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Review

Bladder cancer: Present and future☆

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ABSTRACT

Bladder cancer has a high incidence and involves high associated morbidity and mortality. Since its initial clinical suspicion, early diagnostic confirmation and multimodal treatment involve different medical specialties. For this reason, we consider it important to spread the current consensus for its management. Recent advances in immunology and Chemotherapy make it necessary to expose and reflect on future perspectives.

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Tumor vesical: presente y futuro

Palabras clave:
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RESUMEN

El tumor vesical presenta una elevada incidencia en nuestro medio y comporta una alta morbimortalidad asociada. Desde su sospecha clínica inicial, la confirmación diagnóstica precoz y el tratamiento multimodal involucran a diferentes especialidades médicas. Por ello consideramos importante difundir el consenso actual para su manejo. Los recientes avances en inmunología y quimioterapia hacen necesario exponer y reflexionar sobre las perspectivas futuras.

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Introduction

Bladder cancer, with more than 357,000 new cases and more than 130,000 deaths annually worldwide, is one of the leading causes of mortality in men. In Europe, in 2012, 151,297 new cases of bladder cancer were diagnosed with a standardized incidence rate (per 100,000 people) of 17.7 for men and 3.5 for women. In general, the crude gross incidence rate is 20.4/100,000. In 2012 there were 52,395 deaths from bladder cancer with an annual gross mortality rate of 7.1/100,000.[1]

Spain has one of the highest incidence and mortality rates in Europe with an average of 12,200 new cases per year, 4th more frequent cancer in men and 5th in both sexes. Approximately 70% of patients with bladder cancer are older than 65 years of age. Tobacco use is the best-established risk factor, although occupational exposure, chemotherapeutic agents and pelvic radiation therapy have also been described as causative factors in the development of bladder cancer.

In order to promote and improve the management of these patients, we present this review on the current treatment of bladder cancer and its future prospects.

Clinical manifestations

Haematuria, urinary voiding symptoms (urgency and imperiousness) and recurrent urinary tract infections are the most frequent symptoms in patients with bladder cancer. Most patients are diagnosed by complementary examinations (ultrasound/cystoscopy) requested after presenting a first episode of hematuria.[2] Macroscopic haematuria is the symptom most strongly

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correlated with the diagnosis of bladder cancer; with a positive predictive value at 3 years is 7.4% (95% CI: 6.8–8.1) in men and 3.4% (2.9–4) in women.[3] Therefore, in the case of a patient with macroscopic haematuria, it is recommended to complete the study with ultrasound and refer the patient to urological examination. Ultrasound can detect intravesical lesions larger than 0.5 cm. If clinical suspicion of bladder cancer persists despite a normal ultrasound examination, cystoscopy will be the next diagnostic test.

Screening

Bladder cancer is an important health problem, has a high incidence and prevalence but also a reliable and efficient treatment. Despite the above, there is no scientific evidence to support a bladder cancer screening program in the general population. Not even in major smokers or individuals with environmental exposure to bladder carcinogens.[4] Initially, the urine test strip was proposed as a method of screening for microhematuria (>3 red cells/field), but its positive predictive value is low. In 2015, an analysis of the *Cochrane Library* concluded that the quality of screening methods was too low to support any recommendations.[5]

Diagnosis

In those patients in whom urothelial tumour is suspected, cystoscopy will confirm the involvement of the lower urinary tract and computed tomography with urography that of the upper urinary tract. For the detection of bladder cancer, computed tomography with urography and cystoscopy have a sensitivity of 0.87 and 0.87 respectively, specificities of 0.99 and 1, positive predictive value of 0.91 and 0.98, and negative predictive value of 0.98 and 0.98.[6]

To improve the detection of intravesical lesions new technologies have been introduced, although their use has not become widespread:

Blue light cystoscopy with prior intravesical administration of hexaminolevulinate (Hexvix®) allows to improve the detection rates of carcinoma *in situ* (flat lesions).

Narrow-band imaging allows better vision of blood vessels and detects intravesical lesions more easily.

The increase in costs and the time required for its use have prevented its generalization in clinical practice.

