

# Emerging role of cytoreductive prostatectomy in patients with metastatic disease

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**Abstract:** Traditionally, systemic androgen deprivation therapy (ADT) has been the primary treatment modality in metastatic prostate cancer (mPCa) while treatment of the primary tumor has been reserved for patients with clinically localized disease. Emerging data suggests that treating the primary tumor in patients with metastatic disease may provide a survival benefit. However, these studies are fraught with selection bias towards patients with favorable disease characteristics. Despite these limitations, clinicians are becoming increasingly interested in consolidative treatment of the primary tumor in this setting. Many translational models and observational studies of cytoreduction in mPCa have yielded compelling results, suggesting a potential biological and clinical benefit. While there are no published randomized control trials on cytoreduction in mPCa, the literature regarding safety, feasibility, and potential symptomatic benefit of cytoreductive prostatectomy (CRP) in mPCa supports further investigation. Thus, MEDLINE and PubMed electronic databases were queried for English language articles related to patients with mPCa who underwent radical prostatectomy. Keywords used include: cytoreductive prostatectomy, radical prostatectomy, oligometastatic, mPCa, and oligometastasis. In this review we examine the literature regarding the feasibility of CRP as well as the reported oncologic outcomes, limitations of the literature, and future directions. Since there is currently no level one evidence to support its use, CRP should not be applied outside a clinical trial. A better understanding of the biology driving mPCa, in conjunction with standardization of clinical trials, will help expedite actionable data acquisition that may improve clinical outcomes.

**Keywords:** Cytoreduction; cytoreductive; radical prostatectomy

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## Introduction

Prostate cancer accounts for 9.6% of all cancer diagnoses in the United States, with 11.6% of men diagnosed with prostate cancer at some point during their lifetime. The median 5-year survival for patients with localized disease is 98.6%. In contrast, only half of patients presenting with *de novo* metastatic disease are alive at 5 years (1). Historically, systemic androgen deprivation therapy (ADT) has been the

primary treatment modality in metastatic prostate cancer (mPCa) while local therapy has been reserved only for those with prostate confined disease (1).

Prior to the recent advent of many new systemic agents, disease-specific survival for *de novo* mPCa had been static for many years (2). However, by 2012, five new agents had proven survival benefit in mPCa. While these earliest approvals were for more advanced, heavily pretreated disease states, improved overall survival for patients with *de novo*

mPCa was already being demonstrated in population-based analyses (3). An understanding of the rapid evolution of available systemic options is of paramount importance when considering the retrospective nature of much of the current data on cytoreductive local therapy. Any benefit ascribed to cytoreductive local therapy must be critically appraised with regard to the type of systemic therapy received and any differences in therapeutic responses among comparator groups. The importance of this exercise is demonstrated by the recent publication of two randomized controlled trials in which the addition of abiraterone to ADT demonstrated an overall survival benefit in patients with *de novo* metastatic disease (4,5). Now that abiraterone has joined docetaxel (6) as a treatment option for patients with *de novo* metastatic disease, in the absence of any head to head comparative data, clinicians will be choosing between therapies based on clinical judgment and experience. This type of treatment variability adds another layer of complexity that may alter the benefit profile of cytoreductive surgery, which has thus only been described in retrospective studies from the era of treatment with ADT alone.

We also must consider that there is not only intra-patient heterogeneity in response to systemic treatment, but also potentially intra-patient, inter-metastasis heterogeneity in systemic treatment response, as demonstrated by Morin *et al.* (7). Thus, identifying the mPCa patients that may benefit from local therapy is a complex and difficult task. When reviewing the literature to date, we must carefully dissect all of the data in favor of local treatment with cautious optimism. Only with the completion of several ongoing clinical trials, along with their biological correlative studies, will we begin to understand the applicability of local therapy in metastatic disease. Herein, we have reviewed the current literature in regards to cytoreductive prostatectomy (CRP) feasibility and oncologic outcomes and will discuss the limitations and future directions.

