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Review article

Role of radical prostatectomy in metastatic prostate cancer: A review

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Abstract

Context: Recent demonstration of efficacy with the use of chemohormonal therapy for men with metastatic prostate cancer (mPCa) has expanded the therapeutic options for these patients. Furthermore, multimodal therapy to treat systemic disease in the context of locoregional control has gained increasing interest. Concomitantly, the role of radical prostatectomy (RP) in multimodal treatment for locally advanced prostate cancer is expanding. As a result, there is interest in investigating the potential benefit of cytoreductive RP in mPCa.

Objective: To review the literature regarding the role of cytoreductive prostatectomy in the setting of mPCa.

Evidence acquisition: MEDLINE and PubMed electronic databases were queried for English language articles related to patients with mPCa who underwent RP from January 1990 to June 2016. Key words used in our search included cytoreductive prostatectomy, radical prostatectomy, and metastatic prostate cancer. Preclinical, retrospective, and prospective studies were included.

Evidence synthesis: There are no published randomized control trials examining the role of cytoreduction in mPCa. Local symptoms are high in mPCa and often provide a necessity for palliative procedures with the impact on oncologic outcomes being uncertain. Recently, preclinical and retrospective population-based data suggest a benefit from treatment of the primary tumor in metastatic disease. Potential mechanisms mediating this benefit include prevention of symptomatic local progression and modulation of disease biology, resulting in an improvement in progression-free and overall survival. Current literature supports the feasibility of cytoreductive prostatectomy as it is associated with acceptable side effects that are comparable to RP for high-risk localized disease. In aggregate, these data compel prospective evaluation of the hypothesis that cytoreductive prostatectomy improves the outcome of men with mPCa.

Conclusions: Cytoreductive prostatectomy in mPCa is a feasible procedure that may improve outcomes for men when combined with multimodal management. Preclinical, translational, and retrospective evidence supports local therapy for metastatic disease. However, currently, evidence is limited and is subject to bias. The results of ongoing prospective randomized trials are required before incorporating this therapeutic strategy into clinical practice.

Keywords: Cytoreduction; Cytoreductive radical prostatectomy; Treatment of primary tumor; Radical prostatectomy; Local treatment; Surgery in metastatic; Surgery in systemic; Prostate cancer

1. Introduction

Prostate cancer (PCa) is the most common solid tumor seen in men, with 3.3 million men suffering from PCa in the United States at present and there is an estimated 180,900 cases to be diagnosed in 2016 [1]. Despite the availability of screening with prostate-specific antigen (PSA) and digital rectal examination, PCa remains a significant cause of mortality [1]. Unfortunately, even with significant advances in chemotherapy and androgen axis therapies, the overall survival (OS) and cancer-specific survival for patients who present with metastatic PCa (mPCa) has not significantly improved over the past 20 years [2]. The mainstay of therapy in these patients has been the use of androgen deprivation therapy (ADT) with or without the use of chemotherapy [3–5]. More recently, the role of local therapy through radical prostatectomy (RP) or treatment dose prostate radiation therapy (RT) with or without pelvic RT in mPCa has gained attention.

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Although debulking of the primary tumor in the setting of metastatic disease is an established concept in the treatment of other solid tumors (such as for renal and ovarian cancers [6,7]), cytoreductive surgery in PCa has not traditionally been considered. Owing to the lack of high-level evidence regarding the treatment of the primary tumor in patients with mPCa, current practice guidelines do not recommend surgery or radiation on the primary tumor for patients with mPCa [3–5,8]. Instead, the National Comprehensive Cancer Network guidelines recommend ADT with or without docetaxel chemotherapy and with RT only for palliation of local symptoms [3]. The European Association of Urology guidelines similarly state that surgery is not a standard option, whereas RT is preferred for the control of local symptoms [4,5].

