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Professional paper

SURGICAL TREATMENT OF HIGH-RISK PROSTATIC CARCINOMA AND OLIGOMETASTATIC DISEASE

Ivica Mokos[1], Ahmad El Saleh[1], Tomislav Kuliš[1], Marija Topalović Grković[2], Iva Bačak Kocman[2] and Željko Kaštelan[1]

[1]Department of Urology, [2]Department of Anesthesiology,
University Hospital Center Zagreb, Kišpatićeva 12, Zagreb, Croatia

SUMMARY – Prostate cancer is responsible for the largest number of cancer-related deaths in male population in many countries of the world. Aggressive forms of the disease are associated with an increased risk of local recurrence and death. Treatment of high-risk local prostate cancer most commonly involves radical prostatectomy (RP) or external beam radiation therapy (EBRT) combined with androgen deprivation therapy (ADT) with or without the addition of brachytherapy (BT). The use of surgery for high risk prostatic carcinoma (HRPC) is on the rise, because of its advantages including the possibility of cure with surgery alone without the risk of toxicities from prolonged ADT, accurate staging, and avoiding the influence of PSA originating from benign prostatic hyperplasia on future therapy. Oligometastatic prostate cancer may be considered as the last border of possibly curable disease. Radical prostatectomy in oligometastatic prostate cancer can significantly decrease the risk of local complications but only multimodal approach in selected group of patients may offer opportunities to eradicate tumor or delay its progression. Surgery for oligometastatic disease most commonly targets lymphatic disease with salvage pelvic lymph node dissection, whereas it rarely targets distant metastases. Further prospective, randomized studies are necessary to define the role and value of therapies in oligometastatic prostate cancer.

Key words: *Prostatic Neoplasms, Urologic Surgical Procedures, Lymph Node Excision, Metastasectomy.*

Introduction

Prostate cancer is, after skin malignancies, the second most common malignant disease in male population. Although it usually has an indolent course, "high-risk" prostate cancer (HRPC) tends to recur despite optimal treatment and may have fatal outcome[1].

The European Association of Urology (EAU) defines HRPC with specific criteria, including higher PSA levels of >20 ng/ml, or Gleason score at biopsy of >7 (ISUP Grade 4/5) or clinical stage T2c[2]. HRPC is associated with an increased risk for biochemical and metastatic progression and cancer-related death[3]. When the tumor is not fixed to the pelvic wall or does not invade the urethral sphincter, radical prostatectomy (RP) is considered as the first step for treatment[3]. Other treatment options include EBRT with ADT or EBRT plus BT and ADT. Advantages of RP for HRPC include accurate staging and grading, removal of benign source of PSA and possibly avoiding ADT[4].

The comparative studies of different treatment strategies for HRPC have become a matter of intense debate. As shown in meta-analysis performed by Wallis et al. on 118,300 patients, the risk of mortality, both overall and cancer-specific, was higher in patients treated with radiotherapy than in those who underwent surgery[5]. Similarly, meta-analysis that included patients with only HRPC has shown higher survival rate among patients treated with surgery compared to those who were treated with radiotherapy[6]. A recent paper by Berg et al.[7] showed that in young and healthy men presenting with HRPC, RP resulted with better

Correspondence to: *Ivica Mokos, MD, PhD,* Department of Urology, University Hospital Center Zagreb, Kišpatićeva 12, Zagreb, Croatia
E-mail: ivica.mokos@zg.t-com.hr

overall survival in comparison with combination of EBRT and BT; hazard ratio (HR) ERBT plus BT:RP was 1.22.

Gansler et al. reported that 58% of 6,303 patients with biopsy proven Gleason score 8 were downgraded on final pathology after RP, which led to the lower risk category classification[8]. Based on these observations, it has been concluded that the main advantage of RP is to enable more precise staging of HRPC. Furthermore, the duration of adjuvant ADT (in combination with EBRT) was significantly shorter among patients who were previously treated with RP when compared to those who received ADT plus EBRT as a first-line treatment for HRPC.

Oligometastatic prostate cancer

Oligometastatic prostate cancer (OPC) has increasingly been detected since the introduction of positron emission tomography (PET), using ligands targeted at the prostate-specific membrane antigen (PSMA) or ^{18}F-choline as radiotracers. Although there is no consensus for the exact definition of OPC, it is usually defined by the presence of £ 3 (or less than five) metastatic bone or lymph node lesions that could be treated with surgery or radiotherapy, without rapid dissemination to other sites.

