



MANAGEMENT OF LOCALLY ADVANCED, AGGRESSIVE PROSTATE CANCER – CASE REPORT

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SUMMARY – Treatment of locally advanced prostate cancer (PC) represents a challenge before multidisciplinary team (MDT), typically includes not only local disease control but also systemic therapy and it should be tailored to each individual patient. We present a case of a 58-year-old man, whose PC presented itself as a locally advanced disease. Bearing in mind the patients' age, absence of comorbidities but also his preferences, MDT decided that the rational first step in almost imminent multimodal treatment should be radical prostatectomy (RP). Due to several local adverse factors (positive surgical margins, extracapsular extension, seminal vesicle involvement) on RP specimen pathology and postoperative prostate specific antigen (PSA) of 6.69 ng/ml our MDT determined luteinizing hormone-releasing hormone (LHRH) agonist therapy in the course of 3 years plus immediate salvage radiotherapy. The therapy was well tolerated, although there was one episode of transitory radiation cystitis roughly one year after its completion. After 45 months of follow-up the patient is without signs of biochemical recurrence of PC, with fully restored testosterone level and good quality of life. The main task in advanced PC management, through multidisciplinary approach, is providing good oncological outcome while trying to reduce treatment morbidity and to maintain a good quality of life.

Key words: *Prostatic Neoplasms; Gonadotropin-Releasing Hormone; Radiotherapy; Lymph Node Dissection*

Introduction

Prostate cancer (PC) is the second most common malignancy in men^{1,2}, but it is not a universal entity, with clinical behavior spanning from indolent, slowly progressive disease to aggressive, life-threatening condition^{1,3}, so the treatment should be tailored to specific circumstances of each individual situation/patient. Management of high-risk localized and locally advanced PC is a difficult task and should include a multidisciplinary approach in trying to find the right

treatment modalities and their sequencing, while at the same time avoiding treatments' side effects as much as possible. Therefore the „burning” questions on advanced PC management are discussed biennially at the Advanced Prostate Cancer Consensus Conference (APCCC)⁴. By the European Association of Urology (EAU) risk group classification¹ PC is defined as locally advanced in case of cT3-4 or cN+ disease and any prostate specific antigen (PSA) level and Gleason score (GS). Treatment of locally advanced PC usually includes combination of both local and systemic therapy, where radical prostatectomy (RP) with extended pelvic lymph node dissection (eLND) can be performed in selected patients as a first step in multimodal treatment (which also includes adjuvant or salvage radiotherapy, androgen deprivation therapy [ADT] and more)¹. Here we present a case of a man with lo-

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cally advanced disease, who received multimodal treatment of PC at the Departments of Urology and Oncology in Osijek University Hospital from 2016 to 2019.

Case Report

A 58-year-old man was referred to our outpatient clinic by his general practitioner because of an elevated PSA level of 39 ng/ml (repeated PSA test). The PSA screening was initiated by a physician due to patients' age alone, since the patient had no lower urinary tract symptoms (LUTS) or other urological problems. He was an ex-smoker, with no other chronic diseases and with good health and performance status. On digital rectal exam (DRE) the prostate was initially enlarged, painless and inconspicuous, albeit with subtle hardened consistency in general. There were no clinical or laboratory findings that would suggest a urinary tract infection so the patient was scheduled for an outpatient transrectal prostate biopsy. The procedure went uneventful, while the pathohistological finding revealed GS 4+3=7 adenocarcinoma of the prostate (International Society of Urological Pathology grade 3), with 10 out of 12 biopsy cores positive for cancer. We proceeded with a diagnostic evaluation: bone scintigraphy revealed no metastases and the abdominopelvic computed tomography (CT) scan showed only slightly enlarged prostate (32 g) that was mildly inhomogeneous on native and postcontrast study. Furthermore, CT scan identified three perivesical lymph nodes, the largest being 9 millimeters in diameter. At that time, it was not technically possible to perform multiparametric magnetic resonance imaging (mp-MRI) of the prostate at our hospital, so we were rather deprived of adequate local staging. The patient was presented at the uro-oncological multidisciplinary team (MDT) at the Department of Urology and it was concluded that RP was the treatment of choice, which was also in line with patients' preferences. RP was performed in February 2016 and the procedure, as well as the early postoperative course went uneventful. Patient was discharged on the sixth postoperative day, while on the fourteenth day the outpatient cystography was performed and revealed no urine leakage. The urethral catheter was removed and afterwards the patient urinated normally. Pathohistologically, prostate of 75 g was 90 % infiltrated with tumor tissue, with the largest

