Prostate Cancer in Elderly: Can We Aplly the European Guidelines to Romanian Patients?

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Abstract

With the increase in the incidence of cancer worldwide and the aging of the population, prostate cancer remains a topic of debate in the world of urologists and beyond. In the last years several notable advances were made in the care of men with this disease. In our days, we have a great amount of information regarding cellular, molecular biology and also a series of innovative strategies driven by technological advances. Because in everyday practice there are socio-economic as well as age differences between European patients, we wanted to highlight if the European guidelines can be totally applied to elderly Romanian patients.

Key-words: prostate cancer, elderly, guidelines, Romania

Introduction

Motto:

"I had prostate cancer. It was rather painful and, in many ways, life-changing."

Roger Moore

Located on the third place (together with bladder cancer) in the classification of causes of cancer mortality in Romania, the neoplasm of prostate still raises many problems in the first line of this fight - the urologist specialists. As brachytherapy - radiotherapy with a curative vision in the localized stage of the disease - takes place in the therapeutic urological arsenal of the Romanian urologists, and the PSA test becomes known and feasible in almost all private laboratories or large hospitals, new challenges arise in front of those who need to help in the most competent way the patient in distress.

According to Crawford, the prostate cancer is the most common malignancy among elderly men and is the second leading malignancy in the Western world [1]. Although we accept that statistics are the most elegant form of "eluding the truth" by discussing these figures, we can not ignore the reality that has led to this work: only one-sixth of those diagnosed with prostate cancer will die from the disease. In elderly the situation is even more diffrent, according to Newschaffer et al., prostate cancer is the underlying cause of death in 39% of the prostate cancer patients aged 67 years or more [2].

Results

Diagnosis of prostate cancer is rarely under the age of 50 years (less than 0.1% of patients). Gronberg et al. found that the maximum diagnosis incidence was be-

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tween 70 and 74 years, with 85% of patients being diagnosed after 65 years [3]. If we refer to an autopathological microscopic diagnosis at autopsy, on broad cohorts, 30% of men in the fourth decade, 50% of sixth men and over 75% of 85 years old men have a histological diagnosis of prostate cancer. If we live over 120 years, it is known that we, men, would be the 100% owner of a real prostate cancer! Referring to the previous figures, we can ask: if in the fourth decade of life almost one third of men have histologically identifiable neoplasia as the disease evolution is explained in the sense that, for example, in Sweden, the country with the highest reported mortality, 23 out of 100 000 inhabitants die from prostate cancer per year [4]?

A turning point in the evolution of the formulation of diagnosis and treatment of this disease is considered by many of the widespread use of PSA dosing. The use of this disease diagnosis in localized or locally advanced disease has increased while disease identification in the metastatic stage has decreased. According to Derweesh, in 2004, 75% of patients diagnosed in the US at the stage where the digital rectal examination is normal [5]. Unfortunately, this rises another dilemma in the urological world: some authors, like Tewari et al., support screening based on the fact that an early detection based on PSA helped identify early-stage malignancy and reduced mortality rates [6]. Opponents, like Etzioni et al., argue that there is no evidence that early detection would lower morbidity, and more so, the proposed aggressive treatments would do more harm than good in the context of the long history of the disease and long-term randomized trials are missing [7]. According to Stangelberger et al., besides PSA and Gleason score, age is considered a key prognostic factor in treatment decision making while oservational studies of older men with early stage disease have suggested conservative management as a viable option [8]. On the other hand, the TaskForce of the International Society of Geriatric Oncology recommends that the choice of therapy should not be based on chronological age, which proceeds at the same pace for all, but on biological aging and health status, which differ greatly from one person to another [9]. Therefore is very important to evaluate the health status before taking a decision.

The gold standard for evaluating health status, according to Decoster et al., is the Comprehensive Geriatric Assessment (CGA-G8) [10]. This assessment provides informations on demographic, social, functional, nutritional, cognitive, and mental health status and the presence of comorbidities and geriatric syndromes. Unfortunatelly, is time-consuming and requires specialised staff. Thus, after geriatric screening, according to the European Association of Urology (EAU) guidelines, patients with a CGA-G8 score > 14 should receive standard treatment as for younger patients and those with a score <14 should undergo complete geriatric assessment to evaluate reversibility of any impairments [11].

What is the status of the Romanian patients? After evaluating 600 urological patients by completing the Gronongen Frailty Index, 42.83% were classified as „fragile", this translated into a larger number of post-operative complications and a longer hospitalization period [12]. More than that according to the latest WHO data published in 2018 life expectancy is males in Romania 71.6 years, much smaller compared to 83 years in Sweden or Switzerland or 82 years in United Kingdom, Portugal or Austria [13].

