

REVIEW

The impact of local treatment of the primary tumor site in node positive and metastatic prostate cancer patients

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BACKGROUND: Surgical treatment of the primary tumor in patients with metastatic prostate cancer (mPCa) is gaining traction. We discuss the biological rationale and the existing literature on this approach.

METHODS: We reviewed the literature regarding surgical management of advanced and mPCa disease.

RESULTS: Surgical removal of the primary tumor despite metastases is becoming a standard in an increasing number of malignancies. Basic science data support the use of surgical removal of the prostate in metastatic PCa. In addition, durable long-term survival has been reported in patients with node-positive PCa treated with radical prostatectomy (RP) as mono or multimodal approach. Based on these data, several groups have demonstrated the feasibility and safety of RP in the metastatic setting. Retrospective series have also reported an improvement in survival for metastatic patients treated with RP in addition to systemic treatment.

CONCLUSIONS: Although no level I data exist at this time to support the use of RP in clinically node-positive or mPCa patients, retrospective data together with basic research data and experience from other malignancies suggest that treatment of the primary tumor, in form of a RP, is safe and could improve long-term quality of life and survival. However, prospective evaluations are requested to validate these findings before including in the standard clinical practice.

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INTRODUCTION

Prostate cancer (PCa) is the most common solid malignancy in western countries. It has been estimated that the number of men diagnosed with PCa in 2015 will be over 220 000 in the United States alone.¹ The widespread use of PSA has resulted in a reduction of *de novo* metastatic PCa (mPCa)² with a proportional shift to increased rate of low-risk disease.^{3,4} Despite these changes, still a consistent number of patients are diagnosed with primary mPCa⁵ or develop eventually mPCa as their disease progresses. The current standard of treatment for mPCa remains surgical castration or androgen deprivation therapy (ADT) with or without an antiandrogen agent^{6,7} and eventually docetaxel in association with ADT.⁸ In this setting, there is evidence arising that treatment of the primary organ may be beneficial with regards to quality of life in the late disease stages and possibly even survival.^{9–11}

Stimulated by advances in knowledge based on biological and clinical research paradigm in PCa is slowly but steadily shifting. Historically, when evidence of disease outside of the prostate was found, radical prostatectomy (RP) was aborted.¹² Indeed, RP was even considered best in low-risk cancers that are now served primarily with active surveillance.^{13,14} Then, long-term survivorship has been demonstrated in patients treated with RP for locally advanced¹⁵ and/or node-positive PCa opening the door for the expansion of the indications of RP to more advanced disease stages.¹⁶ Recently, several groups went even farther to propose the hypothesis that combining RP with systemic treatment in locally advanced, node positive and mPCa patients is not only feasible but

can also improve long-term quality of life and potentially survival. In this review, we summarize the available evidence, supporting the hypothesis that surgical treatment of the primary PCa can improve outcomes of patients with mPCa with acceptable side-effects.

PRECLINICAL DATA

Tumor debulking in metastatic patients has been described as a safe and efficacious procedure in several urological¹⁷ and non-urological malignancies.^{11,18} In PCa, several preclinical data support this approach. Kadmon *et al.*¹⁹ used a subcutaneous PCa rat model in which he developed lung metastases and treated them with a single dose of chemotherapy, surgical excision of the primary tumor or a combination of both. All three regimens significantly reduced the number of lung metastases. However, only the combination of tumor excision and chemotherapy prolonged survival in the rats. This can be partially explained by several hypotheses such as tumor self-seeding theory, in which circulating tumor cells not only seed to distant organs but also return locally to stimulate the primary tumor to become more aggressive.²⁰

Another concept is that the reduction of the primary tumor through cytoreduction eliminates the continuous release of tumor cells and tumor-promoting stimuli such as cytokines and growth factors thereby improving the efficacy of systemic therapy and consequently, survival. The seed and soil hypothesis is another potentially expanding concept as it postulates that to develop metastases there is a need of 'a soil' where metastatic cancer cells

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migrate too, invade and grow. The soil need to be prepared to receive metastatic cells. This process is mediated by hematopoietic and other factors secreted by the primary tumor.²¹ These hypotheses explain why treating the primary tumor in mPCa patients could potentially lead to modification in the metastatic tumor site with a delay in the formation of the metastatic ecosystem.