In the past 2 decades, significant improvements in surgical and radiation techniques have shown decreased morbidity and improved outcomes in localized PCa. These include advances in robotic-assisted RP and RT techniques allowing for dose escalation, hypofractionation, intensity-modulated RT, and conformal RT, which have allowed for the increasingly safe and effective treatment of local PCa [9,10]. Therefore, with improved techniques for local control coupled with reduced morbidity as well as with improvements in survival achieved with systemic agents [11–13], the value of local therapy as a means to reduce symptomatic progression and alter tumor biology in mPCa requires a revisit and prospective evaluation [14–18].

The objective of this review is to examine the available evidence supporting the role of cytoreductive surgery in patients with mPCa. We will assess the potential effect of treatment of the primary tumor on systemic disease, address goals of therapy, evaluate safety and feasibility of surgery in this setting, and discuss ongoing clinical trials assessing this concept.

1.1. Preclinical data on the benefit of local control in the management of systemic disease

Several preclinical models have evaluated the use of cytoreduction in mPCa. Kadmon et al. implanted the R3327/MAT-Lu tumor, a PCa cell line that metastasizes to the lung in 100% of cases, subcutaneously into the flank of rats. They then treated the animals with sham surgery, surgical excision of the primary tumor, chemotherapy, or the combination of surgery and chemotherapy. Animals who underwent surgery plus chemotherapy had a survival benefit above those who did not have surgery (42% vs. 0% at 180-day sacrifice) [19]. This has been replicated in an orthotopic model with PC3 cells where it was found that after resection of the prostate, metastases were small and less numerous than in the control population, and that this effect was prolonged [20,21]. These small studies provide preclinical evidence that supports the biologic basis for cytoreduction in PCa.

The cellular and molecular rationale for surgical resection of the primary tumor in the setting of metastatic disease is being investigated. First, it has been shown that despite aggressive systemic therapy there is often viable, aggressive cancer remaining within the primary [22–25]. Tezlepi et al. [26] demonstrated that at RP there is evidence of increased expression of pathways associated with epithelial to mesenchymal transition in the primary tumor despite 1 year of chemohormonal therapy. These molecular profiles have been linked to PCa lethality. For example, preclinical studies have established a role for c-Src and Src family kinases in proliferation, angiogenesis, invasion, and bone metabolism of PCa. Further evaluation has demonstrated that Src signaling is imperative in both epithelial and stromal mechanisms of disease progression, androgen independence, and bone metastases [27]. Therefore, based on this theory it is hypothesized that by removal of the primary tumor the Src signal may be minimized resulting in a reduction in disease progression, androgen independence, and development of metastasis.

Second, several studies suggest an interaction between solid tumors, their circulating and disseminated tumor cells, and development and maintenance of metastatic sites. In mouse models, it has been shown that removal of the primary tumor may prevent development of new metastasis [21]. Kaplan describes a “premetastatic niche” whereby the primary tumor is the predominant source of metastasis through circulating tumor cells [28]. Sanchez et al. [29] extend this concept to exosomes from PCa cells that contain miRNA that may modify this premetastatic niche and may stimulate progression and metastasis. Other similar models such as the “self-seeding model” is based on the idea that the primary tumor acts as a source of metastatic cells that circulate and form metastatic deposits, these sites then further release tumor cells in a circular pattern to communicate with the primary [30,31]. In 2 recent studies, whole genome sequencing was completed on metastatic sites and the primary, when available, within several patients with mPCa [32,33]. Both studies provided an integrated analysis of the subclonal architecture of the tumors, which revealed the patterns of metastatic spread. In the Hong study, they identified 2 of 4 patients who had waves of metastases or prostatic fossa reseeding between the primary tumor and the metastatic sites, with one of the subclones identified as far out as 63 months from RP. The Gundem study characterized the genomic evolution of mPCa from primary site to multiple metastatic sites for 10 patients and 51 tumors. They found metastasis most commonly spread between distant metastatic sites. However, they included seminal vesicle and bladder involved tumors as separate sites of metastases, which were more likely representative of the leading edge of a locally aggressive prostate tumor or local recurrence and not a distinct metastases. Although these mixed patterns of metastatic spread are likely representative of the heterogeneity of PCa and suggest there may be a lack of uniformity in the benefit from local control in mPCa,