Treatment

Any decision is difficult to take because any form of treatment of prostate cancer has flaws and difficulties arise even from diagnosis. To confirm the diagnosis we need to perform a prostate biopsy which can not be mede in patients with coagulopathies, immunosuppression or acute prostatitis. A first problem related to this crucial moment of diagnosis is related to the discontinuation of anticoagulant/antiplatelet therapy (Warfarin, Clopidrogel, Ticlodipine) or non-steroidal anti-inflammatory drugs at least 7-10 days before puncture. Many of our elderly patients has this kind of treatment, in this situation the patients will ask naturally: "Does not happen if I break the medication recommended by the cardiologist?". According to Canadian Association of Urology (CUA) guidelines, the antiplatelet agent has to be reviewed with the patient, his primary care physician or cardiologist and only after that should the antiplatelet agent be stopped [14]. In our daily practice, we did not experience cardio-circulatory problems that occurred when discontinuing medication (Aspenter, Plavix, Trombostop, Sintrom) but we consider that a discussion with the cardiologist is useful.

Antibiotic prophylaxis is unanimously accepted and the regimens used by us included fluorochinolone-associated metronidazole 48 hours before puncture and 3 days after it was performed. Although there are authors, like Djavan et al., who have used quinolone only 30-60 minutes before biopsy and continued therapy for 2-3 days or other treatment regimens, the incidence of

sepsis or bacteriemia in the literature is 0.1% - 0.5% of patients [15]. CUA guidelines recommends that broad-based gram-negative antibiotic prophylaxis (e.g., fluorquinolone) should be administered prior to biopsy and may be continued for 2 to 3 days post-biopsy [14].

Because older men are more likely to have larger and higher-grade tumours, might benefit more from a local treatment including radical prostatectomy. According to Droz et al, for high-risk lesions, cancer-specific survival is up to 91% after surgery combined with adjuvant and/or salvage modalities [9]. Among older men radical prostatectomy was associated with a reduced risk of metastases and use of androgen deprivation therapy. Broadly, the indications of prostate cancer endoscopic surgery are approximately the same as those for benign prostatic hyperplasia: acute urinary retention, recurrent urinary infections, repetitive hematuria (here the goal is to investigate and suppress the bleeding source) a degree of renal insufficiency due to chronical subvezical obstruction. No surgery is simple and the daily experience teaches that starting with the anesthetic act - regional anesthesia (spinal or epidural is the most appropriate and most used in these cases), general anesthesia is not preferred. Regional anesthesia provides increased perioperative comfort and does not show disagreeable situations at the end of the operation due to the cough effort and the resumption of spontaneous respiratory movements - the compressing and hemostatic balloon of the well-placed urethral catheter can change his position and the bleeding from the prostate begins again. Also the position of the patient on the table of endoscopic operations -lithotomy position- is not a negligible feature. It is known that, especially from 75 years up, we can have patients with coxarthrosis or other similar conditions as well as with a history of deep vein thrombosis of the lower limbs that makes it difficult or even contraindicate such positioning. This is another dilemma: is it not simpler to drain the bladder after 75 years than to perform an transurethral resection of the prostate?

Discussions

According to the EAU guidelines, in patients with non-metastatic localised PCa not suitable for curative treatment, immediate androgen deprivation therapy (ADT) should be used only in patients requiring symptom palliation, while in patients with locally advanced T3-T4 disease, patients with PSA > 50 ng/mL may benefit from immediate ADT [11]. In older patients we must carefully consider the toxicities of ADT. In general, agents that result in a hypogonadal state can lead to toxicities within the following domains: metabolic and body composition; sexual health; and mood and central nervous system (CNS) symptoms. The risk of osteoporosis development is important to keep in mind because geriatric syndromes (such as fall risk, delirium, and incontinence) can predispose patients to osteoporotic fractures.

More than that, patients may experience metabolic consequences, such as decreased insulin sensitivity, elevated cholesterol levels, and hypertension, which contribute to an increased risk of metabolic syndrome and cardiovascular disease in this population. Haque et al. showed that ADT is associated with an increased risk of heart failure in men without preexisting cardiovascular disease [16]. Elevated risks of arrhythmia and conduction disorder were only observed among patients with preexisting cardiovascular disease. Although there are no consistent data linking ADT as a causal agent to cardiovascular disease and mortality, there are clear relationships between the metabolic changes that occur on ADT and their contribution to cardiovascular disease development. Once again, according to Eurostat, there are huge differences in the incidence of cardiovascular events between Romania and Western countries. While in the United Kingdom cardiovascular diseases share of all deaths is 23.3% or 26.6% in the Nederlands, in Romania 59.3% of all death are secondary to cardiovascular diseases [17].

A particular feature of prostatic neoplasia is the "active monitoring" approach, also known as active surveillance. Traditionally postponing treatment was considered appropriate for those with life expectancy of less than 10 years with well differentiated tumors (Gleason score between 2-5) [18]. It is becoming more and more important nowadays to apply active monitoring to patients with small, well-differentiated or moderately low-volume prostatic neoplasms to avoid or delay treatments that are not immediately needed.

There has been a problem for urologists for a long time in order to define as accurately as possible which tumors can be observed without aggressive treatment. Thus, Klein et al. defines the "indolent" tumor as being strictly located in the prostate gland with a relatively well-differentiated <0.5 ml volume (other authors call into question other evaluation and follow-up criteria (free PSA / PSA ratio ≥ 0.15, less than 3 neoplastic tissue biopsy samples, and less than 50% of the prostate biopsy fragment was tumor tissue) [19].