Recently, Haffner *et al.*²² performed a whole-genome sequencing and molecular pathological analyses to characterize the lethal clone cell in a patient who died of PCa. Surprisingly, they found that the lethal clone arose from a small, low-grade cancer focus in the primary tumor and not from the bulk, higher grade primary cancer or from lymph node metastases resected at RP. This finding suggests that killer cancers can arise from cells considered 'insignificant'. Therefore, an effective and timely definitive therapy of the primary site may alter this natural history. In context, differential microRNA expression patterns have been observed comparing oligometastatic and disseminated diseases.²³ Following this consideration, treating oligometastatic PCa may not be the same as treating polymetastatic diseases that could be considered as two different biological entities. A local treatment aimed at the removal of the primary tumor in this context might delay the administration of systemic therapies and increase the chance of cure. Metastasis-to-metastasis spread in PCa preclinical models has been proposed.²⁴ Therefore, a greater benefit could be expected when the removal of the primary tumor is coupled with other therapies targeted at the metastatic site.²⁶

THE ROLE OF SURGERY IN THE MANAGEMENT OF NODE-POSITIVE PROSTATE CANCER

Although there is no level 1 evidence regarding the optimal management of node-positive PCa, several retrospective studies have shown a benefit to local treatment in patients harboring nodal metastases.^{27–29} Historically, physicians often aborted RP when node metastases were found on frozen section analysis.^{12,30} However, this practice has fallen out of favor in light of data demonstrating a survival benefit when RP was completed in addition to the removal of nodal metastases.^{27–29} Indeed, several retrospective studies even demonstrated long-term local disease control in patients with node-positive disease, even treated with RP alone.³¹ A recent study including 1011 node-positive patients treated with RP with a median follow-up of 17 years, showed a 20-year cancer specific mortality rate of 31% regardless of adjuvant therapy. Previous investigators reported similar results for patients with node-positive PCa.^{32,33} Despite these promising results, it remains clear that the group of node-positive PCa represents a heterogeneous group of diseases. In fact, approximately one out of three patients with low-volume nodal metastatic disease may be even free of biochemical recurrence on long-term follow-up.³² On the other hand, many of these patients experience biochemical recurrence, clinical metastases,³⁴ and eventually, die from PCa.

With the goal of identifying patients needing multimodal therapy to prevent disease progression, authors have identified these features to be associated with adverse outcomes: node volume,³⁵ pathological Gleason score,^{34,36} surgical margin status,³⁷ the use of adjuvant therapies³⁸ and extranodal extension.^{39,40} A multimodal approach composed by extended pelvic lymph node dissection, adjuvant radiation therapy (RT) and ADT has been recommended by some studies based on retrospective data. The use of ADT after RP improved survival in the only prospective randomized study to date.³¹ Although this trial was well conducted, it has limitations such as the low number of patients enrolled, the lack of any standardized extent of lymph node dissection and the absence of any stratification considering the extent of nodal invasion. An extended pelvic lymph node dissection in node-positive PCa has shown to reduce mortality after RP.⁴¹ However, a further evaluation

is required to evaluate the impact of this surgery on general health-related quality of life with special focus on side-effects. Finally, the role of adjuvant RT in combination of ADT has been explored in several series of patients with node-positive PCa.^{38,42} Because of the high heterogeneity of this population, adjuvant RT was found beneficial in select node-positive patients, such as those with locally advanced but not systemic PCa. This approach supports the need for multimodal therapy in selected patients, who should be carefully individuated on the bases of clinical and pathological characteristics.