## Methods

MEDLINE and PubMed electronic databases were queried for English language articles related to patients with mPCa who underwent radical prostatectomy. Keywords used include: cytoreductive prostatectomy, radical prostatectomy, oligometastatic, metastatic prostate cancer, and oligometastasis.

## CRP

In the past, CRP has not been considered in mPCa, as it

had no potential to be curative in the setting of standard ADT alone. However translational models and observational studies of mPCa have suggested a biological benefit to cytoreduction even in the absence of potential cure (2,3,8-21).

It has been demonstrated that despite 1 year of chemohormonal treatment, with favorable therapeutic response, patients with mPCa continue to have aggressive and active tumor cells within their primary site (22). Molecular mediators from the primary tumor may enable and promote metastatic disease by altering translation and deregulating signaling pathways. This has been shown to promote carcinogenesis, differentiation, migration, and angiogenesis in prostate cancer (23-26).

## Safety of CRP in patients with metastatic disease

Prior to evaluating oncological outcomes of CRP in patients with mPCa, it is prudent to first evaluate safety (27,28). Many retrospective studies evaluating its safety and feasibility have been published. In a multi-institutional retrospective case series published by Sooriakumaran *et al.*, 106 patients with newly diagnosed mPCa underwent CRP and perioperative outcomes were reviewed. Outcomes of interest included continence, readmission, reoperation and overall complication rates at 90 days. Results revealed that 79.2% of patients did not suffer any complications. Of the complications, 8.5% were due to lymphocele formation and 4.7% were due to wound infection (29). No differences in perioperative complications were seen in M1b relative to M1a patients. The authors concluded that CRP is safe in expert hands. In a similar study, the frequency and seriousness of surgery related complications were found to be no greater in CRP patients than in patients with high-risk prostate cancer who underwent radical prostatectomy (30). The same study also found that approximately one third of patients with metastatic disease who received standard of care would require subsequent intervention for complications related to local progression, such as obstruction, hematuria, and hydronephrosis. On the other hand, those treated with initial CRP had significantly reduced complication rates. Other studies have corroborated these findings (8,9). For example, in a study by Gandaglia *et al.*, CRP was found to have an acceptable safety profile, with two Clavien-Dindo grade-III complications and no perioperative mortalities. Like most studies, CRP was deemed safe, but was found to be more technically challenging with increased intraoperative blood loss, increased transfusion requirement, and increased length of

stay relative to those undergoing treatment for localized disease (10). There appears to be consensus that the safety and feasibility profile of CRP is reasonable, in experienced hands, and should encourage further development of clinical trials evaluating surgery for these patients. This may be especially true of patients with bulky primary tumors who may derive maximal symptomatic benefit from CRP.

### ***Patient heterogeneity and oncologic outcomes***

Many recent retrospective studies have investigated the potential oncological benefit of primary tumor treatment in patients with mPCa. The majority of these studies include analyses from three commonly used databases and registries, while others originate from institutional data or post hoc analyses. Two case control studies have also been published. Comparing these studies is problematic due to lack of predefined inclusion criteria, lack of details on the location and number of metastasis and lack of standardization of surgical approach, adjuvant therapy, follow-up schedule, and duration. It is also important to note an additional contributor to patient heterogeneity that is on the horizon. Metastatic staging work up in all of these studies included varying combinations of technetium bone scan and CT. With increasing adoption of more sensitive imaging modalities (i.e., PET/CT with various targeted radiotracers) many of the patients similar to those in these studies will be upstaged compared to older imaging techniques (31). This highlights the intrinsic disadvantage to disease volume-based inclusion criteria when enrolling patients on clinical trials. Volume of disease is subjective and can change based on imaging modality used. When patients are imaged in a heterogeneous fashion, this produces studies with poor generalizability. We believe that the way forward will require standardized imaging along with biological classification of patients using markers predictive of disease response to therapy. However, a large portion of recent literature reports local therapy outcomes in so called “oligometastatic” disease. It is important to further understand the confusion and pitfalls that can arise from this terminology.

