DIAGNOSIS AND TREATMENT OF BLADDER CANCER: FROM ESTABLISHED PARADIGMS TO RECENT ADVANCES AND NEW PERSPECTIVES

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INTRODUCTION

Bladder cancer (BC) certainly represents a challenging disease for the patient, given the significant impact on health-related quality of life, and for the urologist, given the broad spectrum of clinical scenarios that can be presented. Epidemiology studies suggest that this is a common malignancy worldwide, with an estimated 330,400 new cases diagnosed and 123,100 attributable deaths in 2012.[1] In most cases, BC presents as non-invasive into the detrusor muscle, which initially and frequently allows bladder-sparing therapies. Nevertheless, non-muscle invasive BC (NMIBC: tumours staged as Ta, T1, or carcinoma *in situ*) tends to recur (≤80% of cases) and progress to muscle-invasive BC (MIBC) (≤30% of cases), so that close patient follow-up is always needed, as well as more aggressive treatment options.[2,3] In the setting of this quite complex clinical entity, currently available guidelines are extremely helpful to provide evidence-based guidance to the urologists in their daily practice. Four major evidence-based guidelines are available and most widely used, including those published by the American Urological Association (AUA),[2] the European Association of Urology (EAU),[3] the International Consultation on Urological Disease (ICUD),[4] and the National Comprehensive Cancer Network (NCCN).[5] Over the years, these guidelines have been regularly updated whenever evidence supporting the implementation of new diagnostic tools, technologies, and techniques have become available. However, from other points of view, one can reasonably argue that the management of BC patients has been based on the same pillars and concepts over the past two decades.

DIAGNOSIS

The first and most important step in the diagnostic protocol of BC is still represented by the cystoscopy, and subsequent histologic evaluation of the tissue obtained by transurethral resection (TUR). Refinements in technique and surgeon experience are critical for the performance of a thorough, complete, 'high-quality' TUR. Recent technological advances including bipolar electrocautery and regional anaesthetic techniques may help to reduce the risk of complications.[6] Advances in endoscopic imaging technology may improve sensitivity for the detection of BC and ultimately lead to improved cancer control. Fluorescence cystoscopy requires intravesical administration of a photosensitising agent (5-aminolevulinic acid or hexaminolevulinate) and imaging with a blue-light endoscopy system demonstrably improves the detection of papillary and flat bladder lesions compared with conventional white-light cystoscopy.[7] In my daily clinical practice I do prefer to use narrow band imaging (NBI) technology (Olympus, USA), which does not require the use of any dye or agent as it works by providing increased contrast between normal and abnormal tissue on the basis of neovascularity. Evidence shows that NBI is effective in the identification of abnormal lesions including carcinoma *in situ*, and it can provide higher diagnostic precision of BC than white light cystoscopy.[8] Other novel technologies such as optical coherence tomography and confocal laser endoscopy hold promise as useful tools in better characterising bladder tumours.[7] Whenever a TUR procedure is deemed to be 'incomplete' (no muscle is identified in the specimen), or when a high-grade tumour is detected, it is a well-established principle that a second TUR should be performed within 2–6 weeks.[9]

Besides endoscopy, another 'traditional' diagnostic tool is represented by urine cytology, which can be useful for the diagnosis of a high-grade tumour. On the other hand, several urine markers have been extensively studied to aid in the diagnosis of BC, and possibly decrease the need for cystoscopy.[10] However, none of these markers, despite having a higher sensitivity, demonstrated a higher specificity than simple urine cytology; this should be considered in addition to the cost associated with the use of these markers. Therefore, their use in daily clinical practice remains to be determined.

TREATMENT OF BLADDER CANCER

Non-Muscle Invasive Disease

The risks of both recurrence and progression of NMIBC can be estimated for individual patients by using the EORTC scoring system, which is a practical ready-to-use tool to plan further treatment. However, controversies exist regarding this and other available predictive tools.[11] A consolidated concept is that the use of intravesical chemotherapy administered immediately after TUR is likely to reduce the risk of recurrence in NMIBC.[12]

The stratification of patients into low, intermediate, and high-risk groups is pivotal to determining the adjuvant treatment:[3]

- For low-risk patients, one immediate instillation of chemotherapy is recommended
- For intermediate-risk cases, one immediate instillation of chemotherapy should be followed by 1 year of full-dose Bacillus Calmette-Guérin (BCG) intravesical immunotherapy or by further instillations of chemotherapy for a maximum of 1 year
- In patients with high-risk tumours, full-dose intravesical BCG for 1–3 years is indicated
- In tumours at highest risk of progression and those that are BCG-refractory, radical cystectomy (RC) should be considered

