



Outcome of Cyto Reductive Prostatectomy and ADT and Metastasis-Directed Therapy (MDT) in Patients with Oligometastatic Prostate Cancer: A Prospective Cohort

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Abstract

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Objective: We wanted to evaluate the efficacy and safety of a new treatment of Oligometastatic prostate cancer (OMPC) with multimodal approach including local primary tumor therapy, in the form of Cytoreductive Prostatectomy, metastasis-directed therapy (MDT), and hormonal therapy .

Methods: We reviewed data of patients with Oligometastatic Prostate Cancer(OMPC) at diagnosis treated in our institutions with ADT and followed by Cytoreductive Prostatectomy (CP) with or without metastases-directed radiotherapy. In this prospective cohort study, 19 patients underwent Cytoreductive radical Prostatectomy and routine Lymphadenectomy, ADT with Degarelix, Aberateron and Prednisolone in the form of neoadjuvant setting during the period of Jan 2016 - March 2021. Of these, 05 patients (26.31%) received stereotactic body radiation therapy (SBRT) to all metastatic sites as a MDT in addition to above protocol.

Results: The median follow-up period was 46.2 months. Perioperative outcomes, clinical progression, and cancer-specific mortality (CSM) were evaluated. Median age was 72 yr. Median operative time, blood loss, and length of hospitalization were 176 min, 850 ml, and 6 d, respectively. Overall, two patients (10.52%) experienced grade 3 complications in the postoperative period. All received blood transfusions. Overall, 15 (78.94%) and 8 (42.10%) patients had lymph node invasion and positive surgical margins, respectively. Adjuvant Radiation Therapy and androgen deprivation therapy was administered to all 8 patients (42.10%) who confirmed margin Positive status. Of the 19 patients, the 3-year castration-resistant prostate cancer (CRPC)-free survival and cancer-specific survival was 100%. Our findings support the safety and effectiveness of Cytoreductive Prostatectomy (CP) in a highly selected cohort of PCa patients with bone metastases and long-term follow-up

Conclusion: This Prospective cohort revealed the feasibility of combining ADT and Cytoreductive prostatectomy and metastasis-directed radiotherapy for newly-diagnosed Oligometastatic Prostatic Cancer. This treatment strategy has the potential to delay the progression to CRPC.

Keywords: Oligometastatic, Prostate Cancer (OMPC), Stereotactic Body Radiation Therapy(SBRT), Androgen Deprivation Therapy, Cytoreductive Prostatectomy(CP), Metastasis-Directed Therapy(MDT).

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Introduction

Oligometastatic Prostate cancer (OMPC) was defined as the presence of five or fewer metastatic lesions with the absence of visceral metastases. The current standard of care for metastatic prostate cancer (mPCa) is androgen deprivation therapy (ADT) with or without anti-androgen and chemotherapy. Out of the 1.3 million prostate cancer cases diagnosed worldwide in 2018, approximately 20% had metastatic disease.¹

Oligometastatic prostate cancer (OMPC) is one of the clinical states observed along the spectrum of the natural history of prostate cancer and has continued to be an area of interest since it was originally proposed by Hellman and Weichselbaum in 1995.² The concept has been developed to achieve a cure using more intensive or targeted treatment in this patient with OMPC population while preserving functional and clinical status.

Oligometastatic prostate cancer (OMPC), generally defined by presence of five or fewer metastatic sites on imaging, represents a transitional state between localized and widespread metastatic disease and encompasses a wide spectrum of disease biologies and clinical behaviors. An effort is ongoing to determine the genomics of OMPC. The prevalence of OMPC varies significantly in the literature and is likely to change further as substantial improvements in imaging improve our ability to reclassify a subset of patients with biochemical recurrence by conventional imaging as OMPC and another subset from OMPC to polymetastatic disease.

Patients with Oligometastatic Prostate Cancer are more likely to succumb to their disease, and they therefore represent a significant treatment challenge. The traditional approach of ADT plus Adrenal axis inhibitors with or without Chemotherapy with Docitaxel. Currently the treatment of OMPC is being complemented by evolving multimodal approaches such as newer radiation therapies or Cyto reductive Prostatectomy as primary treatment with adjuvant or salvage therapies (or both) when appropriate. To make a significant impact in this cohort of patients, our team was committed to layer treatment options to improve outcomes.

