

Is it truly outrageous to consider radical prostatectomy for men with metastatic prostate cancer?

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ABSTRACT

Radical prostatectomy is a leading form of treatment for non metastatic prostate cancer. It has been shown to improve survival in the long term as well as delay or prevent the onset of metastatic disease. However, as the treatment of metastatic prostate cancer has evolved in the last few years with the introduction of newer agents, the possible role of 'cytoreductive' radical prostatectomy is now being explored. Preliminary evidence suggests that radical prostatectomy may have a future role in this clinical scenario with a potential to improve quality and quantity of life in selected patients with metastatic disease.

Key words: Metastatic prostate cancer, prostate cancer, radical prostatectomy

Radical prostatectomy (RP) is a leading treatment option for clinically organ confined prostate cancer (CaP) in men with a life expectancy greater than 10-15 years.^[1] Of late, there is growing evidence to suggest that patients with high-risk and/or locally advanced disease may benefit from RP and have prolonged disease free and overall survival (OS), especially when treated with a multimodal approach in combination with androgen deprivation therapy (ADT) and/or radiation therapy.^[2] It is probably not just pure coincidence, that these newer data have been accompanied by a growing body of evidence of a lack of benefit of RP in patients with low risk disease, especially in older men.^[3] All clinical guidelines now make it mandatory to counsel men with low risk organ confined CaP about the option of active surveillance vis a vis immediate treatment as a means of reducing morbidity without compromising survival.^[1] As the RP pendulum shifts from low risk to high-risk and locally advanced disease, is it now time to actually go to the other extreme and offer RP to

patients with metastatic prostate cancer? Is it possible that in the years to come RP + ADT would be a frontline treatment option for otherwise healthy men with metastatic CaP? As provocative and outrageous this may seem at present, there is some recent data to suggest that this statement may not be far from the truth.

A recent study by Culp *et al.* has evaluated the role of definitive local treatment (RP or brachytherapy [BT]) in patients with metastatic CaP.^[4] In this retrospective analysis, the authors identified 8185 men with metastatic CaP over a 7 year period (2004-2010) from the surveillance epidemiology and end results (SEER) database and comparatively evaluated those who underwent definitive treatment of the primary tumor, with the rest, who did not receive local treatment. A comparative analysis was performed between patients undergoing RP ($n = 245$) or BT ($n = 129$) and those not receiving surgery or radiation (NSR, $n = 7811$). They found that men with metastatic disease who underwent RP or BT had a significantly better disease specific survival (DSS) and OS when compared to the NSR group (5 years DSS: 75.8% vs. 61.3% vs. 48.7%, respectively, $P < 0.001$; 5 years OS: 67.4% vs. 52.6% vs. 22.5%, respectively, $P < 0.001$). There was no significant intergroup difference in the survival of patients dying from nonprostate cancer causes thereby lending credence to the argument that there was a true beneficial effect of the local intervention and that the observed advantage cannot completely be attributed to a selection bias. Although survival benefits were maintained even in patients with prostate-specific antigen (PSA) >20 ng/ml or those above 70 years of age, the authors did identify certain factors associated with an improved response to local treatment. These included age <70 years, clinical stage $\leq T3$,

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Gleason score ≤ 7 , PSA <20 ng/ml and an absence of pelvic lymphadenopathy.

Although, this particular study is fraught with potential shortcomings due to its retrospective nonrandomized design, inherent selection bias due to unmeasured variables, lack of standardized follow-up and a lack of information regarding adjuvant and salvage treatments, There is little doubt that it does ask some provocative questions and implores us to look at the biological role of definitive primary treatment in the setting of metastatic prostate cancer. While hypothetical explanations for this observed benefit can be many (decreased tumor burden, immune modulation, improved response to secondary treatment, avoidance of secondary complications attributable to local tumor growth), it still remains to be seen whether these findings can be replicated in prospective trials.

The impact of prior local treatment in patients being treated for metastatic CaP has been studied earlier. In a secondary analysis of the SWOG 8894 study, the authors found that patients who had undergone RP and then subsequently developed metastatic disease, had a significantly better survival with a hazard ratio of 0.77 (95% confidence interval 0.53–0.89) when compared to those who never received the procedure.^[5] This survival advantage was however, not replicated in a similar study published later.^[6] Indirect evidence also exists in the form of a positive impact of RP in patients with locally advanced disease and metastatic lymph node involvement. In a recent analysis of patients from the Munich cancer registry, Engel *et al.* demonstrated a survival advantage for patients who underwent RP in spite of an intraoperative detection of positive lymph nodes when compared to those in whom the procedure was abandoned.^[7] In this study, encompassing 938 lymph node positive patients, those who proceeded with RP ($n = 688$) had a significantly better 5 and 10 year OS (84% and 64%) when compared to those in whom RP was abandoned (60% and 28%). The estimated 5 and 10 years DSS was also better in the former group (95% and 85%) as compared to the latter (70% and 40%). The quality of evidence presented in these studies, however, is far from ideal. All these analyses suffer from selection bias inherent to their retrospective design and, short of a prospective randomized trial, continue to be debatable.

Another major factor to be studied is the quality-of-life after a palliative surgery performed in the setting of metastatic prostate cancer. The proponents of this approach would cite potential benefits of removing the malignant prostate and

avoiding the complications of local tumor growth, including hematuria, urinary tract infections, outflow obstruction, involvement of ureteric orifices and consequent upper tract deterioration requiring multiple surgical procedures and their consequent morbidity. These quality-of-life issues tend to blur the lines between a palliative and a definitive surgical intervention in prostate cancer.

Although, as of now, we may not have the evidence to offer RP to all men who present with metastatic prostate cancer, the day may not be far when this approach may become standard for highly selected patients. At the very least, the urology community needs to debate and evaluate this topic, and lay the ground for future prospective studies to clarify it further. After all, literature abounds with the beneficial effect of the treatment of the primary tumor in other metastatic malignancies such as breast, colon, ovary and closer home-renal cell carcinoma.^[8] The era of “cytoreductive prostatectomy” may be upon us, sooner than we think!

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