The administration of BCG immunotherapy has certainly become the standard of care for high-grade NMIBC and carcinoma *in situ* in terms of prevention of recurrence and progression. Nevertheless, despite its wide usage over the past two decades and the wide implementation of the standard 6-week induction course, the optimal duration of BCG treatment remains unknown, and should be the subject of further studies.[13]

All guidelines advocate the use of cystoscopy during follow-up of NMIBC:

- In the case of Ta tumours: the AUA2 and the ICUD4 panel do not make recommendations regarding the timing. The EAU3 recommend that patients should have cystoscopy at 3 months. If negative, subsequent cystoscopy is advised 9 months later and then yearly for 5 years (Grade C). No recommendations are made about cytology or imaging. The NCCN panel recommends cystoscopy at 3 months and then at "increasing intervals as appropriate."[5] Neither cytology nor upper tract imaging are advocated
- In the case of high-grade Ta, T1, and clinically isolated syndrome (CIS): the EAU recommends cystoscopy and urine cytology at 3 months. If negative, subsequent cystoscopy and cytology should be repeated every 3 months for 2 years, then every 6 months until 5 years, and then yearly. For CIS, the ICUD panel recommends cystoscopy and cytology every 3 months for 2 years, every 4 months in the 3rd year and every 6 months in the 4th and 5th years, and then yearly. Moreover, the ICUD does recommend "periodic" imaging of the upper urinary tract for patients with CIS. Similarly, the NCCN panel recommends cystoscopy and urine cytology every 3–6 months for 2 years, followed by increasing intervals "as appropriate", and they also recommend to consider upper tract imaging every 1–2 years for high-grade Ta, T1 tumours, and CIS

Muscle-Invasive Disease

When BC presents or progresses to muscle invasive disease, there is a major shift in the treatment paradigm, as a more aggressive approach is needed to optimise the oncological outcome. Neoadjuvant chemotherapy followed by RC with bilateral pelvic lymph-node dissection currently represents the standard of care for patients with MIBC.[14,15] Timely diagnosis and prompt surgical treatment are keys in the management of MIBC, as multiple studies have shown that a delay in diagnosis or treatment adversely impacts outcomes.[16]

A complete metastatic workup and medical evaluation considering age, nutrition, and performance status are necessary before starting treatment. For patients with T2 disease on TUR, staging studies of the chest, abdomen, and pelvis, including upper-tract evaluation, must be

performed to rule out metastases. Currently, the gold standard for staging in BC is computed tomography, although more recently multiparametric magnetic resonance imaging and positron-emission tomography imaging have shown promise.[17]

Over the past 5 years, there has been an ongoing discussion with regard to the best surgical approach for RC (open versus robotic), and the optimal extent of lymph-node dissection. With the increasing role of robotic surgery, many centres have adopted robot-assisted RC (RARC), and there has been growing evidence in the literature comparing open RC with RARC. In a recent systematic literature review, Novara et al.[18] found that RARC can be performed safely with acceptable perioperative outcome, although complications are common. Operative time was shorter with RC, whereas RARC may provide some advantages in terms of blood loss and transfusion rates and, more limitedly, for postoperative complication rates. In another recent systematic review, Yuh et al.[19] examined oncologic and functional outcomes following RARC from 87 studies, and they concluded that data remain immature. Their cumulative analyses demonstrated that lymph node yields and surgical margin rates are similar between RARC and open RC, but long-term survival outcomes for RARC are still limited. High volume robotic surgeons are also implementing intracorporeal urinary diversion following RARC,[20] and the debate in this field is still ongoing as data are maturing. Besides the surgical technique, innovations have also been implemented in the perioperative management of BC patients undergoing RC. Several enhanced recovery protocols have been developed with the aim of expediting bowel function recovery and shortening hospital stay after RC and urinary diversion.[21] Last but not least, the role of systemic chemotherapy represents another field of ongoing debate. Despite available evidence supporting its role as standard of care for MIBC, neoadjuvant chemotherapy remains underused, and strategies to fill this gap should be investigated.[22]

CONCLUSIONS

BC represents an exciting field of clinical research, as many questions remain unanswered, and diagnosis and treatment of the disease remain suboptimal. Recent innovations might pave the way for future paradigm shifts in the management of this very challenging multifaceted disease. As clinicians and investigators, it is our role to stay tuned and updated with the ultimate aim of providing the best care to our patients.

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