressive. Therefore, 36 Gy delivered in 6 fractions without chemotherapy provides a reasonable chance at extended survival in this older population, and it compares favorably to patients receiving palliative treatments or no treatment.<sup>8</sup>

Another objective in treating frail and older patients is to account for logistical considerations, such as the number of treatments and the degree of patient inconvenience. This is

particularly important during the COVID-19 pandemic to limit patient exposure to the virus.<sup>14</sup> Recent data indicate that moderately accelerated hypofractionation allows physicians to reduce the overall treatment time from 6 to 7 weeks to 4 weeks, increasing convenience, reducing travel-related costs, and allowing patients to complete treatment before significant radiation-associated fatigue can set in. A dose of 21 Gy in 3 fractions on alternate weekdays over 1 week was shown to be equivalent to daily palliative radiation therapy treatment (35 Gy in 10 fractions) in a multicenter randomized phase 3 trial for patients with MIBC (MRCBA09); 3 alternate fractions seems feasible in the population discussed by Huddart et al, although this regimen had poorer local control, as detailed previously.<sup>8</sup> The alternative ultra-hypofractionated therapy schedule of 6 Gy per fraction given weekly, over 5 to 6 weeks, which has a higher biological dose to the tumor than the BA09 schedules, appears now as a reasonable option.

Finally, adaptive radiation therapy is a promising approach, especially when a high dose per fraction must be given conformally to a mobile target close to organs at risk, such as for bladder cancer. Target volume coverage and healthy tissue sparing could lead to better tumor control and reduced toxicity compared with standard strategies. In this study evaluating a library of plans approach, AP did not result in clinically meaningful improvements in outcomes. Two or more plans were believed to be necessary in "only" 79% of the patients and, after central review of plan selection, "only" 78% of concordance was found with plan selection. QOL at 3 months was comparable between the AP and SP groups. The additional time and cost of AP does not appear to be justified by these results. Because the results from the phase 2 RAIDER trial (ISRCTN26779187) are not yet available, the implementation of the plan of the day strategy might be reserved to expert centers. Moreover, considering the reported results between the AP and SP groups, it seems that adaptive radiation therapy is not mandatory to be able to propose such an ultra-hypofractionated approach.

Despite the low number of patients included in this study, a weekly ultra-hypofractionated radiation therapy schedule, without concomitant chemotherapy, appears as a feasible, safe, and symptomatically and oncologically efficient standard for older patients who are not eligible for radical treatment. Geriatric assessment is an essential component to be implemented to improve treatment decision accuracy. Adaptive radiation therapy seems not mandatory in this setting, but it is a promising tool to enhance the efficacy-to-toxicity ratio of radiation therapy in bladder cancer as a part of a tailored approach.

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