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Review

Role of age in prostate and bladder cancer. A critical overview

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Age has been suggested to be a relevant prognostic factor in several diseases. According to the latest statistics, prostate and bladder cancer are among the most frequent urogenital tumors and their incidence increases with age. Available data suggest that age may drive the diagnostic and therapeutic pathways of both prostate and bladder cancer. Contrary to common perception, age seems to have a negative prognostic impact on many aspects of such cancers. Age *per se* does not seem to represent a contraindication to actively search for and treat such cancers but it would rather be a factor to be taken in due account in the decision-making process.

Key words: Bladder cancer, Prostate cancer, Ageing, Diagnostic issues, Treatment options

INTRODUCTION

According to the latest worldwide cancer statistics [1], prostate cancer (PCa) ranks first cancer in males and bladder cancer (BC) ranks seventh cancer in both genders. Their incidence increases with age, reaching age-standardized incidence rates of 283.3 and 51.1, respectively. Therefore, these tumors stand out as major health problems and, in the elderly, they pose additional issues related to patients' comorbidities as well as treatment efficacy and adverse reactions.

Herein, we attempted to provide a comprehensive overview regarding diagnostic and treatment issues in elderly patients with PCa or BC with special attention to the role of age in such patients.

PROSTATE CANCER

In male patients, the incidence of PCa diagnosis increases steadily with age. The GLOBOCAN 2018 worldwide estimated age-standardized incidence rates range from 10.2 (age group < 65y) to a stunning 283.3 (age group ≥ 65y) [1].

Diagnostic issues

According to European guidelines [2], age is the main parameter to determine which men should be offered PSA testing (level of evidence 2b, strong rating) since the test is not offered in men < 40 years and is often considered of poor utility in those aging > 80 years. Elderly men are however obtaining increasing attention; consequently, an increase as high as 70% in PCa diagnosis in elderly (> 65y) men is expected by 2030 in Western Countries [2]. Moreover, elderly patients are more likely than the younger ones to be diagnosed with aggressive cancers [3].

As a clinical factor, age is also taken into account when deciding to perform first and/or repeat biopsy in men at risk for PCa. In several predictive models and nomograms [4-6] age has proven to independently predict PCa diagnosis.

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Another issue to be taken into account in the diagnostic pathway is the frequent association of aging with benign prostatic hyperplasia (BPH) as well. Indeed, BPH is a chronic disease whose incidence increases with age, reaching 80% in males aging 70 to 80 years [7].
Elderly males tend to seek medical advice due to symptoms related to BPH and benign prostatic obstruction (BPO); such symptoms have been shown to play a role in the differential diagnosis between these two common urological conditions of the elderly male [8-10]. However patients may suffer both conditions but its frequency is not definitely known.
Emerging novel tools in the differential diagnosis between BPH/BPO and PCa include novel biomarkers such a Pentraxin 3 and EGR2 [11-13] and multiparametric magnetic resonance imaging (mpMRI). Their role is currently under definition. In the meanwhile, optimizing prostate biopsy protocol [14-16] and pathology report [17] play a key role in obtaining diagnosis and defining patient's risk.

Treatment options

The extent of expected survival is a key factor in choosing the proper treatment strategy in PCa patients [2]. Recent reports suggest that in current clinical practice old men with PCa receive insufficient diagnostic workup and subsequent curative treatment [18]; accordingly, US data provide evidence that old age (> 75 years) is an independent predictor of receiving external beam radiation therapy instead of radical prostatectomy in men with localized PCa [19]. This may be partially due to the putative occurrence of adverse post-surgical side effects in the elderly, although our data failed to find a significant association between age and anastomotic urinary leakage following retropubic radical prostatectomy [20].
External beam radiotherapy seems to provide similar cancer control regardless of age [21] but reported 5-y biochemical recurrence-free survival in high-risk PCa remains relatively low and patients should be warned about possible urinary and gastro-intestinal side effects.
Androgen deprivation therapy (ADT) is not indicated for elderly patients in good general condition with locally confined prostate cancer. Conversely, PSA recurrences after radical prostatectomy should be treated primarily with hormonal therapy. In case of asymptomatic metastases, ADT is associated with a lower progression rate than initiating treatment only when symptoms arise. However, ADT is associated with several adverse reactions such as depression, cognitive impairment, osteoporosis and cardiovascular complications, that should be taken in to account, particularly in elderly patients. This scenario sets a potential role for novel minimally invasive procedure such as cryotherapy, whose role in the elderly deserves to be investigated.

