Role of Cytoreductive Radical Prostatectomy in the Treatment of Metastatic Prostate Cancer

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There is controversy regarding the survival benefits of eliminating primary tumors via cytoreductive radical prostatectomy (CRP) in patients with metastatic prostate cancer (mPCa). The purpose of this article is to review the theoretical background of and rationale for CRP, and the current knowledge base. The Scopus and PubMed databases were searched for studies investigating CRP published between January 2000 and October 2019. The retrieved articles were nonsystematically reviewed. Based on preclinical data, retrospective patient case studies, retrospective population-based studies, and prospective studies, CRP has been reported to afford benefits for the treatment and prevention of local symptoms through the removal of primary tumors, and the management of neo-metastatic disease and overall survival. However, despite the results from these studies, the current review mostly addresses small case studies and uncontrolled population-based studies with weak evidence. Based on this weak evidence, therefore, clinical use has not yet been recommended. Further research investigating the role and timing of CRP in patients with mPCa is needed, in addition to studies screening the most suitable populations for CRP. (*Korean J Urol Oncol* 2020;18:161-169)

Key Words: Cytoreductive radical prostatectomy · Local treatment · Metastatic prostate cancer · Prostate cancer · Radical prostatectomy

INTRODUCTION

Most prostate cancers are considered to be less aggressive in terms of malignancy and have a relatively good prognosis compared with other carcinomas; however, metastatic prostate cancer (mPCa) has a different prognosis.¹ Five-year survival rates are close to 100% for patients with local prostate cancer, but <30% for those with mPCa.¹ These metastatic prostate cancers account for approximately 4% of ini-

tially diagnosed prostate cancers, and 33% of local prostate cancers will progress to mPCa when diagnosed.^{2,3} Conventional treatment of patients with mPCa is converted to chemotherapy with docetaxel when proceeding to castration-resistant prostate cancer (CRPC) after androgen deprivation therapy (ADT) based on androgen axis control.^{1,4} However, the treatment of mPCa has changed significantly in the past few years. Recently, hormone drugs with new indications—before and after chemotherapy—have been developed.⁵ In addition, existing treatment options have been merged to broaden the scope of alternative therapies. The addition of ADT and 6-cycle docetaxel chemotherapy in patients with M1 mPCa has been reported to confer a survival advantage over treatment with ADT alone.⁶ However, despite these new drugs and methods, at approximately 30%, the 5-year survival rate of patients with mPCa at a

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stage higher than M1a has not improved significantly.⁷ Local treatment (LT), such as radiation therapy (RT) and radical prostatectomy (RP), have been used only for palliative purposes and locoregional symptom relief.^{1,4} However, cytoreductive RP (CRP) for primary tumors in those with mPCa is not recommended due to the lack of evidence supporting its oncological benefits. Cytoreductive surgery for these primary tumors has proven to be beneficial in colorectal, breast, ovarian, and kidney cancers.^{8,9} Recent advances in surgical techniques and understanding suggest a potential role for CRP in mPCa. In the present review, we examine the theoretical background of CRP, and the results of preclinical, retrospective case-control, population-based, and prospective studies.

MATERIALS AND METHODS

The purpose of this article is to review the theoretical background of and rationale for CRP, and the current knowledge base. The Scopus and PubMed databases were searched for studies investigating CRP published between January 2000 and October 2019. The retrieved articles were nonsystematically reviewed. Based on preclinical data, retrospective patient case studies, retrospective population-based studies, and prospective studies. Articles related to the topic were searched using the keywords “cytoreductive” and “radical prostatectomy,” “metastatic prostate cancer,” “local therapy in metastatic prostate cancer,” “local treatment in metastatic prostate cancer,” “radical prostatectomy in metastatic prostate cancer,” “cytoreductive prostatectomy,” “cytoreductive radical prostatectomy,” “cytoreductive surgery.” The pubmed.gov and Scopus databases were searched, duplicates were removed, and titles and abstracts were reviewed. Studies investigating the survival benefits of CRP in node-positive patients were excluded, as were those addressing differences between robotic CRP and open CRP procedures. Finally, retrospective case studies with <10 patients were also excluded.