Urinary markers

To date, the role of urinary molecular markers or cytology in the initial diagnosis of bladder cancer is very limited. In the past decade, the joint determination of NMP22 and cytokeratin markers (CYFRA 21-1 or UBC) was proposed as an alternative to urinary cytology.[7] A review[8] designed to compare urinary cytology and urinary molecular markers, showed a low sensitivity (34–55%) for cytology, especially in low grade tumours, but a high specificity (>90%), as well as poor inter- and intra-observer reproducibility. The pooled sensitivity of most molecular markers varies between 50% and 80%, higher than that of urine cytology, and the specificity of most of these markers ranges from 70% to 90%, lower than urinary cytology.

Currently, there is no molecular marker available with enough sensitivity and specificity to replace cystoscopy. The combination of cystoscopy and cytology is the most reliable method.

Bladder tumour grading and staging

Most bladder cancers are urothelial, presenting as non-muscle-invasive (75%) at the time of diagnosis as opposed to muscle-invasive or disseminated (25%). About half of non-musculoskeletal tumours are low-grade tumours, while the muscle-invasive or disseminated tumours are high-grade. Cellular grade is the most important prognostic factor.

Table 1
TNM Staging according to the European Association of Urology.

Category T: Primary tumour (T)
TX: Primary tumour cannot be assessed
T0: No evidence of primary tumour
Tis: Carcinoma in situ: "flat tumour"
Ta: Non-invasive papillary carcinoma
T1: Tumour invades subepithelial connective tissue
T2: Tumour invades muscular layer
T2a: Tumour invades superficial muscular layer
T2b: Tumour invades deep muscular layer
T3: Tumour invades perivesical fat
T3a: Microscopically
T3b: Macroscopically
T4: Tumour invades any of the following structures: prostate, uterus, vagina, pelvic wall, or abdominal wall
T4a: Tumour invades prostate, uterus, or vagina
T4b: Tumour invades pelvic or abdominal wall
Category N: Lymph node involvement (N)
Nx: Regional lymph nodes cannot be assessed
N0: Regional lymph node metastases are not demonstrated
N1: Metastasis in a single lymph node, maximum diameter ≤2 cm
N2: Metastasis in a single lymph node, maximum diameter >2 cm, but ≤5 cm or in various lymph nodes, none of them >5 cm of maximum diameter
N3: Metastasis in a single lymph node, maximum diameter >5 cm
Category M: Metastasis (M)
Mx: Distant metastases cannot be assessed
M0: No distant metastases
M1: Distant Metastasis

The first anatomopathological classification introduced by WHO dates back to 1973 and classifies them numerically as 1, 2 or 3 according to cellular anaplasia.

The classification of high or low grade is given by cellular architecture and cytological atypia. The WHO classification[9] of 2004 includes a third category, that of urothelial papillary tumours with low malignant potential. The WHO 2004 classification is the most widely used at present. The recent update of the WHO classification in 2016[10] does not present great variations with respect to the previous one.

Traditionally bladder cancers had been staged according to the T scale: Ta, T1, T2, T3 or T4 (Table 1), considering a muscle-invasive tumour the one which reaches or surpasses stage T2. The current nomenclature divides them into non-muscle-invasive or muscle-invasive, which implies large differences in therapeutic options and vital prognosis. Among non-muscle-invasive tumours those classified as T1 (involvement of the lamina propria) deserve a special consideration, since this involvement illustrates the invasive nature of bladder cancer. As the inter-observer variability is quite significant,[11] other data should be used when making therapeutic decisions.

Prognostic factors for T1: vascular invasion and growth pattern (solid *vs* papillary)[12]; depth of invasion,[13] the one greater than 1.5 mm was associated with a higher staging of the cystectomy specimen (sensitivity of 81% and specificity of 83%) and with 5-year survival.

If doubts still exist, re-staging may be considered. Re-staging by repeat transurethral resection (TUR) of the T1 should be performed at 2–4 weeks to select candidates for early cystectomy[14] or improve the results of Calmette-Guérin bacillus (BCG) treatment[15]; this re-staging is not always indicated when muscle invasion is present in the specimen submitted, rather, it should be evaluated individually.[16]

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