tumor nodus of 35 x 15 mm. The tumor was composed of acinar and mucinous (colloid) subtypes of prostate adenocarcinoma. There was an upgrading of the initial biopsy GS of 7 to definitive GS of 4+4=8. There were several local adverse factors: extracapsular extension, bilateral seminal vesicle involvement and multifocal and bilateral positive surgical margins. There was also perineural invasion present, but without lymphovascular invasion. From 3 examined lymph nodes, one was infiltrated with tumor tissue.

Six weeks after RP the patient was well and had regained full recovery of urinary continence. Considering postoperative PSA of 6.69 ng/ml and adverse pathologic features of RP specimen, our uro-oncological MDT decided to start luteinizing hormone-releasing hormone (LHRH) agonist therapy with 3-month formulation of goserelin (which was continued for 3 years overall, from April 2016 until January 2019) and salvage radiotherapy of the prostatic bed plus whole pelvis was initiated in June 2016, where patient was treated to a dose of 66 Gy in 33 fractions. Radiotherapy was well tolerated and in October 2016 PSA was 0.02 ng/ml, with castration testosterone level as the LHRH agonist therapy was continued.

In May 2017 the patient presented himself with gross hematuria and subsequently underwent outpatient urethroscopy which revealed a shallow, irregular, ulcer-like lesion on the posterior bladder wall, 15 mm in diameter, without the presence of active bleeding. The clinical suspicion of postirradiation lesion was confirmed pathohistologically at an inpatient bladder biopsy, as there were histopathological features of inflammation, with no sign of malignancy and with negative urine cytology. Hematuria had not recurred, and patients' voiding was normal afterwards.

Hereafter, oncological and urological surveillance was continued, with LHRH therapy every three months until January 2019 when the therapy was concluded with twelfth LHRH agonist administered and with a PSA of 0.0 ng/ml and testosterone level of 0.36 nmol/L. After the cessation of LHRH agonist therapy the patients' testosterone level was fully restored. Meanwhile, a cardiological evaluation was carried out and the patient was suitable for erectile dysfunction therapy with sildenafil. His last checkup was in September 2019, still with undetectable PSA and without micro- or macro-hematuria and he was scheduled for the next control in six months.

Discussion

Opportunistic screening or early detection of PC has been increasingly used in Croatia (e.g. PSA testing is performed during regular yearly checkup of war veterans of Croatian War of Independence), even though population screening is not introduced by health authorities. The topic of mass screening is globally controversial^{5,6,7} and not recommended by the EAU¹ as it had not led to a decrease in PC mortality, which is the main endpoint in PC diagnosis and treatment. However, opportunistic screening in the case of our patient has certainly resulted in a timely diagnosis and consecutive treatment of what proved to be an aggressive disease.

We performed systemic transrectal prostate biopsy without previous mp-MRI of the prostate which is an acceptable approach according to EAU Guidelines¹. Nevertheless, 2019 edition of EAU Guidelines recommend performing prostate mp-MRI before first biopsy if possible^{1,8}. In the beginning of 2016 mp-MRI was not available in our institution and when it became available the practice was to use it prior to a planned repeat biopsy and not in biopsy-naïve patients. Unavailability of mp-MRI at the time was also the reason for not performing it in local staging prior to RP.