### ***Oncological outcomes of CRP in oligometastatic disease***

Oligometastases are thought to be the consequence of less aggressive clonal evolution, resulting in metastatic deposits that are not biologically dissimilar from localized disease. It has been likened to an intermediate state, a tipping point between localized disease and widespread metastasis. This

incomplete understanding of the complex events leading to differential metastatic outgrowth has spurred investigations of aggressive systemic therapy along with cytoreductive local therapy, for potentially curative intent in patients with “low volume oligometastatic” disease (11,12).

The definition of the disease state has been assigned a number of metastatic lesions ranging from less than or equal to 3 up to 5 (32-37). In recent studies the definition has been amended to include only osseous lesions (10,13,30). However, there is also data that suggests all metastatic lesions should be included in the determination of oligometastatic disease (38). In fact, multiple publications have demonstrated that degree of lymph node involvement significantly affects disease progression and CSS (39-43). However, we are limited to preoperative imaging, when determining extent of lymph node involvement prior to primary treatment. Greater investigation into new imaging modalities will need to be completed in order to better determine optimal imaging modalities for elucidating preoperative nodal status. To date, all published data appears to suggest that there is no increased benefit for adjunct imaging modalities relative to CT scan alone, when looking for lymph nodes prior to primary treatment.

In a prospective trial of functional imaging for nodal staging, Bergh *et al.* compared sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of <sup>11</sup>C-choline PET-CT, and DWI-MRI for nodal staging in patients with high risk PCa. They found a low sensitivity of 8.2% and 9.5% and a PPV of 50.0% and 40.0% for <sup>11</sup>C-choline PET-CT and DW-MRI, respectively. They also combined imaging modalities and found sensitivity values remained too low to be clinically useful (44). In another study, GA-PMSA PET CT imaging was obtained for two cohorts of intermediate and high risk PCa patients, those with biochemical recurrence and those undergoing primary staging. GA-PSMA CT was found to be more impactful on patients with biochemical failure after definitive surgery or radiation treatment compared to those undergoing primary staging (45).

Additional retrospective studies and literature reviews evaluating the role of CRP in oligometastatic disease have attempted to exclude patients with large volume nodal metastases. One such study from Heidenreich *et al.* is a retrospective case control study using data from Uniklinik. This study reviewed a total of 23 patients with biopsy proven prostate cancer and oligometastatic disease defined as 3 or fewer osseous metastases on bone scan, absence of visceral or extensive lymph node metastases, and PSA decrease to less than 1.0 ng/mL after neoadjuvant ADT. An unmatched

group of 38 men with mPCa received treatment with ADT alone, no local therapy (NLT), and served as the “control” group. This group did not require PSA nadirs <1 ng/mL, had no limit on extent or location of their metastatic disease, and were not required to have sustained responses to their initial systemic therapy. Patients were followed up at scheduled intervals for examination and lab work, during which they were assessed for symptoms and recurrence. Median follow up was 34.5 months in the CRP group, and 47 months in the control NLT group. From the CRP group, there were 5 (21.7%) patients with postoperative biochemical recurrence. Thirteen patients either had positive margins or positive nodal invasion after CRP. Those with positive margins underwent adjuvant radiation. Patients who underwent CRP had significantly improved progression-free survival (38.6 *vs.* 26.5 months,  $P=0.032$ ) and cancer specific survival (95.6% *vs.* 84.2%,  $P=0.043$ ) relative to the NLT group. Also, time to castration resistant prostate cancer was 40 months in the CRP group and 29 months in the NLT group.