Interesting is the conclusion reached by appling the

Kattan nomograms: 20% of patients treated with radical prostatectomy met the criterion of "indolent" tumor, insignificant, which could only be followed in a first phase....So the contradiction appears: "It works early in cancer if you want to heal" versus "properly monitors the patient with localized tumor to avoid being more aggressive than it should". The only way we look for a new dilemma is to look at the patient's age, comorbidities, and last but not least, his options and possibilities. On the other hand, if the level of PSA is increasing, transrectal echocardiography reveal the increase in volume and the new prostatic biopsy indicates the spread of the neoplastic process, the treatment must be instituted.

We highlight a dialogue between patient, family, cardiologist, urologist, anesthesiologist and oncologist, adapted to the level of understanding, anatomopathological outcome of the disease state, comorbidities and predictive risks from the perspective of literature and experience.

Conclusions

The final treatment-related decision belongs to the patient influenced more or less by the family. But the urologist will be free of worm of conscience by properly informing the patient and the family and advising the other specialists. Surely we swept between prejudices, confusions, mistakes and misinterpretations. We know that "an error is even more dangerous as it contains more truth" (H.F. Arniel) and that "the shorter the error, the better it is" (Molière). So we preferred dilemmas...

References

1. Crawford ED. *Epidemiology of prostate cancer.* Urology. 2003 Dec 22;62(6 Suppl 1):3-12.
2. Newschaffer CJ, Otani K, McDonald KM, Penberthy LT; *Causes of Death in Elderly Prostate Cancer Patients and in a Comparison Nonprostate Cancer Cohort*, J Natl Cancer Inst 2000 Apr 92;(8):613–621.
3. Gronberg H: *Prostate cancer epidemiology*, Lancet. 2003 Mar 8;361(9360):859-64.
4. Walsh PC, Brooks JD. *The Swedish Prostate Cancer Paradox*. JAMA. 1997;277(6):497-498.
5. Derweesh IH, Kupelian PA, Zippe C, Levin HS, Brainard J, Magi-Galluzzi C, Myles J, Reuther AM, Klein EA. *Continuing trends in pathological stage migration in radical prostatectomy specimens.*Urol Oncol. 2004 Jul-Aug;22(4):300-6.
6. Tewari A, Horninger W, Pelzer AE, Demers R, Crawford ED, Gamito EJ, Divine G, Johnson CC, Bartsch G, Menon M. *Factors contributing to the racial differences in prostate cancer mortality.* BJU Int. 2005 Dec;96(9):1247-52.
7. Etzioni R, Cha R, Feuer EJ, Davidov O. *Asymptomatic incidence and duration of prostate cancer.* Am J Epidemiol. 1998 Oct 15;148(8):775-85.
8. Stangelberger A, Waldert M, Djavan B. *Prostate cancer in elderly men.* Rev Urol. 2008;10(2):111-9.
9. Droz, JP., Albrand, G., Gillessen, S. et al. *Management of Prostate Cancer in Elderly Patients: Recommendations of a Task Force of the International Society of Geriatric Oncology.* Eur Urol 20017;72(4), 521–531.
19. Decoster L, Van Puyvelde K, Mohile S, et al. *Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations.* Ann Oncol. 2015 Feb;26(2):288-300.
11. Mottet N, Bellmunt J, Bolla M et al. *EAU Guidelines on Prostate Cancer.* Eur Urol. 2017 Apr;71(4):618-629.
12. C. Pricop C, Miron AV, Rosca M, Puia D. *Groningen score applied to 600 urologic patients over 60 years of age - preliminary results.* Eur Urol Suppl 2018 Oct;17(12):e2671
13. ***https://www.worldlifeexpectancy.com/romania-life-expectancy
14. El-Hakim A, Moussa S. *CUA guidelines on prostate biopsy methodology.* Can Urol Assoc J. 2010;4(2):89-94.
15. Djavan B, Ravery V, Zlotta A, et al. *Prospective evaluation of prostate cancer detected on biopsies 1, 2, 3 and 4: when should we stop?* J Urol. 2001 Nov;166(5):1679-83.
16. Haque R, UlcickasYood M, Xu X, Cassidy-Bushrow AE, Tsai HT, Keating NL, Van Den Eeden SK, Potosky AL. *Cardiovascular disease risk and androgen deprivation therapy in patients with localised prostate cancer: a prospective cohort study.* Br J Cancer. 2017 Oct 10;117(8):1233-1240.
17. ***https://ec.europa.eu/eurostat/statistics-explained/pdfscache/37359.pdf
18. Catalona WJ, Han M. *Definitive Therapy for localized prostate cancer – an overview in Campbell Walsh Urology*, 9th Edition , Elsevier 2007, vol 3, p.2932-2946.
19. Klein EA, Elizabeth Platz, Thomson IM: *Epidemiology, Etiology and Prevention of Prostate Cancer,* in Campbell Walsh Urology, 9th Edition , Elsevier 2007, p. 2854-2873.