The mainstay of OMPC treatment remains the multimodal therapy of which the local therapy of the prostate is the most important and adjunct another important adjunct is the Metastasis-Directed Therapy (MDT). An improvement in outcomes, including failure-

free survival in several retrospective studies. Cyroreductive Prostatectomy (CP) or Radiation Therapy (RT) to the Prostate has specifically demonstrated an overall survival (OS) advantage in patients of OMPC with low-volume disease in a clinical trial. A good outcome has been observed with skeletal metastasis Stereotactic Body Radiation Therapy (SBRT) distant metastatic sites in retrospective studies. Understanding of the biology, imaging modalities, and treatments may allow for more aggressive multimodal therapies with an effort to obtain deeper responses and, potentially, cures for selected patients with OMPC. Clinical trials or institutional registries are strongly encouraged for patients with OMPC who opt for an aggressive multimodality approach to achieve a cure. We should be able to prioritize treatment regimens in a relatively efficient manner with a relatively small number of patients and identify the most promising treatment combinations. After this, we can scale-up these treatment combinations for large-scale trials. We anticipate the follow-up trial to be initiated shortly. It is an important first step, but it will require larger studies with longer follow-up time.

The number and location of metastatic sites have an impact on survival.³⁻⁶ Surveillance, Epidemiology, and End Results (SEER)-Medicare analysis of 3,857 patients found that median OS was 43 months for lymph node (LN)-only metastases, 24 months for bone-only metastases, 16 months for visceral-only metastases, and 14 months for bone plus visceral metastases.⁷

In a meta-analysis of 8,820 patients enrolled in nine phase III trials of metastatic castration-resistant prostate cancer, 72.8% of patients had bone with or without nodal metastases, 20.8% had visceral metastases, and 6.4% had nodal-only metastasis. Patients with liver metastases experienced the worst median OS (13.5 months; 95% CI, 12.7-14.4 months) followed by those with lung metastases (median OS, 19.4 months; 95% CI, 17.8-20.7 months), bone metastases (median OS, 21.3 months; 95% CI, 20.8-21.9 months), and nodal-only metastases (median OS, 31.6 months; 95% CI, 27.9-35.5 months).⁸

Outcomes are also progressively worse for increasing numbers of nodal and distant metastases, which serve as a surrogate for tumor burden.⁹ In a single-center study of 207 patients with LN metastasis treated with radical prostatectomy and bilateral pelvic LN dissection (PLND), median time to biochemical recurrence in patients with one, two, and three or more LNs was 59

months, 13 months, and 3 months respectively.¹⁰ Another study of 703 patients with localized prostate cancer with clinically positive LNs treated with radical prostatectomy and extended PLND found that patients with two or fewer positive nodes had significantly better cancer-specific survival outcomes at 15 years of follow-up compared with patients with more than two positive nodes (84% vs. 62%; $p < .001$).¹¹ It is also well known that patients with high-volume metastatic prostate cancer have poorer outcomes compared with those with low-volume metastatic prostate cancer.^{12,13}

Genomic landscapes of localized, locally advanced, and metastatic prostate cancers have been studied in great detail¹⁴ but the biology of OMPC remains undefined. In genomic studies of localized and locally advanced prostate cancer, polyclonal tumors were found to be associated with a higher risk of metastatic disease. In addition, the phenomenon of nonlinear clonal evolution in metastatic sites, where clones from metastatic sites can seed other sites, including the primary tumor, has been described in prostate cancer.¹⁵ A study of 42 samples of primary and metastatic tumors of patients who were treated with stereotactic RT found differences in micro RNA expression profiles between samples of patients who developed oligometastatic versus polymetastatic disease. Investigators also evaluated the functional role of microRNAs, finding that miRNA-200c enhancement in the oligometastatic cell line was associated with polymetastatic disease progression. These studies suggest that oligometastatic disease may have a potentially less diverse and differing landscape than polymetastatic disease and the primary tumor. A systematic collaborative effort to elucidate the genomic landscape of OMPC is ongoing.¹⁶ The incidence of germ line mutation in DDR genes among men with metastatic Prostate Cancer varies between 11% and 33%, and it is significantly higher compared to the incidence in men with localized PCa.³⁶