Another single institution study by Gandaglia *et al.* looked at CRP in 11 patients with oligometastatic disease, defined as the presence of five or fewer bone lesions on bone scan with or without suspicious pelvic or retroperitoneal adenopathy (10). The patients were followed for a minimum of five years. Unlike Heidenreich *et al.* there was no neoadjuvant ADT administration or PSA decline requirement in the study (30). Two patients did, however, receive neoadjuvant ADT prior to CRP and all patients received extended lymph node dissection. Kaplan-Meier estimates of clinical progression and CSM were obtained. Post operatively 10 patients (91%) exhibited nodal invasion and 8 patients had positive margins on pathology. Ten (91%) patients received adjuvant ADT and 7 (64%) received adjuvant radiation. Seven-year clinical progression free survival was 45% (95% CI, 30–85%) and CSM-free rate was 82% (95% CI, 62–99%). At the 7-year follow up, only one patient in this study died of prostate cancer.

What is unclear is whether these patients received benefit from the CRP or whether they were, as a result of their selection criteria, the more favorable prognostic group. In the absence of a randomized trial design such studies do not shed much light on the potential oncologic benefit of CRP, and should not be used as data to support adoption of this treatment approach.

### ***Oncological outcomes of CRP in metastatic disease***

Population based studies inherently lack the granularity of

smaller retrospective studies to determine metastatic disease volume. Thus, while they may include some patients who would fit any number of definitions of “oligometastatic” previously discussed, they also include patients with more widely metastatic disease. All SEER based retrospective studies, investigating the oncological outcomes of CRP in mPCa, have described improved cancer specific mortality (CSM) (14–18).

Using SEER data from 2004–2010 Culp *et al.* reviewed 8,185 patients with metastatic (M1a–M1c) prostate cancer at diagnosis (14). From that group, 245 patients had CRP and 129 had primary brachytherapy. A stepwise multivariable competing risk regression analysis was used to identify factors independently associated with CSM and a competing risks regression analysis was used to calculate the cumulative incidence of prostate cancer specific death. Disease specific survival probabilities using non-prostate cancer related deaths were used as the competing variable. At a median follow up of 27 months they found that 5-year OS was greater in the CRP group (76.5%; 95% CI, 67.0–83.7) than in the NLT group (30.6%; 95% CI, 28.9–32.4). Additionally, CSM was decreased in patients treated with CRP [subhazard ratio (SHR): 0.37; 95% CI, 0.26–0.54;  $P<0.001$ ] with 5-year disease specific survival of 75.1% compared to 46.9% in the NLT group. In fact, CRP was associated with decreased CSM at all M stages relative to the NLT group. However, other factors were also found to have independent association with cancer specific mortality. Those factors included age greater than 70, high-grade and high-stage (T4) disease, PSA  $\geq 20$  ng/mL, and pelvic lymphadenopathy.

In a similar study, men with M1a–M1c metastatic prostatic cancer at diagnosis were reviewed by Antwi *et al.* (15). Survival probabilities of men who underwent CRP or brachytherapy were compared to men who did not receive definitive local therapy (NLT). Using a conventional multivariable survival model and propensity scoring, socioeconomic and disease specific confounders were minimized. Specifically, age, race, marital status, tumor grade, and PSA were accounted for. In this study, CRP was associated with a 72% lower risk of death from prostate cancer (aHR 0.28, 95% CI, 0.20–0.39) and a 73% lower risk of death from all causes (aHR 0.27, 95% CI, 0.20–0.38) when compared to patients with no definitive local therapy. These authors observed an increase in all-cause mortality and cancer specific mortality in patients with greater metastatic burden, however CRP still demonstrated a survival benefit with decreased CSM and overall mortality (OM) regardless of metastatic extent.

