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Early or Delayed Radical Cystectomy for High-risk Non-muscle-invasive Bladder Cancer: A Hard Dilemma to Solve

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In a recent issue of *European Urology Open Science*, Grossmann et al. [1] report on their comparison of oncological outcomes between early and deferred radical cystectomy (RC) in patients with non-muscle-invasive bladder cancer (NMIBC). Although their study is retrospective, it has the merit of reflecting daily clinical practice and evaluating a highly heterogeneous disease.

Grossmann and colleagues evaluated a cohort of 908 patients treated at three academic centres between 2003 and 2015. Patients were divided in four groups: (1) primary high-risk (HR)-NMIBC; (2) primary MIBC; (3) recurrent HR-NMIBC; and (4) NMIBC that progressed to MIBC, termed “secondary MIBC”. Recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were the primary endpoints, while adverse pathological outcomes (defined as upstaging, positive lymph nodes, or \geq pT3) at the time of RC were secondary endpoints. Although 12 yr was the time frame for study inclusion, the median follow-up was 37 mo.

According to their results, the group with recurrent HR-NMIBC experienced a similar survival outcome in comparison to the group with primary MIBC. Furthermore, patients with secondary MIBC had the worst outcomes. Finally, recurrent HR-NMIBC is a risk factor for adverse pathological outcomes on RC. These results are in line with a previous meta-analysis of 14 studies involving 4075 patients that observed worse CSS for patients with secondary MIBC (pooled hazard ratio 1.29, 95% confidence interval [CI] 1.07–1.56; $p = 0.008$).

Notwithstanding all these positive findings, the study has some limitations. In particular, data on previous intravesical treatments and patient characteristics (smoking status, hydronephrosis, histological variants, frailty status) have not been analysed. It is notable that 56% of the study cohort, with a median age of 66 yr (interquartile range

60–73), died from other causes. Furthermore, the proportions of patients unresponsive to bacillus Calmette-Guérin (BCG) and with persistent carcinoma in situ were not reported. The BCG protocol and follow-up strategy were not uniform among centres, and might have been inadequate. Finally, as stated by the authors, the oncological and pathological characteristics of the cohort may not be consistent with previous studies or with real-world patient populations, considering that patients who received neoadjuvant chemotherapy were excluded from the study.

NMIBCs are heterogeneous cancers and the ranges for recurrence (31–78%) and progression (0.8–45%) are wide, probably because of different cancer-specific (biology, multifocality, histological variants) and patient factors (smoking, comorbidities, frailty). Future studies evaluating HR-NMIBC should include all these characteristics to reduce the risk of bias and to improve the clinical value of the results. For instance, a repeat transurethral resection of bladder tumour for high-risk and very high-risk NMIBC, which was not included in the Grossman study, is mandatory in this setting considering the 27–51% risk of understaging [2]. Although randomised controlled trials (RCTs) are regarded as the most reliable and effective method for evaluating health care interventions, we must acknowledge that in the case of very different interventions such as RC versus intravesical therapies, it is extremely difficult to perform an RCT, as recently evidenced by the BRAVO study [3].

Furthermore, although RC represents the standard treatment for MIBC and selected high-risk NMIBC cases, this surgical procedure has a significant impact on patient wellbeing and quality of life and is frequently associated with significant perioperative morbidity, particularly in elderly patients [4–6]. In this scenario, a comprehensive preoperative evaluation, including the patient's characteristics and expectations, is always necessary to optimise the

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decision-making process [7]. Patients should be appropriately counselled on the risk of progression and the poor outcomes for very high-risk NMIBC, as well as the impact of radical treatment on quality of life. The risk of overtreatment should be minimised in these patients.

Preliminary results for bladder-sparing treatments will probably provide new strategies and data for patients not eligible for or refusing RC. For instance, the PD-L1 inhibitor pembrolizumab, recently approved by the US Food and Drug Administration as an alternative to RC for NMIBC unresponsive to BCG, showed a complete response rate of 41% (95% CI 30.7–51.1) at 3 mo [8]. Likewise, the recent trend in adenoviral-based cancer gene therapy has also been extended to BCG-unresponsive NMIBC with the aim of increasing the secretion of interferon α 2b protein and enhancing the natural antitumour immune response. Early results seem to be promising, with a complete response observed in 53.4% of patients [9]. Unfortunately, these studies are ongoing and data on survival are not yet available.

Finally, considerable knowledge is being accrued in the development of new biomarkers to predict response to BCG therapy. For instance, the European UROMOL project has identified 12 mRNAs with strong prognostic information and has classified NMIBC into three molecular classes with different risks of progression [10]. Thus, it is reasonable to suppose that several predictors will soon be available to help in selecting the best candidates for early RC. At present, clinicians should discuss with every patient the pros and cons for early versus delayed RC. The data reported by Grossman et al will help in this decision-making process.

Conflicts of interest: The authors have nothing to disclose.

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