Only few studies exist in the context of clinical node metastases. Preoperative imaging has shown low sensitivity in the detection of node metastases in contemporary patients,⁴³ therefore the usage of nomograms⁴⁴ in predicting pathologically node metastases still represents the most accurate approach in a preoperative setting. In the STAMPEDE trial, clinical node-positive PCa patients were included and investigators tested the efficacy of RT as primary treatment in comparison with ADT only. The results showed increased survival for patients treated with RT+ADT even with clinical evident metastases compared with ADT only treated patients. The beneficial impact of an active treatment was also reported in a surgical series⁴⁵ using a cN+ PCa data set from San Raffaele and Mayo Clinic. Specifically, no differences in survival outcomes were found for pN+ patients surgically treated in respective of the presence of clinically evident or non-evident preoperative node metastases. However, these findings need to be validated in a prospective randomized trial.

THE ROLE OF SURGERY IN THE MANAGEMENT OF METASTATIC PROSTATE CANCER

The surgical management of the primary tumor site in mPCa patients is a new concept. The use of debulking surgery in patients affected by metastatic cancer has been demonstrated in several tumors and preclinical studies. Several population-based studies recently reported the impact of local prostate treatment in mPCa (Table 1). In an analysis based on 8185 mPCa patients from the SEER (Surveillance Epidemiology and End Results) database, Culp *et al.*⁴⁶ found that 245(3%) and 129(1.6%) patients had been treated with RP and brachytherapy, respectively. The 5-year overall survival rates were 67.4% vs 52.6% vs 22.5% in patients treated with RP vs those treated with brachytherapy vs those who had no treatment of the primary tumor site, respectively. Similar findings were found by Gratzke *et al.*,⁴⁷ who analyzing the Munich Cancer Registry, found that 74 (5%) of mPCa patients were treated with surgery. Patients in surgical group reported a 55% 5-year overall survival rate compared with 21% for non-surgically treated patients ($P < 0.01$).

Local treatment of the prostate with RP or intensity-modulated RT but not with conformal RT showed better survival results if compared with patients who did not undergo any local treatment for mPCa.⁴⁸ Finally, Fossati *et al.*⁴⁹ identified the optimal candidates for local treatment among mPCa patients, assessing that tumor characteristics and patients selection is essential to avoid either over or under-treatment in this heterogeneous group of patients. In a feasibility case-control study, Heidenreich *et al.*⁵⁰ reported the outcomes of RP in 23 PCa patients who harbored, minimal osseous metastasis and absence of visceral or extensive node metastases. The outcomes compared this population with 38 patients who were treated with ADT only and found a significant improvement in clinical progression and cancer-specific survival rates for the RP group. However, this study was limited by the selection of the patients and the absence of any match between the two populations as a direct result of the small retrospective cohort.

In a recent multi-institutional study, Sooriakumaran *et al.*⁵¹ investigated the role and feasibility of surgery in metastatic patients treated between 2007 and 2014 at six international centers. Almost 80% of these patients did not suffer any

Table 1. Studies evaluating the role of local treatment in patients diagnosed with primary metastatic prostate cancer