Prostate Cancer is a clinically heterogeneous disease and commonly show variable responses to treatments that result in different clinical outcomes. This clinical variability may reflect molecular heterogeneity. Therefore, molecular profiling could have a meaningful translational relevance. This may help to distinguish PCa with indolent behavior from those with a lethal course. Several studies explored the prognostic role of BRCA mutations in localized PCa and in mCRPC patients treated with standard therapies.³⁷ In a large retrospective study, BRCA1/2 mutations correlated

with higher Gleason score, nodal involvement, metastatic disease at diagnosis, and T3/4 stage.³⁸ Moreover, BRCA2 was an independent prognostic factor that was associated with poorer outcomes. In localized PCa, the 5-year CSS and MFS were significantly shorter in BRCA2 carriers than in noncarriers (82% vs. 96%; 77% vs. 93%, respectively) [38]. Given conflicting results reported in retrospective studies, it is currently uncertain whether BRCA2 mutation may affect the clinical outcome of mCRPC patients treated with standard treatments [40, 41]. Annala and colleagues retrospectively analyzed 319 charts of mCRPC patients, including 22 germline DDR (gDDR) carriers (16 BRCA2-mutated).

Method:

The STAMPEDE trial has shown a survival benefit for local radiation therapy in men with oligo-metastatic prostate cancer. Observational studies have suggested such benefit may also be seen with radical prostatectomy (RP) but before starting systemic therapies. Multivariate logistic regressions were used to determine which co-variables, PSA doubling time, ongoing androgen deprivation therapy and time to recurrence.³⁶ We reviewed data of patients with PCa and bone Oligometastases at diagnosis treated in our institutions with ADT and followed by Cytoreductive surgery with or without metastases-directed radiotherapy. In this prospective cohort study, 19 patients underwent Cytoreductive radical Prostatectomy and routine Lymphadenectomy, ADT with Degarelix, Abirateron and Prednisolone in the form of neoadjuvant setting during the period of Jan 2016 - March 2021. Of these, 05 patients (26.31%) received stereotactic body radiation therapy (SBRT) to all metastatic sites as a part of MDT in addition to above protocol.

Results:

The median follow-up period was 46.2 months. Perioperative outcomes, clinical progression, and cancer-specific mortality (CSM) were evaluated. Median age was 72 yr. Median operative time, blood loss, and length of hospitalization were 176 min, 850 ml, and 6 d, respectively. Overall, two patients (10.52%) experienced grade 3 complications in the postoperative period. All received blood transfusions. Overall, 15 (78.94%) and 8 (42.10%) patients had lymph node invasion and positive surgical margins, respectively. Adjuvant Radiation Therapy and androgen deprivation therapy was administered to all 8 patients (42.10%) who confirmed

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Discussion

Oligometastatic PCa is defined as a disease state which is limited in total disease burden and not rapidly spreading to other sites.¹⁷ Genomic data have shown different biological pathways between widespread and limited metastatic diseases in several primary cancers, as well as PCa.^{18,19} From the “seed and soil” theory, if the facilities of metastatic growth such as fitness of individual cancer cells are not fully developed and the quality of the site for such growth is restricted, tumors may have metastases limited in number and location.²⁰

The concept of oligometastatic was first proposed in 1995, and since that time there has been considerable interest in this disease space. This implies that there is an intermediate space between patients who have localized disease with cancer restricted to the organ of origin and widely metastatic disease with metastases spread throughout the body. In this oligometastatic disease space, patients are expected to have a better prognosis and may have the potential for cure. Now, currently available prospective trials have demonstrated improvement in survival outcomes when local treatment approaches have been applied to these metastatic foci. However, to date, the ability to render a cure is somewhat limited in metastatic disease due to an inability to accurately characterize all metastatic sites.