1. Evidence Supporting the Benefit of Primary Tumor Control in Metastatic Disease

There is no confirmed theory supporting the benefits of primary tumor therapy in metastatic disease. However, there are studies that support the hypothesis that treatment of pri-

mary tumors is beneficial in the treatment of metastatic disease.¹⁰⁻¹³ Kaplan et al.¹³ proposed a premetastatic niche hypothesis, in which metastasis is caused by circulating tumor cells disseminated from primary tumors. When progenitor cell proliferation is activated by tumor-specific chemokines, the premetastatic niche of bone marrow is activated. Activated premetastatic niche helps the precursor cells move into the circulatory system.¹³ Progenitor cells move to other organs through the blood to cause the microenvironmental changes necessary for metastasis.¹³ The cancer self-seeding model is the theory that primary tumors act as a source of metastatic cells.¹⁰ Circulating tumor cells derived from primary tumors mediate metastasis and accelerate tumor growth by promoting stromal recruitment and angiogenesis through seed-derived factors at metastasized sites.¹⁰ It also releases additional metastatic cells at the site of metastasis, which return to primary tumors and grow.¹⁰ Genetic sequencing studies of metastatic spread patterns in mPCa have reported a characteristic pattern for many metastases from primary tumors to primary tumors, although there is also spread from metastasis to metastasis.^{11,12} Based on these findings, therefore, controlling primary tumors can eliminate one of the main causes of metastasis.^{11,12} The exact mechanism of the effects of CRP for primary tumor control on metastatic disease remains unclear; however, studies investigating various carcinomas have demonstrated that primary tumor control has advantages for overall survival (OS).⁸ In particular, CRP has a known survival benefit in colorectal, ovarian, breast, and kidney cancers.⁸

2. Preclinical Studies of CRP

There have been preclinical, experimental animal studies investigating the clinical utility of CRP in mPCa.^{14,15} Cifuentes et al.¹⁵ studied the metastatic dynamics of mPCa and the effects of CRP in animal models of mPCa by injecting prostate cancer cells into immunocompromised mice. The development and growth of primary tumors were confirmed to contribute to the growth and understanding of metastasis.¹⁵ Other studies have investigated the effects of reducing cell numbers at the metastasis stage.¹⁴ CRP was performed on orthotopic mice with mPCa, and less metastasis was observed in the operated mice.¹⁴ These small studies provide preclinical evidence supporting the benefits of eliminating primary lesions in mPCa.^{14,15}

3. Benefit of CRP on Local Symptoms in mPCa

Traditional CRP in patients with mPCa has played a palliative role in controlling locoregional progression. Approximately 80% of individuals with mPCa are likely to experience locoregional complications as the disease progresses.¹⁶ Moreover, approximately 30% of urinary tract complications, such as bladder outlet obstruction, are expected to require surgical intervention.¹⁷⁻¹⁹ In a retrospective study involving patients with CPRC, Steinberg et al.²⁰ reported that individuals who had previously received LT, such as RP and RT, demonstrated lower rates of local complications requiring surgical intervention than those who did not. In particular, patients who underwent RP exhibited the lowest complication rate. CRP has the benefit of lowering local complications in patients with mPCa. Heidenreich et al.²¹ reported that patients treated with CRP had a 30% lower rate of local complications than those treated with ADT alone. Won et al.¹⁹ reported that patients treated with RP and ADT, and RT and ADT, demonstrated a lower rate of local complications (by approximately 34%) compared to those treated with ADT alone. Grimm et al.²² reported that patients treated with RP, RP, and ADR exhibited a lower rate of local

complications (34%–38%) than those treated with ADT in a study of node-positive patients. LTs, such as RT and RP, can reduce symptoms by inhibiting locoregional progression by approximately 20%–50% in patients with mPCa.¹ Leibovici et al.²³ used palliative RP and cystoprostatectomy with urinary diversion to alleviate symptoms in 78% of patients with advanced systemic refractory mPCa. These findings suggest that CRP may help reduce local complications caused by locoregional progression and improve the quality of life of patients with mPCa.

