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Review Article

Cytoreductive prostatectomy in metastatic prostate cancer: current knowledge and future directions

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Abstract: The current standard of care for patients with metastatic prostate cancer is systemic androgen deprivation therapy, and addressing the primary tumor has been reserved for patients with localized disease. However, emerging data has called into question the universality of this paradigm. Recent studies have found treatment of the primary tumor in patients with metastatic disease not only can provide the patient with symptomatic relief but also may provide a survival benefit. The potential biological and clinical benefit for cytoreductive surgery has been also been suggested in several translational models. Thus, PubMed electronic database was queried for publications on patients with metastatic prostate cancer who underwent cytoreductive prostatectomy, using keywords including: cytoreductive prostatectomy, radical prostatectomy, metastatic prostate cancer. In this review we examine literature regarding feasibility of cytoreductive prostatectomy, oncologic outcomes, and future directions including the ongoing clinical trials in this arena. While the retrospective data is encouraging, results of these ongoing prospective trials are needed before this option is offered to patients as a reasonably safe treatment with demonstrated benefits to survival and quality of life.

Keywords: Prostate cancer, metastatic prostate cancer, cytoreductive radical prostatectomy, safety, feasibility, cancer survival

Introduction

Treatment options for metastatic prostate cancer (mPCa) have significantly evolved over the last several years. In addition to androgen deprivation therapy (ADT) and traditional chemotherapeutic agents, like docetaxel, many new hormonal agents have been approved by the FDA for unique indications within the spectrum of mPCa [1]. Despite adoption of these new therapies, survival has not dramatically improved and remains poor with 5-year relative survival of 30% in patients with distant metastatic disease (M1a or greater) [seer.cancer.gov/statfacts/html/prost.html]. Cytoreductive radical prostatectomy (CRP) has garnered research interest in the last several years, with a few Phase I studies published and ongoing Phase II and III trials; however, its role as a standard treatment for mPCa has yet to be established.

The general concept of cytoreductive surgery is well-established and, in fact, beneficial with regard to oncologic outcomes in many other cancers including ovarian, various gastrointestinal malignancies, and renal cell carcinoma [2-5]. With regard to mPCa, data in support of local therapy, including CRP or radiation therapy, has largely been retrospective and registry based. At this point, CRP is not recommended outside of a clinical trial as there is limited data on safety, effect on functional outcomes, and oncologic benefit. In this review, current, available data on CRP in mPCa is discussed, with attention to safety/feasibility, oncologic outcomes, and ongoing, prospective research.

Methods

A PubMed query was performed for English language articles relevant to this topic using the following keywords: ‘cytoreductive’, ‘cytoreductive surgery’, ‘local therapy in metastatic prostate cancer’, ‘metastatic prostate cancer’, and ‘radical prostatectomy’. Attention was given to studies involving cytoreductive techniques and remaining articles were excluded based on title

and abstract review. Based on our search, only three prospective studies have been published related to cytoreductive prostatectomy.

Discussion

Safety/feasibility

Previous retrospective studies and more recent prospective studies have evaluated both safety and feasibility of CRP. With improvements in robotic surgery and overall in techniques for radical prostatectomy, CRP feasibility is becoming more widely accepted, allowing for an increase in studies of the procedure's efficacy. One retrospective, multi-institutional study by Sooriakumaran et al. included 106 men with M1a and M1b prostate cancer across 6 institutions. Open approach was favored at 5 out of the 6 institutions and overall complication rate was 20.8%, with the most common complications of blood transfusion (14.2%), symptomatic lymphocele (8.5%), and anastomotic leak (6.6%) [6]. There was no significant difference observed when stratified by M1a and M1b [6].

An earlier study by Heidenreich et al. compared two groups. Group 1 consisted of 23 men with prostate cancer and minimal osseous metastases (3 or fewer lesions on bone scan) who received CRP and Group 2 was a control of 38 men with mPCa treated with ADT without local therapy [7]. A complication rate of 21.7% was observed in Group 1, with no Clavien IV or V complications noted [7]. In Group 2, 9/38 patients required transurethral resection of prostate due to disease progress and bladder outlet obstruction indicating CRP reduces the incidence of future local complications [7].

The first published prospective study of CRP in mPCa was performed by Poelaert et al., known as the LoMP Trial. Two groups were compared: Group A, a carefully selected cohort of 17 asymptomatic men with mPCa who received ADT and underwent CRP, and Group B, 29 men with mPCa who received ADT and were ineligible or unwilling to have surgery [8]. Men in Group A were significantly younger, had lower prostate specific antigen (PSA) and had lower volume of metastases [8]. Robotic prostatectomy was performed in 16/17 patients, and overall, there were 7 complications by three months after surgery, 5 grade I and 2 grade II [8]. A prospective, case-control study by Steuber et al. compared 43 patients with low volume bony mPCa (one to three bone lesions) who underwent CRP matched with a comparator group of 40 patients receiving best systemic therapy [9]. There was no post-operative complication rate reported for this study, but similar to the above studies, a reduction in future locoregional complications was noted for the CRP cohort [9].