In an effort to more specifically predict optimal candidates for local treatment in the presence of metastatic disease, Fossati *et al.* reviewed 8,197 patients with M1a–M1c disease in the SEER database (16). A total of 628 patients underwent local treatment with CRP or brachytherapy. Multivariable cox regression analysis was used to analyze CSM in patients that did not receive local therapy (NLT). Predictors included age, PSA, Gleason score, and TNM stages. The predictive model was used to obtain a CSM risk at three years for each of the patients within the study. This information was then used to assess whether the benefit of local treatment diminishes with risk. They found that local treatment of the primary tumor conferred survival benefit and decreased CSM rate in patients with a predictive risk <40%. For those with predicted risk exceeding 40%, local treatment did not yield a survival benefit. However, this analysis assumes that patients with longer overall survivals achieve a greater benefit from CRP. Patients with lower predicted CSM risk may have favorable prognosis irrespective of local therapy. Additionally, this does not take into consideration the potential quality of life benefit in men with more aggressive primary tumors who may also have more advanced systemic disease and poorer overall prognosis.

All SEER based reviews have an inherent selection bias, resulting from the lack of information regarding patient performance status, comorbidities, site specific EBRT, time and dose of chemotherapy, ADT, and location and number, of metastases. In an attempt to minimize that selection bias Satkunasivam *et al.* identified patients sixty-six and older with M1a–c disease in the SEER database and linked with Medicare to obtain additional clinical information (17). On multivariable analysis CRP was associated with a 52% decrease (HR 0.48, 95% CI, 0.27–0.85) in the risk of prostate cancer specific mortality after adjusting for socioeconomic, primary tumor characteristics, comorbidities, ADT, and bone radiation within 6 months of diagnosis. After propensity score adjustment CRP was associated with a 45% lower risk of CSM relative to NLT. This risk did not reach significance, except when narrowed to a subset of patients who underwent CRP with PSA 20 ng/mL or less (HR 0.07, 95% CI, 0.02–0.23).

Similar to Satkunasivam *et al.*, work by Leyh-Bannurah *et al.* aimed to statistically shrink selection bias inherent to the SEER database, while retrospectively reporting on the reduction in cancer specific mortality among men with mPCa who received local therapy (CRP or brachytherapy) relative to those that did not have local treatment (17,18).

The CRP treated group was matched to the NLT group using propensity score matching. In order to delineate whether independent predictors of CSM such as Gleason score ( $\geq 8$ ), clinical stage (cT4 or greater), and degree of metastasis (1b–1c subset), changed the benefit of primary tumor treatment, a risk scheme was used. Patients were classified in one of two groups: one risk factor or two or more risk factors. Independent predictors of CSM were considered risk factors. Their computational analysis revealed that CRP had a strong protective effect on patients with one risk factor (SHR 0.16, 95% CI, 0.09–0.28). In patients with two or more risks, this protective effect diminished but CRP was still effective at decreasing CSM relative to patients with NLT (SHR 0.6). In order to account for survival bias, multiple landmark analyses were performed at 6, 12, 18, and 24 months after CRP. No change in the decrease in CSM recorded after CRP was found. Unlike prior studies, sensitivity analyses were included to test the effect of a potential unmeasured confounder. These analyses revealed that an unmeasured confounder with a SHR of 2 would render the effect of CRP statistically insignificant, if it affected 70% of NLT patients and 10% of CRP patients. Ultimately, this study reiterated the inverse risk related benefit of CRP that other prior studies had while acknowledging the possibility of an unaccounted confounder.

Löppenber *et al.*, Parikh *et al.*, and Rusthoven, *et al.*, using the National Cancer Database (NCDB), have also done companion studies to the previously discussed SEER reviews. Unlike the SEER database, NCDB provides comorbidity status, intent of treatment, prior treatments and demographics, allowing for exclusion of patients receiving palliative treatment and chemotherapy (19,20,46).