4. Oncological Outcomes From Population-Based Studies Investigating RP in mPCa

Several population-based studies have demonstrated that CRP can benefit survival in patients with mPCa (Table 1).²⁴⁻²⁹ In a study using the Surveillance Epidemiology and End Results database, Culp et al.³⁰ compared 245 patients who underwent CRP and 129 who underwent brachytherapy among 8185 patients with M1 PCa compared with those who did not receive LT. OS rates were 22.5%, 67.5%, and 52.6% in those who underwent CRP, brachytherapy, and those without LT, respectively. In the CRP group, OS was highest in those who also underwent brachytherapy,

Table 1. Population based studies evaluating the role of radical prostatectomy in metastatic prostate cancer

Study	No. of patients	Stage	Intervention group	Results
Culp et al. ³⁰	8,185	M1a-c	CRP, BT, Non-LT	5-Year OS: 67.4%, 52.6%, 22.5% 5-Year CSS: 75.8%, 61.3%, 48.7%
Antwi and Everson ³¹	7,858	M1a-c	CRP, BT, Non-LT	Median survival time: 29, 31, 17 months
Satkunasivam et al. ²⁹	4,069	M1a-c	CRP, CRT, IMRT, Non-LT	3-Year OS: 73%, 37%, 72%, 34% 3-Year CSS: 79%, 49%, 82%, 46%
Fossati et al. ²⁴	8,197	M1a-c	LT, Non-LT	3-Year DSS (PPCSM 30%): 82%, 65% 3-Year DSS (PPCSM 40%): 78%, 58% 3-Year DSS (PPCSM 50%): 48%, 52%
Leyh-Bannurah et al. ²⁶	13,692	M1a-c	LT (RP, RT), Non-LT	CSM (LT < Non-LT): HR 0.40, 95% CI 0.32-0.50 CSM (RP < RT): HR 0.59, 95% CI 0.35-0.99
Parikh et al. ²⁸	6,051	M1a-c	LT (CRP, CRT, IMRT), Non-LT	5-Year OS: 45.7%, 17.1%
Löppenbergs et al. ²⁷	15,501	M1a-c	LT (RP, RT), Non-LT	3-Year OMFS: 69%, 54% 3-Year OMFS (OM risk ≤20%): 15.7% 3-Year OMFS (OM risk ≥70%): 0%
Gratzke et al. ²⁵	1,538	M1	CRP, Non-LT	5-Year OS: 21%, 55%

CRP: cytoreductive radical prostatectomy, BT: brachytherapy, LT: local therapy, OS: overall survival, CSS: cancer specific survival, IMRT: intensity-modulated radiation therapy, DSS: disease specific survival, PPCSM: predicted prostate cancer-specific mortality, CSM: cancer specific mortality, HR: hazard ratio, CI: confidence interval, CRT: conformal radiation therapy, RP: radical prostatectomy, RT: radiation therapy, OMFS: overall mortalityfree survival, OM: overall mortality.