A Phase I prospective study by Yuh et al. sought out to demonstrate feasibility and assess safety in a cohort of 32 patients with mPCa across four international institutions [10]. Eligible men with mPCa included N1, M1a and M1b prostate cancer. The primary endpoint in determining safety was 90-day major complication rate defined as Clavien grade III or greater [10]. Overall there were 10 complications observed, 8 minor (Clavien grade I or II) and 2 major, including one death in which a patient developed rapid liver metastases within 6 months after surgery [10].

The above studies note complication rates for CRP in line with those of radical prostatectomy in non-mPCa. As CRP is becoming accepted as a feasible procedure with reasonable complication rates in experienced hands, Phase II and III studies are warranted to determine efficacy. Nonetheless, current studies have acknowledged the experimental nature of the procedure with a need for strict counseling on potential risks and do not recommend its application outside of clinical trials.

A rather recent retrospective analysis comparing patients undergoing CRP versus radical prostatectomy in non-mPCa utilized the National Inpatient Sample database [11]. Through propensity score matching and multivariate logistic regression modeling to help control for differences between groups, investigators found statistically higher rates of overall, intraoperative, and miscellaneous surgical complications (odds ratios 1.34, 2.61, and 1.69, respectively) [11]. Despite these significant differences, the absolute overall complication rates for CRP was 14.9% compared to 12.3% in non-metastatic patients, which is acceptable risk considering the nature of the procedure [11].

Oncologic outcomes

Published data on oncologic outcomes with respect to CRP is mostly limited to registry

studies which carry inherent limitations. Retrospective comparator studies and even prospective studies can be limited due to selection bias, where patients selected for CRP are more often younger, healthier, and with a lower burden of metastatic disease. Herein, various studies will be discussed with these limitations in mind. Nonetheless, they shed light on the possibility of a survival benefit which opens the field to Phase II and III studies.

One of the early registry studies utilizing the Surveillance Epidemiology and End Results (SEER) database from 2004 to 2010 was performed by Culp et al. 8185 men with M1a to M1c prostate cancer were identified, with CRP performed in 245, brachytherapy in 129, and the remainder with no surgery or radiation [12]. Five-year overall survival (OS) rates for CRP and brachytherapy were significantly higher than the no local therapy group (67.4% and 52.6% versus 22.5%, respectively) [12]. Disease specific survival was also significantly higher for the two treatment groups when compared with those receiving no local therapy [12]. SEER database does not provide information on patient selection or any indication of systemic/hormonal therapy. Therefore, these survival benefits may be heavily confounded. Also utilizing SEER data, Satkunasivam et al. analyzed 4069 men with M1a to M1c prostate cancer, of which 47 received CRP, 88 received intensity modulated radiation therapy (IMRT), 107 received conformal radiation therapy (CRT), and 3827 had no local therapy performed [13]. Both CRP and IMRT were associated with a significant risk reduction in prostate cancer specific mortality (CSM) when compared with those who received no local therapy (52% and 62% lower risk, respectively) [13]. Unlike the previous SEER study, these analyses were able to be adjusted for receipt of therapies including ADT and bone radiation [13].

The National Cancer Database (NCDB), another registry dataset collecting treatment patterns and outcomes, was employed by Parikh et al. to evaluate outcomes in patients with mPCa who received CRP, IMRT, CRT, and no local cytoreductive therapy [14]. 6051 men were included with M1a to M1c prostate cancer diagnosed in 2004 to 2013, with 622 receiving CRP, 52 IMRT, 153 CRT, and 5224 with no local therapy [14]. Five-year OS for those receiving any local therapy compared to no local therapy group was 45.7% versus 17.1%, respectively [14]. On multivariate analyses, receipt of CRP or IMRT was associated with higher OS and the difference remained significant after propensity score matching [14]. NCDB does not capture data on cancer specific survival (CSS) and reliance on OS alone may be confounded by non-cancer causes of mortality in these elderly populations.

A few of the smaller scale retrospective studies and one prospective study described above included evaluation of varied oncologic outcomes [6, 7, 9]. Sooriakumaran et al., in analyzing 106 men with M1a or M1b who underwent CRP, noted a CSS of 88.7% at just under two years of follow up [6]. The case-control series by Heidenreich et al. compared 23 men receiving ADT plus CRP versus ADT alone with a median follow up of 34.5 months [7]. For those receiving CRP versus ADT alone, there was significantly longer time to clinical progression (38.6 months versus 26.5 months) and better CSS (95.6% versus 84.2%) [7]. No differences in OS were noted. The study with perhaps the longest follow up (median 63 months) by Gandaglia et al. included 11 patients with M1a or M1b prostate cancer with up to 5 bony lesions [15]. All surviving patients had a minimum follow up of 60 months. Although there was no comparison group, 7-year clinical progression-free and CSM-free survival rates of 45% and 82% were noted, respectively [15].

