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News and Topics

The reorganization in the post-COVID recovery period requires a rationalization of old schedules of surveillance of non—muscle invasive bladder cancer

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Abstract

The non-muscle invasive bladder cancer (NMIBC) continues to represent a real challenge, especially in times of COVID-19 pandemic. Despite the pandemic period, patients with newly diagnosed or recurrent NMIBC have had priority concerning the waiting list for treatment. Since these patients are treated, it is therefore necessary to verify the results of therapy through endoscopic evaluation. In order to optimize the clinical management, it is useful to select the best patients and to consider a full re-evaluation of NMIBC follow-up supported by rigorous studies.

Keywords: COVID-19; Reorganization of NMIBC follow-up; Tailored follow-up schedule

Introduction

The NMIBC continues to represent a real challenge, especially in times of COVID-19 pandemic.

Due to the natural characteristics of this pathology, the patient needs to be monitored, despite the social restrictions induced in this period.

An important factor to be taken into consideration concerns the average age of the NMIBC patient, around 70 years, that is, the average age most affected by the COVID-19 infection; this group of patients presents a risk to develop an acute respiratory distress syndrome after contracting COVID-19 up to 30% [1].

Some ongoing trials are evaluating the use of Bacillus of Calmette-Guerin (BCG) vaccination as prophylaxis and control of COVID-19 infection; this certainly needs attention from all urologists, who are already struggling with the periodic shortage of the BCG [2].

Furthermore, despite the pandemic period, patients with newly diagnosed or recurrent NMIBC have had priority concerning the waiting list for treatment, both for the shortness of post-trans-urethral resection of bladder tumor (TURBT) operative hospitalization (practical reason) and to avoid the access to emergency department due to macrohemia (clinical reason).

Furthermore, according to international recommendations, patients who deserved intravesical induction treatment were treated with priority, unlike patients undergoing maintenance cycles.

In light of the aggressiveness of the tumor, the patients were however exposed to the risk of the side effects [3] of intravesical therapy, mostly local, but which could have required the use of nonsteroidal anti-inflammatory drugs; these drugs, as known, can worsen the COVID-19 infection.

The restrictions imposed by the government in terms of crowd put a strain on the referral centers where a large number of patients suffering from NMIBC are treated daily. This involved a considerable effort in terms of organization of personnel and economic resources with the aim to continue offering the optimal clinical management (including follow-up) of patients who experienced a double psychological impact, both for the tumor itself and for the need to access hospital facilities.

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The role of follow-up

The follow-up of the patient with NMIBC requires the serial and periodic performance of cystoscopy, urinary cytology and radiological study of the upper urinary tract; these exams suffer from low sensitivity and only their combination represents the standard clinical management [4].

Low-risk NMIBC. The positive anamnesis for an oncological pathology, the real likelihood (albeit low) of an intravesical recurrence (best treated if diagnosed first), the low sensitivity of urinary cytology and radiological study of the upper urinary tract collide with the necessity to reduce both the economic burden of bladder tumor on National Health System and the negative influence of invasive follow-up on the patient’s quality of life. However, these patients might represent the ideal population to evaluate in rigorous studies the opportunity to delay the interval between cystoscopies, for example every 18 months, after the first year of follow-up, and/or even its replacement with others noninvasive diagnostic approaches (such as with radiology alone).

High-risk NMIBC. The aggressiveness of the disease, the need to perform a second resection and intravesical therapy, the greater possibility of recurrence and progress in the first 2 years after the first diagnosis and the possible prognosis impairment in case of a diagnostic delay make it ethically necessary to continue a close monitoring of these patients, especially in higher risk classes and in younger patients [5]. In these cases, it might be worthy to consider the lengthening of the interval (and not the replacement) between the cystoscopies (after at least 3 years of disease-free follow-up), thanks to the employment of new noninvasive approaches (more accurate in case of high-grade tumor) in the development of new follow-up schedules. However, even this crucial issue needs to be supported by rigorous studies.