compared with the non-LT group.³⁰ Antwi and Everson³¹ reported reduced overall mortality (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.20–0.38) and cancer-specific mortality (CSM: HR, 0.28; 95% CI, 0.20–0.39) in patients who underwent CRP compared to those who did not receive LT. Satkunasivam et al.²⁹ compared mPCa patients who underwent CRP, intensity-modulated radiation therapy (IMRT), and conformal radiation therapy (CRT) and did not receive LT. Among the 4,069 patients with M1 prostate cancer, 47 who underwent CRP, 88 who underwent IMRT, 107 who received CRT, and those who did not receive LT were compared.²⁹ Patients who underwent CRP (HR, 0.48; 95% CI, 0.27–0.85) and IMRT (HR, 0.38; 95% CI, 0.24–0.61) demonstrated significantly reduced CSM compared to those who did not undergo LT.²⁹ Fossati et al.²⁴ compared 8,197 patients with M1 mPCa with those who received LT, including CRP and brachytherapy, and those without LT. Multivariate Cox regression was used to calculate the 3-year CSM risk at diagnosis.²⁴ According to CSM, the group treated with LT and the group not treated were compared.²⁴ In patients with a predicted CSM <40%, patients who underwent LT demonstrated higher CSM-free survival than those who did not receive LT.²⁴ In the case of >50% predicted CSM, LT demonstrated no survival benefit.²⁴ Leyh-Bannurah et al.²⁶ compared M1 mPCa patients with those who received local RP and RT, and those without LT. Of the 13,692 mPCa patients, 313 underwent RP and 161 RT. Patients who received LT (HR, 0.40; 95% CI, 0.32–0.50) demonstrated significantly reduced CSM compared to those who did not receive LT.²⁶ In the LT group, RP (HR, 0.59; 95% CI, 0.35–0.99) resulted in a lower CSM than RT.²⁶

In a study using the National Cancer Database, Parikh et

al.²⁸ compared mPCa patients who underwent CRP, IMRT, and CRT and did not receive LT. The 5-year survival rates were 45.7% versus 17.1% in the patients who were treated and were not treated LT. In multivariate analysis, CRP (HR, 0.51; 95% CI, 0.45–0.59; $p < 0.01$) and IMRT (HR, 0.47; 95% CI, 0.31–0.72; $p < 0.01$) were significantly associated with better OS, respectively.²⁸ Löppenberget al.²⁷ analyzed 15,501 mPCa patients and compared the groups with and without LT, such as RP and RT. A total of 1,470 patients (9.5%) underwent LT, and the 3-year OS for LT and non-LT was 69% versus 54%, respectively.²⁶ There was a survival benefit for LT in the group with low predicted overall mortality risk and no LT survival benefit in the group with $\geq 70\%$ of the estimated overall mortality risk.²⁷ In a study using the Munich Cancer Registry, Gratzke et al.²⁵ compared 74 patients who underwent CRP of 1,538 mPCa patients to those who did not receive LT.²⁵ The 5-year survival rates were 55% versus 21% in the CRP and non-LT groups, respectively.

5. Oncological Outcomes in Retrospective Case Studies Investigating RP in mPCa

Several retrospective studies have demonstrated that CRP can benefit survival in patients in mPCa (Table 2).^{21,32,33} Heidenreich et al.²¹ compared oligometastatic prostate cancer in 23 patients who underwent CRP after neoadjuvant ADT, and 38 patients who underwent ADT alone. The CRP group included patients with prostate-specific antigen (PSA) levels <1.0 ng/mL after neoadjuvant ADT for 6 months. In the CRP group, 13 patients had a positive margin and were node-positive, and 5 experienced biochemical recurrence (21.7%).²¹ Time to CRPC was 40 months versus 29 months

Table 2. Retrospective case studies evaluating the role of radical prostatectomy in metastatic prostate cancer

Study	No. of patients	Stage	Intervention group	Results
Heidenreich et al. ²¹	61	M1b (Oligometastatic)	Neoadjuvant ADT+CRP, ADT	OS: 91.3%, 78.9% DSS: 95.6%, 84.2%
Heidenreich et al. ³²	113	M1b (Oligometastatic)	CRP	3-Year OS: 87.6%, 5-year OS: 79.6% Clinical RFS: 72.3 months
Gandaglia et al. ³³	11	M1b (Oligometastatic)	CRP	7-Year clinical PFS: 45% CSS: 82%

ADT: androgen deprivation therapy, CRP: cytoreductive radical prostatectomy, CSS: cancer specific survival, OS: overall survival, DSS: disease specific survival, RFS: relapse-free survival.