After the histopathological confirmation of PC, and according to PSA value and GS, we carried out abdominopelvic CT and bone scintigraphy for metastatic screening. Bone scan was unremarkable and without metastatic spread while CT scan revealed three perivesical lymph nodes, the largest being 9 millimeters in diameter. The usual lymph node size threshold for lymph nodes in the pelvis suspicious for metastasis is 8 mm^{1,9} which could classify the disease in our patient as locally advanced (N+) and not high-risk localized PC. The patient was presented at Hospitals' uro-oncological MDT which concluded that despite our risk-group stratification dilemma the reasonable first step in his treatment should be RP with extended pelvic lymph node dissection (eLND), especially considering his young age and absence of comorbidity. The procedure and early postoperative period went uneventful, but the local adverse factors (extracapsular extension, bilateral seminal vesicle involvement and multifocal and bilateral positive surgi-

cal margins) on histopathological specimen, as well as high postoperative PSA, necessitated further oncological treatment. There were also only three lymph nodes removed which does not qualify as eLND. In APCCC 2017⁴ there was a panel question on the adequate number of lymph nodes removed during eLND and 49 % of experts answered 11-19, while 27 % considered 20 lymph nodes or more as adequate sampling. While we failed to provide important staging information with eLND, it does not, though, influence the overall oncological outcome¹⁰.

ADT was initiated and the patient underwent salvage 3D conformal radiotherapy (3D-CRT) of the prostatic bed and whole pelvis. Intensity-modulated radiotherapy (IMRT) and volumetric arc external-beam radiotherapy (VMAT), which are a gold standard for external-beam radiotherapy (EBRT)¹, were only later introduced at our institution. There were no early complications of EBRT but roughly one year after its completion the patient presented himself with hematuria and ulcer-like bladder lesion which proved to be inflammatory postirradiation consequence rather than metachronous transitional cell carcinoma of the bladder. In further course, after three years of ADT the treatment was completed and shortly thereafter the patients' testosterone level was fully restored, and he was without signs of biochemical recurrence after 45 months of follow-up.

In conclusion, the treatment of PC, especially locally advanced disease represents a challenge. Bearing in mind that PC is not a unique clinical entity, each patient should have his treatment tailored individually and based upon up-to-date scientific evidence. Patients' preferences, age and performance status, as well as advantages and shortcomings of treatment modalities should be taken into consideration when deciding upon certain PC therapeutic route. The goal of PC treatment is not only in achieving a good oncological outcome but also in reducing treatment morbidity and maintaining a good quality of life, where reduction of overdiagnosis and overtreatment plays a crucial role. MDT assessment reduces the possible bias of one specialist decision-making in every oncological disease, and thus in PC as well.

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Sažetak

LIJEČENJE LOKALNO UZNAPREDOVALOG, AGRESIVNOG KARCINOMA PROSTATE – PRIKAZ SLUČAJA

B. Sudarević

Liječenje lokalno uznapredovalog karcinoma prostate (PC) predstavlja izazov za multidisciplinarni tim (MDT), najčešće uključuje kombinaciju lokalne kontrole bolesti i sustavnog liječenja te bi trebalo biti prilagođeno svakom pojedinom bolesniku. Prikazujemo slučaj 58-godišnjeg bolesnika čiji se PC očitovao kao lokalno uznapredovala bolest. Uzimajući u obzir bolesnikovu dob, odsutnost komorbiditeta, ali i njegove želje, MDT je odlučio kako bi prvi korak u gotovo sigurno multimodalnom liječenju trebala biti radikalna prostatektomija (RP). Zbog brojnih nepovoljnih lokalnih čimbenika (pozitivni kiruski rubovi, ekstrakapsularno širenje i zahvaćenost sjemenih mjehurića) na patohistološkom preparatu nakon RP-a i zbog postoperativnog prostata specifičnog antigena (PSA) od 6,69 ng/ml naš MDT je odlučio provesti liječenje agonistima hormona oslobađanja luteinizirajućeg hormona (engl. luteinising hormone-releasing hormone; LHRH) kroz 3 godine te neodgođenu *salvage* radioterapiju. Bolesnik je liječenje dobro podnio, premda se otprilike godinu dana nakon završetka radioterapije pojavila prolazna epizoda radijacijskog cistitisa. Bolesnik je bez znakova aktivne bolesti nakon 45 mjeseci praćenja, dobre kvalitete života i potpuno oporavljene serumske razine testosterona. Glavni cilj liječenja uznapredovalog PC-a, uz multidisciplinarni pristup, jest postići dobar onkološki ishod, ali i smanjiti morbiditet liječenja na najmanju moguću mjeru te održati kvalitetu života dobrom.

Ključne riječi: *Neoplazme prostate; Gonadotropin-oslobađajući hormon; Radioterapija; Disekcija limfnih čvorova*