There are at least four clinical scenarios of the occurrence of OPC: 1) initial presentation of oligometastatic disease in the patient who has not been previously treated and is castration-naive (synchronous disease); 2) oligometastatic disease develops subsequently after keeping the cancer under control with surgical treatment or radiotherapy in the patient who is usually castration naive (metachronous disease); 3) recurrence of previously treated oligometastases in the patient who may be castration naive or not (oligo-recurrent disease); 4) systemic therapy of widely metastatic prostatic cancer was successful considering the most of metastases, but a minority of metastatic lesions have advanced; the patients are castration resistant (oligo-progressive disease).

Recent multi-institutional study has been conducted on 113 patients with small pelvic lymph node or bone-only metastatic disease who were treated with cytoreductive radical prostatectomy and pelvic lymphadenectomy combined with ADT[9]. The treatment resulted in 5-year overall survival in nearly 80% of patients, whereas a mean relapse-free survival was 6 years.

Surgical treatment of metachronous disease that is restricted to pelvic nodes without metastases in retroperitoneal lymph nodes includes salvage pelvic lymph node dissection (sPLND), and treatment of other isolated lesions involving metastasis-directed therapy (MDT). As reported by Ost et al., ADT-free survival period was significantly longer in patients who underwent MDT when compared to the surveillance group; additionally, among patients in the MDT group no grade 2 or greater toxicity was observed[10]. Karnes et al. performed a retrospective study of patients who underwent sPLND for prostate cancer nodal recurrence after radical prostatectomy. No additional treatment was employed in 46.2% of patients. After 3 years of follow-up, 45.5% of patients remained biochemically recurrence-free; cancer specific survival was 92.5%, and systemic progression-free survival was 46.9%[11]. The results of recently reported, largest retrospective trial of 654 patients with nodal recurrent prostate cancer revealed that 75% of patients experienced no clinical recurrence during the period of 1 year following sPLND, whereas a median time to clinical recurrence was approximately 3 years[12].

In conclusion, in recent times a significant progress in understanding the oligometastatic concept of prostate cancer has been made. However, further efforts are needed to clarify different prognostic subgroups of OPC concerning clinical manifestations and preferable therapeutic approach.

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Sažetak

KIRURŠKO LIJEČENJE KARCINOMA PROSTATE VISOKOG RIZIKA I OLIGOMETASTATSKE BOLESTI

I. Mokos, A. El Saleh, T. Kuliš, M. Topalović Grković, I. Bačak Kocman i *Ž. Kaštelan*

Rak prostate ostaje najčešći uzrok smrtnosti od karcinoma u mnogim zemljama svijeta. Bolesnici s agresivnijom bolešću izloženi su većem riziku od neuspjeha lokalnog liječenja i smrti. Liječenje visoko rizične lokalne bolesti najčešće uključuje radikalnu prostatektomiju, radioterapiju (EBRT) s androgenom deprivacijskom terapijom (ADT) ili EBRT plus brahiterapiju (BT) i ADT. Kirurško liječenje karcinoma prostate visokog rizika (HRPC) je u porastu zbog svojih prednosti koje uključuju mogućnost izlječenja samo operacijom, točno određivanje stadija bolesti, uklanjanje dobroćudnog izvora PSA koji je čimbenik za određivanje buduće terapije, te mogućnost izbjegavanja toksičnosti dugotrajne primjene ADT-a. Čini se da je oligometastatska bolest posljednja barijera potencijalno izlječivog karcinoma prostate. Radikalna prostatektomija u oligometastatskom karcinomu prostate može značajno smanjiti rizik od lokalnih komplikacija, ali samo multimodalni pristup odabranoj skupini bolesnika može pružiti mogućnosti za potpuno uklanjanje tumora ili usporavanje njegovog napredovanja. Kirurško liječenje oligometastatske bolesti najčešće je usmjereno na limfogeno širenje s disekcijom zahvaćenih zdjeličnih limfnih čvorova, a rjeđe može biti usmjereno na udaljene metastaze. Potrebna su daljnja prospektivna, randomizirana istraživanja za definiranje uloge i vrijednosti terapije oligometastatskog karcinoma prostate.

Ključne riječi: *tumori prostate, urološke kirurške procedure, limfadenektomija, metastazektomija.*