in the CRP and ADT groups, respectively, and progression-free survival was 38.6 months versus 26.5 months. Cancer-specific survival (CSS) was 95.6% versus 84.2%, and OS was 91.3% versus 78.9%.²¹ Heidenreich et al.³² compared the oligometastatic PCa of 113 patients with CRP, and 36.8% of patients had a positive margin and 61.6% of patients were node-positive.³² The 3-year OS of CRP patients was 87.6% and the 5-year OS was 79.6%. Clinical relapse-free survival was 72.3 months.³² Gandaglia et al.³³ compared oligometastatic prostate cancer in 11 patients who underwent CRP. Eight patients had a positive margin and 10 were node-positive. The 7-year clinical progression-free survival and CSS were 45% and 82%, respectively.³³

6. Oncological Outcomes in Prospective Case Studies Investigating RP in mPCa

Steuber et al.³⁴ used prospective data to compare 43 patients with oligometastatic prostate cancer and 40 who underwent ADT. There was no significant difference in OS and castration resistant-free survival between the 2 groups. However, in the case of local complications, the CRP group and ADT group had a significant decrease in the CRP group (7.0% vs. 35%).³⁴ Preliminary results of the Local Treatment of Metastatic Prostate Cancer (LoMP) trial have been published.³⁵ The LoMP trial was conducted among patients with mPCa who underwent CRP.³⁵ Patients with mPCa who showed no symptoms associated with metastatic lesions, had a resectable tumor, and a condition suitable for surgery

Table 3. Studies evaluating the role of the metastasis direct therapy in oligometastatic PCa patients

Study	Study type	No. of patients	Stage	Intervention group	Results
Palma et al. ³⁸	Randomized phase II trial	99	Oligorecurrent CRPC	MDT, SOC	Median OS: 41, 28 months Median PFS: 12, 6 months Median AFS: 21, 13 months
Ost et al. ³⁹	Randomized phase II trial	62	Oligorecurrent HSPC	Surgery or SBRT, Surveillance	6-Month PFS: 67%, 33%
Tran et al. ⁴⁰	Randomized phase II trial	36	Oligorecurrent HSPC	SBRT, Surveillance	1-Year PFS: 58%, 2-year PFS: 39%
Siva et al. ⁴¹	Prospective	50	Oligorecurrent PCa	SBRT	2-Year FFTE: 51.7%
Bowden et al. ⁴²	Prospective	199	Oligorecurrent PCa	SBRT	Median bDFS: 11 months, 2-year AFS: 48%
Kneebone et al. ⁴³	Prospective	57	Oligorecurrent HSPC	SBRT	1-Year bPFS: 57%, 2-year bPFS: 40% Median AFS: 27.8 months
Deek et al. ⁴⁴	Retrospective	156	Oligorecurrent PCa	MDT	2-Year bPFS: 54% 2-Year PFS: 45% 2-Year OS: 83%
Muldermans et al. ⁴⁵	Retrospective	66	Oligorecurrent PCa	MDT	2-Year bPFS: 44%
Ingrosso et al. ⁴⁶	Retrospective	40	Oligorecurrent HSPC	MDT	1-Year bPFS: 69%, 1-year PFS: 69% 1-Year AFS: 78%
Moyer et al. ⁴⁷	Retrospective	66	Oligorecurrent PCa	MDT	Median AFS: 25 months 1-Year AFS: 82%, 2-year AFS 60%
Decastecker et al. ⁴⁸	Retrospective	50	Oligorecurrent HSPC	MDT	Median AFS: 38 months 1-Year AFS: 82%, 2-year AFS 54%
Berkovic et al. ⁴⁹	Retrospective	24	Oligorecurrent HSPC	MDT	

PCa: prostate cancer, CRPC: castration-resistant prostate cancer, MDT: metastasis direct therapy, SOC: standard of care, OS: overall survival, PFS: progression free survival, HSPC: hormone sensitive prostate cancer, SBRT: stereotactic body radiotherapy, AFS: androgen deprivation therapy free survival, FFTE: freedom from treatment escalation, bDFS: biochemical disease-free survival, bPFS: biochemical progression free survival.