The first of the studies by Löppenber *et al.* evaluated the effect of primary treatment on OM in patients with M1a–M1c prostate cancer (19). Similar to Fossati *et al.*, the two arms consisted of patients that underwent local therapy (CRP and radiation) and patients with no local treatment (NLT). The two groups were matched using propensity scores to minimize selection bias (16). A multivariate Cox regression tested the association between OM and covariates in NLT group. From this, baseline risk of OM at three years was predicted for both groups and then used as a covariate in a second multivariate Cox model. The predicted probability of survival at 3 years and the interaction between patients who underwent local treatment and OM was subsequently obtained. Patients who received local treatment had better 3-year OM free survival rates

(63%; 95% CI, 61–66%) when compared with their NLT counterparts (48%; 95% CI, 47–49%;  $P < 0.001$ ). However, similar to prior studies, the patients that yielded the greatest benefit from primary treatment were those with the lowest predicted OM risk, favorable disease burden and little to no comorbidities. Patients with predicted OM risk greater than 70% had no survival benefit from local treatment.

Parikh *et al.* evaluated the independent effect of CRP, radiation therapy (RT), and NLT, on OM in men with M1a–M1c prostate cancer in the NCDB (20). Using a multivariable cox proportional hazards model and propensity score matching, overall survival was found to be greater in patients who received local therapy. Results revealed OS of 45.7%, compared to 17.1% in those without local treatment (NLT) at 5 years. The risk of death in patients that had CRP was significantly lower than those without local treatment (HR 0.51, 95% CI, 0.31–0.41). Although confounding factors were statistically minimized, the study also revealed significant disparities among patients who received primary treatment and those that did not. Patients who received cytoreductive therapies were younger, had lower Gleason scores, lower TNM staging, higher income, and received care from academic or research centers.

Congruously, Rusthoven *et al.* queried the NCDB for men with newly diagnosed mPCa from 2004 to 2012 (46). They reviewed 6,382 men, and primarily focused on OS outcomes for men with mPCa treated with ADT and RT versus ADT alone. However, a comparison of OS was also made among mPCa patients receiving RT + ADT, at high and low doses, CRP + ADT, and ADT alone. Survival estimates were obtained using the Kaplan-Meier method and multivariate cox models were adjusted for RT, age, diagnosis year, race, comorbidity score, Gleason score, clinical tumor stage, nodal stage, PSA, treating facility, insurance status, and chemotherapy administration. A total of 69 patients with mPCa treated with CRP plus ADT were identified during this time frame. On univariate and multivariate analyses, both high dose RT and CRP were superior to ADT alone. No differences were observed between high dose RT and CRP. The respective 5-year OS were found to be 59% (HR 0.454; 95% CI, 0.382–0.540;  $P < 0.001$ ) and 64% (HR 0.383; 95% CI, 0.254–0.579;  $P < 0.001$ ), compared to a reference 5-year OS of 25% for ADT alone. OS was similar between low dose RT and ADT alone.

Data from the Munich Cancer Registry (MCR) has also been retrospectively reviewed, reproducing many of the findings from the SEER and NCDB studies. Gratzke *et al.*

examined a group of 1,538 patients with newly diagnosed mPCa, from which 74 patients (5%) underwent CRP. When evaluating survival, the patients who underwent CRP had a 55% 5-year OS rate compared with 21% in NLT group ( $P < 0.01$ ) (21).

### *Oncological outcomes of CRP in prospective studies*

To date, there are no completed prospective studies evaluating the role of CRP in metastatic disease. There is a prospective “case control” study by Steuber *et al.* which reviewed the impact of CRP in 43 patients with oligometastatic prostate cancer, defined as one to three bone metastases on bone scan and CT or MRI (13). Inclusion criteria for both the control group and the CRP group included newly diagnosed asymptomatic oligometastatic prostate cancer without visceral metastases, deemed to be locally resectable, with a PSA less than 150 ng/mL, and no prior radiation of metastases. All patients, CRP and NLT, were treated with ADT. Relative to the control group, the CRP was younger with a lower clinical stage and fewer bone metastases. The CRP group was followed for a median of 32.7 months while the control group was followed for a median of 82.2 months, with median time to castrate resistance greater than 40 months. Positive margin rate was 67.4% in CRP patients. There is no mention of adjuvant radiation. No difference in castration resistant-free survival or overall survival was appreciated. However, this study did reveal a significant reduction in local symptoms and subsequent interventions in the CRP group. The oncological outcomes in this case control are in contrast to the retrospective studies previously discussed, highlighting the need for more prospective evaluation.