Outcome issues

Age-standardized mortality rates rise almost tenfold with advancing age at diagnosis, ranging from 16.0 in the 55-69 age group to 142.8 in the > 70 age group [1]. Some evidence however exists that in case of localized PCa mortality is decreasing with age, due to high incidence of life-threatening diseases in the elderly [22]. Moreover, a meta-analysis of articles addressing the role of age in localized PCa from 1966 to 2000 outlined that age has no significant prognostic effect in contemporary series [22]. Obviously, these estimates may be biased by the vast treatment (mostly surgery alone and radiotherapy alone) and population's heterogeneity. However, similar results have been achieved by a most recent report of more than 2000 patients treated by radical retropubic prostatectomy for PCa staged up to pT3b [23]. The authors assessed the prognostic role of age without the effect of the primary confounding variables (serum PSA level, Gleason score, percentage of positive biopsy cores) by a direct-paired analysis, and found that age was not an independent prognostic factor. One study, whose clinical endpoint was biochemical recurrence, yielded similar results [24], while another one yielded different results [25].
In spite of such controversies, age is incorporated in risk classification systems, such as the age-adjusted Charlson Comorbidity Index, to predict disease outcome after radical prostatectomy [26].
Aging has also been proved to be related to clinical and pathological parameters both directly and indirectly associated to outcome, such as advanced disease, postoperative upgrading [27], high Gleason score and grade group [28], and occurrence of bone metastasis [25].

BLADDER CANCER

Bladder cancer (BC) is traditionally regarded as a disease of the elderly. Its overall incidence increases abruptly from a very low age-standardized rate of 2.3 in patients < 65y to a 51.1 rate in patients ≥ 65y; [1] its mortality rates range from 0.5 to 20.4 in the same age groups, and such data apply to both genders. The most common risk factors for BC are smoking [29 30], male gender, exposure to environmental or occupational carcinogens and the age.
From a clinical standpoint, two types of BC exist, namely non-muscle invasive bladder cancer (NMIBC) that account for approximately 75% of all tumors [31] and muscle invasive bladder cancer (MIBC). Such proportion remains constant throughout ages.

Diagnostic issues

Transurethral resection of the bladder tumor (TURBT) remains the first and mainstay method of local tumor

staging. Not to mention that in elderly people with other malignancies TURBT is essential to rule out other primaries. In other words, the onset of hematuria and/or a bladder mass in an elderly patient should not prompt a diagnosis of bladder primary without a TURBT, as secondary lesions from more frequent tumors such as colon, breast, or lung cancer may occur in this age group [32-35].

Patients diagnosed with NMIBC are stratified in risk categories based on several clinico-pathological parameters (EORTC) and such stratification is used to plan treatment. Age belongs to prognostic parameters as it has been shown to represent the most important prognostic factor for overall survival along with tumor's grade [31].

EAU guidelines however recognize that available clinico-pathological prognostic factors are not that efficient in assessing tumor biology and consequent behavior. In order to choose the proper treatment for NMIBC patients, especially those ones with high-risk tumors, several attempts have been made to achieve an optimal stratification by assaying different molecular markers [36]. Since intravesical instillation of Bacillus Calmette-Guerin (BCG) is the standard treatment for high-risk NMIBC, attempts have been made to identify molecular markers, such as Retinoblastoma protein (pRb), Human epidermal growth factor receptor 2 (Her-2), p53, p21, or survivin, which could reliably predict response to such treatment and consequent disease outcome [41]. Moreover, there is emerging evidence that the combination of markers is more effective than the single ones in predicting treatment response and disease outcome [42-44]. Further focused studies on a validated combination of clinic-pathological and molecular markers are necessary.

Treatment options

The standard of care in high-risk NMIBC remains intravesical instillation of BCG. However, being based onto efficiency of the immune system, the efficacy of such treatment in elderly has been questioned. Moreover, a greater risk of adverse events has been postulated, such as fever, hematuria, urinary symptoms and clot retention or more severe related to intravascular dissemination of tubercle bacillus [45]. This issue deserves attention in order to avoid patients not receiving effective treatment for their high-risk NMIBC only on the basis of anagraphic age.

As for MIBC, radical cystectomy (RC) stands out as the treatment of choice in most cases [46]. RC seems, however, to carry a complication rate as high as 40-60% in the elderly [47]; on the other hand, evidence exists that RC is associated with the greatest risk reduction in disease-related and non-disease-related death in patients > 80y [48]. Having said this, biological age (i.e. presence of comorbidities) is far more important than chronological age as a prognostic factor for MIBC patients undergoing RC [46 47]. As always, a careful patient's evaluation should be carried out in planning treatment for MIBC and validated tool, such as the Charlson Comorbidity Index (CCI) [47] may be useful in the decision-making process. On the other hand, like for other common urological conditions, treatment should be tailored to local conditions and wise intraoperative clinical judgment [49-51]. RC is more and more accepted also in octogenarians but the use of continent urinary diversion in such age population remains controversial. Moreover, case volume seems to impact on outcomes, as in other surgical fields [52]. Robotic RC offers the advantage of reduced invasivity, but this is counter balanced by length of the procedure and pneumoperitneum [53]. Moreover, potential complications associated to specific procedural steps should be taken into account [54].

Finally, questions remain regarding feasibility, efficacy and safety of adjuvant systemic chemotherapy in the elderly patient with MIBC, as the potential benefit should be carefully weight against the almost inevitable toxicity of such treatment. Like in other urological cancers [55 56], immunotherapy is recently emerging as a promising option in patients with advanced disease. Specifically, checkpoint inhibitors (PDL-1 and PD1) yield great promise in patients failing or unsuitable for chemotherapy. Whether or not immunosenescence may impair response to such treatment deserve further investigation.

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Conflict of Interest

The authors declare no conflict of interest.

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