This is the citation of this recently published work in *European Urology*, led by Dr. Rachel Glicksman as first author and Dr. Alejandro Berlin as senior author.⁴²

Prostate cancer represents a good model for this oligometastatic treatment paradigm, because firstly, we have a biomarker using PSA, which is sensitive for the early diagnosis of recurrent disease, and we have recently developed novel imaging approaches, which allow for early identification and localization of these metastatic foci.

Recently published data have shown that metastasis-directed therapy may delay the initiation of non-curative ADT approaches, however, the authors here sought to assess whether we could use 18fluoride DCFPyL PET-CT to allow for earlier identification and localization

metastatic disease, which could be amenable to treatment with curative intent directed at those sites. To do this, the authors included patients with pathologically confirmed prostate cancer, who had undergone prior treatment with either radical prostatectomy and subsequent postop radiotherapy. There had to be at least 1 year since the cessation of androgen deprivation therapy if this was given concurrently with radiotherapy. The authors defined disease recurrence as three consecutive PSA increases in an absolute PSA between 0.4 and 3 nanograms per milliliter. Patients had to be non-castrated with normal testosterone, and have negative conventional imaging based on CT and bone scan. Patients were excluded if they had prior use of ADT that did not fit the previous criteria, prior use of chemotherapy, or any contraindications to MRI or IV contrast.

The authors then initiated a single-institution, open-label, single-arm phase 2 study, and in doing so, they undertook a PET-MR/CT within 6 weeks of registration introduced. So, they performed a PET-MR, which was followed immediately by a PET-CT. The results of these scans were reported to the patient and the treating physician, and all cases were then discussed at a multidisciplinary tumor board and patients were seen in consultation by urologists and radiation oncologists. On the basis of the multidisciplinary tumor board and patient consultations, patients were then offered metastasis-directed therapy with either surgery, being a salvage node dissection, or SABR with radiation given in three fractions. Following a metastasis-directed therapy, patients were followed up at 2 weeks and then 1, 2, 3, and 6 months. A repeat PET-MR was performed at 4 months following metastasis-directed therapy. The second course of metastasis-directed therapy in the form of SABR was allowed for newly developed PSMA-avid untreated lesions.

The first objective of the study was to determine if 18F-DCFPyL PET-MR/CT could identify early oligorecurrent disease, and this was captured in terms of detection rates and patterns of recurrence. And secondly, the authors sought to determine whether treating PET-MR/CT detected lesions could result in clinical benefit, and they quantify this in terms of biochemical response, which could be either partial or complete. Secondly, the authors assessed adverse events associated with metastasis-directed therapy, PSA progression, following metastasis-directed therapy, and ADT-free survival.

The authors employed Simon's optimal two-stage phase 2 clinical trial designs to test their approach. The first stage required 12 response-evaluable patients be treated, and in stage two, if at least one of the initial 1200 patients had a response, the trial continued to accrue an additional 25 patients. Overall, the study would be deemed effective if at least four objective responses were seen, and based on the literature, the authors expected a 50% detection rate using PSMA PET-MR. The authors performed descriptive statistics and examined the change in PSA as well as response capture using waterfalls and swimmers plots, respectively. Survival data were captured using a Kaplan-Meier technique, and univariable Cox models were used to assess for predictors.⁴²

There is a theory that cancer cells that are left in the primary tumor as circulating tumor cells have the ability to seed metastases to distant organs. Uncontrolled local tumor may act as a source for seeding to distant organs and self-seeding the primary tumor itself. Therefore, the longer the primary cancer remains in place, the higher is risk of new malignancies and progression of metastases.²¹⁻²³

More recently, there is a new emerging concept about the role of RP for the treatment of oligometastatic PCa. The role of surgery in mPCa is supported by several preclinical models. Kadmon et al.^{24,25} injected rats with 3327/MAT-Lu tumor which is a prostatic cancer cell line that has the potential to cause lung metastasis in 100% of cases. They found that rats underwent surgical excision of the primary tumor plus chemotherapy had improved survival comparing with those received chemotherapy alone (42% vs. 0% at 180-day sacrifice). Cifuentes et al. used PC3 cells which were derived from a bone metastasis of a human PCa patient for orthotopic injection into mouse prostate^{26,27}. They discovered that after resection of the prostate, the metastatic sites were smaller and less numerous comparing with the control group. These preclinical studies support the hypothesis of cytoreductive surgery in mPCa.