References	Population	Treatment	Median follow-up (months)	Complications	Survival benefits	Conclusions
Culp <i>et al.</i> ⁴⁶	SEER database	Radical prostatectomy (<i>n</i> = 245) vs brachytherapy (<i>n</i> = 129) vs no treatment (<i>n</i> = 7811)	16	-----	Radical prostatectomy or brachytherapy associated with reduction of CSM when compared with no treatment	Definitive treatment of the prostate in men diagnosed with mPCa suggests a survival benefit
Gratzke <i>et al.</i> ⁴⁷	Munich Cancer Registry	Radical prostatectomy (<i>n</i> = 74) vs no treatment (<i>n</i> = 1464)	NA	-----	Patients in the radical prostatectomy group showed 55% 5-year OS rate vs 21% in the non-radical prostatectomy group	Definitive treatment of the prostate with radical prostatectomy in mPCa associated with survival benefit
Fossati <i>et al.</i> ⁴⁹	SEER database	Local treatment (<i>n</i> = 628) vs non-local treatment (<i>n</i> = 7569)	36 vs 31	-----	Local treatment of the primary tumor, compared with non-local treatment conferred a higher CSM-free rate survival in men with an expected risk of CSM < 40% 94/106 (88.7%) men were still alive with a median follow-up of 22.8 months	Local treatment of the prostate in mPCa associated with an increase in survival rates when compared with non-local treatment in selected patients Radical prostatectomy for mPCa appears safe in expert hands for meticulously selected patients.
Sooriakumaran <i>et al.</i> ⁵¹	Multi-institutional cohort	106 mPCa patients treated with radical prostatectomy	22.8	20.8% of complications. Lymphocele (8.5%), anastomotic leak (6.6%), wound infection (4.7%)		
Heidenreich <i>et al.</i> ⁵⁰	Single center	ADT only (<i>n</i> = 38) vs radical prostatectomy (<i>n</i> = 23)	34.5 vs 47	22 (58%) and 9 (39%) complications for ADT only and radical prostatectomy patients, respectively	Patients treated with radical prostatectomy showed better clinical progression free-survival and cancer-specific survival rates (but no better OS) when compared with patients non-surgically treated	Cytoreductive radical prostatectomy is feasible in well-selected men with mPCa
Satkunasivam <i>et al.</i> ⁴⁸	SEER-medicare database	Radical prostatectomy (<i>n</i> = 47), conformal radiotherapy (<i>n</i> = 107), intensity-modulated RT (<i>n</i> = 88), no local treatment (3827)	20	-----	Intensity-modulated RT was associated with a 62% reduction of CSM. Radical prostatectomy with a reduction of 52%. No reduction for conformal RT	Local therapy with radical prostatectomy and intensity-modulated RT but not with conformal radiotherapy was associated with a survival benefit in mPCa patients Men with mPCa receiving prostate RT and ADT lived longer than men treated with ADT alone
Rusthoven <i>et al.</i> ⁵²	National Cancer Database	ADT alone (<i>n</i> = 5844) vs ADT plus RT (<i>n</i> = 538)	61	-----	Superior median and 5-year OS for patients treated with RT plus ADT compared with ADT alone	

Abbreviations: ADT, androgen deprivation therapy; CSM, cancer specific mortality; mPCa, metastatic prostate cancer; OS, overall survival; RT, radiation therapy; SEER, Surveillance Epidemiology and End Results.

complications related to surgery. Considering survival, with a median follow-up of 22.8 months, 88.7% patients were still alive at the end of the study. Finally, Rusthoven et al.⁵² recently investigated the role of external beam radiotherapy in mPCa patients using the national cancer database to evaluate overall survival of men treated with ADT with or without radiotherapy. Authors described superior median (55 vs 37 months) and 5-year overall survival (49 vs 33) in favor of patients treated with prostate radiotherapy plus ADT when compared with ADT alone ($P < 0.001$).

Although interesting, it should be stressed that the clinical applicability of these studies is limited and the treatment of the primary tumor in the context of mPCa is not recommended by guidelines and should be proposed exclusively in the context of a clinical trial.

At the time, STAMPEDE (NCT00268476), HORRAD (NTR271) and PEACE-1 (NCT01957436) trials are examining the role of RT in mPCa patients. From the surgical prospective, a trial from MD Anderson cancer center (NCT01751438) is studying the differences from active local treatment (surgery or radiotherapy) vs standard systemic therapy in mPCa patients.

CONCLUSION

Surgical local treatment in locally advanced and node positive has become a standard approach with durable local disease control linked with adequate quality of life. Recent data on mPCa has shown excellent results in term of feasibility and improvement of survival when compared with patients treated only with ADT. However, prospective randomized trials are needed to further explore this novel strategy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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