Preliminary, prospective data from the LoMP (Local Treatment of Metastatic Prostate Cancer) Trial has also been published (8). The patients selected for this patient choice, prospective study had at least one histologically confirmed metastatic lesion, excluding pelvic lymphadenopathy. CRP was offered to patients without symptoms, with resectable tumor, and with operative fitness, as determined by an anesthesiologist. All CRP patients underwent extended lymph node dissection. Both the CRP group and the NLT group had scheduled follow up with lab work. Surgical complications within 3 months postoperatively were evaluated. Preliminary results revealed sustained PSA response in 23.5% of CRP patients without death or development of castrate resistance. On the other hand, 44.8% of patients in the NLT, or standard of care

group, became castrate resistant and 24.1% of patients died. A difference in overall survival, cancer specific survival, and castrate resistant free survival favored the CRP group. However, the CRP group was found to be significantly younger, had significantly lower initial PSA, and had significantly less high volume metastatic disease compared to the standard of care group.

### Ongoing trials

Although aggressive treatment with CRP in men with mPCa is an exciting proposal, there is limited high quality data and no level one evidence supporting its role. Fortunately, there are ongoing prospective RCTs that will provide additional data in the near future. The first surgical trial out of UT MD Anderson Cancer Center, titled “*Best Systemic Therapy or Best Systemic Therapy (BST) Plus Definitive Treatment (Radiation or Surgery)*” (M1 NCT01751438) is a phase II study comparing best systemic therapy to best systemic therapy plus CRP or RT. The primary outcome is progression free survival. The trial is ongoing and has completed accrual but is waiting for the data to mature before performing the analysis. An expanded phase III study (SWOG1802) with a similar design will be opening in 2018, and is expected to be activated in June 2018.

Other surgical trials are underway, including a trial out of Germany, titled “*Impact of Radical Prostatectomy as Primary Treatment in Patients With Prostate Cancer With Limited Bone Metastases (g-RAMPP)*” (NCT02454543) which is designed to investigate the role of radical prostatectomy with extended lymphadenectomy on CSS, time to castration-resistance, time to progression, and quality of life in patients with a limited mPCa to the bone. This trial is still actively accruing. Another trial out of the UK, titled “*Testing Radical prostatectomy in men with prostate cancer and oligometastases to the bone (TRoMbone): a randomized controlled feasibility trial*” (ISRCTN15704862) is similar in design to the g-RAMPP trial. In this trial they also compare the role of radical prostatectomy with extended lymphadenectomy plus standard of care in, patients with limited mPCa to the bone, to standard of care alone. Quality of life and time to castrate resistance will be the primary outcomes. These trials will hopefully improve the understanding of the potential role of CRP in mPCa.

Similarly, there are nonsurgical radiation RCTs that are ongoing such as STAMPEDE NCT00268476, HORRAD NTR271, and PEACE-1 NCT01957436 that will provide information on systemic therapies and the role of cytoreductive radiation.

### Conclusions

The concept of CRP in the setting of mPCa is enticing, but in the absence of prospective data we feel it should not currently be applied outside a clinical trial. Translational models and observational studies of mPCa have yielded compelling results, suggesting a potential biological benefit of cytoreduction. The primary tumor is believed to orchestrate and maintain the ideal microenvironment for tumor cell proliferation and subsequent metastases and the concept that intervention would alter the natural course is intriguing (47,48). Extrapolating clinical outcomes from other metastatic, solid tumors, such as renal and ovarian, would suggest that cytoreductive surgery might have a role in prostate cancer (49,50). Aggressive treatment with CRP in men with mPCa with curative intent is an exciting proposal with limitations based on the current supporting data. A better understanding of the biology driving mPCa may help expedite actionable data acquisition that will help improve clinical outcomes.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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