Although there is several ongoing randomized controlled trials (RCTs) regarding the surgical management of the primary tumor in mPCa, all reports to date are observational data or retrospective reviews. Aggressive transurethral resection of the prostate (TURP) is another form of cytoreductive surgery. Qin et al. retrospectively reviewed patients with metastatic hormone-sensitive PCa underwent palliative TURP and found that this resulted in a better and more prolonged

response to ADT with a trend toward improvement in disease specific and OS. TURP may provide an alternative approach for cytoreductive surgery besides RP.²⁸

Antwi and Everson also analyzed patients from the same SEER database with propensity score methods for risk adjustment and found similar results. They also observed that patients underwent RP after diagnosis with mPCa was associated with 73% (Hazard ratio [HR] 0.27, 95% CI: 0.20-0.38) lower risk of all-cause mortality, and 72% (HR 0.28, 95% CI: 0.20-0.39) reduced risk of death from PCa.²⁹

Heidenreich et al reported a case-control study to compare patients with minimal metastatic disease who underwent RP along with ADT with patients with mPCa who received only ADT in control group. A total of 23 patients who underwent RP in addition to ADT were the patients who had clinically localized PCa with equal or less than 3 bone metastatic sites and no visceral disease. Whereas, the other 38 patients in the control group received only ADT. Patients in RP group had significantly better clinical progression-free survival (38.6 vs. 26.5 months, $P = 0.032$), cancer-specific survival rates (95.6% vs 84.2%, $P = 0.043$), and longer median time to castration-resistant PCa (40 vs. 29 months, $P = 0.04$), but OS was not different. There was no statistically significant difference in terms of clinical stage, Gleason score, PSA, and extent of metastases between two groups. However, there were some limitations in this study that the patients in this study were not randomized, and median follow-up time of patients in the control group was longer (47 vs. 34.5 months).³⁰

Gratzke et al. evaluated patients diagnosed with mPCa from the Munich Cancer Registry. Of a total of 1,538 patients in their cohort, 74 patients underwent RP. There was 55% 5-year OS rate in RP group in comparison with 21% in patients who did not undergo RP ($P < 0.01$). However, this study had a limitation that they did not evaluate baseline characteristic and pathologic reports of the patients in their study.³¹

Recently, Gandaglia et al. reported outcomes of 11 patients with oligometastatic PCa who underwent RP in a single-institutional series. These patients had a 7-year progression-free survival and cancer-specific survival rates of 45% and 82%, respectively. Although they reported favorable long-term follow-up outcomes in patients with PCa with bone metastases, this study had several limitations. First, this study was a small

retrospective review with only 11 patients. Second, patients who underwent RP had good performance status, low disease volume, and favorable PSA level, therefore significant selection bias was observed. Third, there was no control group in this study, thus the oncologic outcomes could not be determined.³²

Another possible advantage of RP in mPCa is that it may prevent late symptomatic local progression. Patrikidou et al. found that up to 78% of patients who have de novo mPCa will suffer significant local symptoms such as pelvic pain, dysuria, hematuria, and urinary retention throughout their disease course. These patients required palliative RP, cystectomy, or pelvic exenteration to alleviate the symptoms. Therefore, initial definite locoregional treatment at earlier time point in these patients may have a role to prevent the development of late local symptoms.³³

Recently, there are two prospective RCTs evaluating the effect of radiotherapy in patients with newly diagnosed metastatic PCa which are HORRAD (effect on survival of ADT alone compared to ADT combined with concurrent radiation therapy to the prostate in patients with primary bone metastatic prostate cancer in a prospective randomized clinical trial) and STAMPEDE trials. The HORRAD trial reported outcomes of patients with primary bone metastatic PCa who received ADT combined with concurrent radiation therapy comparing with the patients who received ADT alone. There was no significant difference in OS between two groups (HR 0.9; 95% CI: 0.7-1.14) with median OS of 45 months in the radiotherapy group and 43 months in the control group. However, the median time to PSA progression in the radiotherapy group (15 months with 95% CI: 11.8-18.2) was differed significantly from the control group (12 months with 95% CI: 10.6-13.4) (HR 0.78; 95% CI: 0.63-0.97, $P = 0.02$).³⁴