International recommendations unanimously confirmed the need to treat these patients, with particular reference to the induction cycle, even in time of pandemic; although an optimal maintenance cycle scheme does not currently exist, it is recommended to continue with this program, considering acceptable the administration of 2 of the 3 doses of BCG or at least guarantee the first maintenance cycle after the induction cycle [6].

Since these patients are treated, it is therefore necessary to verify the results of therapy through endoscopic evaluation.

The effect of delayed diagnosis

The effect of delayed surgery from the first diagnosis was assessed mainly and widely in muscle-invasive bladder cancer (MIBC) and prostate cancer.

Many studies predominantly evaluated the association of the time between TURBT and radical cystectomy and most studies showed a significant association with survival.

Despite the evidence of this issue is weaker than in the MIBC, in the context of the NMIBC the therapeutic delay appears to be significantly more relevant in cases of high risk than in low-risk neoplasms.

Wallace et al. examined the different diagnostic and therapeutic steps of the patient with the first diagnosis of bladder cancer. The authors highlighted 3 crucial moments: patient-derived delay, general practitioner-derived delay, and hospital-derived delay.

The authors showed that the reduction in the delay between the onset of the first symptoms and the visit to the general-practitioner is associated with a lower pathological stage and an improvement in 5-year survival, with an ideal cut-off of patient-derived delay of about 14 days.

The authors did not associate hospital-derived delay with survival, albeit with results adjusted by tumor stage. In conclusion, when considered together, the total delay between the onset of early symptoms and TURBT did not appear to be significantly associated with survival [7].

New diagnostic approaches

Several efforts have been focusing for many years on the development of noninvasive diagnostic procedures but the sensitivity and specificity rates achieved did not reach those of the standard tests.

A wide quantity of potential biomarkers are described in the literature aiming to detect genomic, transcriptomic, epigenetic or protein changes in serum or in urine samples, in order to optimize the diagnostic accuracy of new tests and to create alternatives to cytology and/or cystoscopy.

The urine is currently the ideal sample for this research due to the ease of collection, the stability and the richness of specific tumor proteins directly released [8].

One of the aims of these efforts consists of the reduction in the number of cystoscopies, or in any case to lengthen their time interval; this would limit the frequency of an invasive and expensive procedure, and, at this moment in pandemic era, would reduce the exposure of the cancer patient (more susceptible to infections) to the hospital environment.

The urinary cytology, nuclear matrix protein 22 (NMP22) kit, NMP22 BladderChek Test, BTA-TRAK and BTA stat kits, Cell Search, UroVysion have been FDA-approved for the initial diagnosis and surveillance of bladder cancer while other tests, such as uCyt +, have been approved only for follow-up.

Although they do not yet have FDA approval, other European conformity approval tests such as Epicheck and Uromonitor showed promising sensitivity and specificity rates. The development of the above tests demonstrated all the efforts in developing a test that can improve the quality of life of the patient with bladder cancer [9].

Moreover, Tan et al. evaluated the minimum sensitivity accepted by the patient in case of use of a urinary biomarker and how this could influence the decision to accept the replacement of the cystoscopy. The quantitative analysis suggested that patients preferred to tolerate cystoscopy due to its high sensitivity rate despite its invasiveness,
discomfort and the possibility of adverse events related to the procedure. In addition, patients were comfortable with cystoscopy and appreciate the possibility of actively and visually following the procedure [10].

Conclusions

It is crucial to detect and to treat the bladder cancer as early as possible.

Once the NMIBC is treated, the follow-up remains an essential item, to perform and to tailor according to neoplastic and patient characteristics.

The reorganization of the postpandemic recovery might represent the occasion to rationalize standard (and old) clinical management programs, even in the issue of NMIBC follow-up.

A tailored follow-up schedule should consider both “standard” and new noninvasive tests: their combination might reduce the economic and psychological burden of a too close follow-up, in order to perform the right test to the right patient in the right time.

However, the reorganization needs to be supported by rigorous studies and might be intended to maintain or, better yet, to improve the effectiveness of follow-up, avoiding the inconvenience or unnecessary exposure to the patient.

Conflicts of interest

The authors declare no competing interests.

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