The only prospective study to report data on oncologic outcomes was by Steuber et al. Based on their analysis, no significant oncologic benefit, in terms of overall and castrate-resistant free survival, could be demonstrated between the CRP group and a comparison group of patients receiving best systemic therapy [9]. There was a significant reduction in locoregional complications for patients undergoing CRP, 7% versus 35% for the best systemic therapy only group [9]. Conflicting data with respect to oncologic benefits of CRP further confirm the need for well-developed Phase II and III studies.

Future directions

Numerous animal [16, 17] and retrospective studies [7, 12] have shown indirect evidence in support of cytoreductive prostatectomy and

Table 1. Current prospective trials evaluating CRP in mPCa

Trial Number	Location	Design	Arms	Primary Outcome
ISRCTN15704862	United Kingdom	Phase I/II	1-BST	QoL, time to castrate resistance
			2-BST and CRP with eLND	
NCT01751438	USA	Phase II	1-BST	PFS
			2-BST + CRP or RT	
NCT02454543	Germany	Phase II	1-BST	CSS
			2-BST + CRP with eLND	
NCT02971358	Austria	Phase I/II	CRP with eLDN	90-day complication rate
NCT03456843 (SIMCAP)	USA	Phase II/III	1-BST	FFS at 2 years/Overall Survival if Phase III expansion triggered
			2-BST + CRP	
NCT03655886	Belgium	Phase II	1-CRP	Feasibility of randomization
			2-pelvic RT	

Information obtained from Clinical Trials Registry [www.clinicaltrials.gov] and ISRCTN Registry [www.isrctn.com]; ADT: androgen deprivation therapy, BST: best systemic therapy, CRP: cytoreductive radical prostatectomy, CSS: cancer specific survival, eLND: extended lymph node dissection, FFS: failure-free survival, QoL: quality of life.

the surgery has been shown to be feasible, i.e the benefits of the surgery outweigh the increased risk of operating on patients with advanced disease. However, several key questions remain: can these retrospective observations be replicated in well-designed prospective clinical trials and will we be able to confirm on a cellular and molecular level the hypotheses as to why local control improves OS?

There are currently several ongoing prospective trials listed in **Table 1**. The TRoMbone (Testing Radical prostatectomy in men with prostate cancer and oligoMetastases to the bone) trial is a multicenter study to test the feasibility of randomization of patients to either current gold standard treatment (ADT) or ADT and CRP with pelvic lymph node dissection [18]. The study has closed accrual and results are pending. Other surgical trials are currently underway in the United States, Germany, Austria and Belgium which are comparing CRP with extended lymphadenectomy plus ADT, against ADT for patients with mPCa. Primary outcomes include feasibility, quality of life, various survival rates, complications, time to castrate resistance, and time to progression.

One uniquely designed trial (NCT03456843) is highlighted in the original Phase I study by Yuh et al. Known as SIMCAP (Surgery in Metastatic Cancer of Prostate), this study plans to accrue and randomize 190 patients into two arms: Arm 1 patients will receive BST (ADT ± abiraterone ± docetaxel) with or without docetaxel, Arm 2 patients will receive BST + CRP [10]. SIMCAP is described as a Phase II/III study. This indicates if the Phase II analysis meets the primary endpoint of improvement in failure-free survival for CRP group compared to the group receiving best systemic therapy alone, the study will be expanded into a Phase III design, with overall survival as the primary outcome of interest [10]. Failure in the context of this study's primary outcome is defined as PSA, clinical, or radiographic progression, or death from prostate cancer [10].

Conclusions

Cytoreduction as a surgical principle is widely employed as a standard of care in several other solid malignancies. Early beliefs of CRP as a difficult, morbid procedure have precluded its acceptance in the treatment paradigm of men with mPCa. The safety and feasibility of CRP has been demonstrated in retrospective studies and supported in subsequent prospective analyses. While there are still some prospective, Phase I studies which have yet to be reported, current published data has opened the door for Phase II and III studies planning to evaluate efficacy.

Thus far, there are suggestions of oncologic benefit to cytoreductive local therapy in mPCa based on registry and other retrospectively evaluated datasets. From our review of available literature and data, with so much heterogeneity in definitions of metastatic disease for inclusion criteria and potential for selection bias in comparator studies, a discrete recom-

mendation cannot yet be made as to when or to which individuals cytoreductive prostatectomy should be offered. As more robust, prospective data is collected and analyzed, CRP may become standard of care in certain populations of men with metastatic disease.

Disclosure of conflict of interest

None.

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