were included.³⁵ The standard care and CRP groups were compared.³⁵ Two-year OS and CSS in the CRP group and the standard care group were 100% versus 61%, and 100% versus 55%, respectively.³⁵ The CRP group demonstrated no progression to CRPC, 23.5% exhibited a PSA response, 44.8% had CRPC, and 24.1% died in the standard care group.³⁵

7. Metastasis Direct Therapy in mPCa

In addition to local therapy of primary tumors, several studies have reported that reduced treatment of metastatic burden is associated with survival benefit.³⁶⁻⁴⁹ It is based on Halstead and Hellman's hypothesis that cancer ranges from locally defined too broadly metastatic.^{36,37} According to these 2 hypotheses, the metastasis state is divided into an oligometastatic state, which is considered to be an early sign of systemic macrometastasis with a limited number of metastases less than 5, and a high-volume metastatic state with 5 or more metastases.^{36,37} Metastasis direct therapy (MDT) in oligometastatic states, which are metastatic in this early short-term, helps to prolong survival by reducing the burden of metastatic lesions. Table 3 shows the results of studies related to the treatment of metastatic lesions in these oligometastatic PCa patients.³⁸⁻⁴⁹ Several RCT studies have shown that MDT, such as surgery or stereotactic body radiotherapy (SBRT), has an advantage over survival in patients with Oligorecurrent PCa. Palma et al.³⁸ reported median OS and PFS improvement in the MDT group compared to the standard of care group. Ost et al.³⁹ reported that median ADT free survival was improved in Surgery or SBRT group compared with surveillance group. Tran et al.⁴⁰ reported a 6-month PFS improvement in the SBRT group compared to the surveillance group. Several prospective and retrospective studies report median ADT free survival of approximately 21 to 38 months and 2-year PFS of approximately 39% to 54% in the MDT group.⁴¹⁻⁴⁹

8. Feasibility of Cytoreductive Radical Prostatectomy

Retrospective studies have been conducted on the safety and feasibility of CRP.^{21,33,50} Heidenreich et al.²¹ compared patients with mPCa treated with RP and pelvic lymph node dissection who had low-volume skeletal metastasis and those treated with ADT without local therapy. The Clavien-Dindo classification of the complications in the CRP group

was as follows: grade IV-V, 0%; grade III, 13%; grade II, 8%; and grade I, 17%.²¹ The ADT group had complications that required surgery or intervention, with approximately 30% local progression, and the CRP group had no complications due to local progression.²¹

Gandaglia et al.³³ reported a 5-year follow-up of CRP-treated patients among those with oligometastatic mPCa. In their study, only approximately 18% of patients reported complications of Clavien grade 3 or higher after CRP.³³ In a multicenter study of CRP for distant mPCa, post-CRP complications occurred in 21% of the patients and Clavien-Dindo classification grade III or higher complications occurred in 8%.⁵⁰ The functional result after surgery was 82% in the patients who used less than one pad a year after surgery and 64% in those who were pad-free.⁵⁰ This was not significantly different from the post-RP outcome in patients with high-risk prostate cancer. Even patients with prostate cancer with distant metastasis may be similar to those with locally advanced prostate cancer if the disease is limited to the prostate area. For this reason, functional outcomes and complication rates may be similar, and in the case of mPCa without metastasis to peripheral organs, CRP is feasible. In terms of stability and functionality, CRP is unlikely to differ significantly from high-risk prostate cancer surgery.

CONCLUSIONS

CRP for mPCa has been reported to confer benefits for the treatment and prevention of local symptoms and improvement of survival outcomes through the removal of primary tumors, the management of neo-metastatic disease, the control of tumor burden. However, the rationale for CRP is based mainly on preclinical and retrospective studies, without large-scale prospective and randomized controlled trials. Further research investigating the role and timing of CRP in patients with mPCa is needed, as well as studies screening populations most suitable for the procedure.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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