STAMPEDE, a multicenter randomized controlled Phase III trial compared the outcomes of ADT plus radiotherapy to the primary tumor to ADT alone, in patients with de novo mPCa[36]. This trial showed survival benefit of radiotherapy in oligometastatic PCa. There was no significant difference in OS between two groups (HR: 0.92, 95% CI: 0.80-1.06; $P = 0.266$). However, radiotherapy could improve failure-free survival (HR: 0.76, 95% CI: 0.68-0.84; $P < 0.0001$). Moreover, metastatic burden was randomized and classified using the definition from CHARTED trial. High metastatic burden was defined as four or more bony metastases with one or more outside the pelvis or vertebral bodies,

or visceral metastases, or both; all other patients were classified to have low metastatic burden.³⁵ OS was improved significantly in patients with a low metastatic burden who underwent radiotherapy (HR: 0.68, 95% CI: 0.52-0.90; $P = 0.007$). In addition, failure-free survival was also improved in men with low metastatic burden (HR: 0.59, 95% CI: 0.49-0.72; $P < 0.0001$). In contrast, radiotherapy did not improve OS (HR: 1.07, 95% CI: 0.90-1.28; $P = 0.420$) and failure-free survival (HR: 0.88, 95% CI: 0.71-1.01; $P = 0.059$) for men with high metastatic burden. By conclusion, although there was no improvement in unselected patients, radiotherapy could improve survival in men with a low metastatic burden [36]. The result from the STAMPEDE trial support the treatment of primary tumor by radiotherapy in patients with oligometastatic mPCa and is likely to set a new standard of care.

The 'Will Rogers phenomenon' is an apparent epidemiological paradox named after a remark made by the humorist Will Rogers about migration during the American economic depression of the 1930's: "When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states." In 1985, Alvan Feinstein proposed the name 'Will Rogers Phenomenon' to describe the 'stage migration' he observed in patients with cancer. Changes in the criteria for assigning patients to the various stages of a disease can produce spurious improvements in stage-specific prognosis, even though the outcome of individual patients has not changed. In oncology, new imaging tools allowed detection of cancer metastases before they became evident clinically. In consequence, more patients are classified into the more severe metastatic disease stage from the less severe single tumour stage. Such a 'stage migration' resulted in an improved survival of patients in both the less and the more severe disease stages.⁴³

In the era of new imaging tools, like the PSMA PET scans, allow for detection of cancer metastases before they became evident clinically. So now the clinical application may be many T2 and T3 stage may be escalated to metastatic Prostate cancer (Wills Rogers Phenomenon). However, the Will Rogers phenomenon, which is recognized as one of the most important biases limiting the use of historical controls groups in experimental treatment trials, compromises the interest of this approach. In this context, the use of different diagnostic criteria may generate spurious improvements in the medium-term prognosis of multiple sclerosis, which may be wrongly interpreted as treatment effects.⁴⁴

There are several ongoing prospective RCTs evaluating the role of surgery in mPCa such as a prospective multi-institutional randomized, Phase II trial of best systemic therapy (BST) vs BST plus definitive local therapy (surgery or radiation) in patients with mPCa (NCT 01751438), the impact of RP as primary treatment in patients with PCa with limited bone metastases (GRAMPP, NCT 02454543) which comparing patients received BST alone with BST plus RP, and testing RP in men with PCa and oligometastases to the bone (TRoMbone, ISRCTN15704862) which comparing patients with oligometastatic PCa to bone receiving RP plus standard care with standard care alone.⁴⁴

At present, select patients with a good performance status, limited disease sites amenable to SBRT, and a strong desire to avoid the side effects of long-term ADT may be considered for consolidative therapy after a discussion of goals of care, treatment alternatives, and shared decision-making. In the future, risk stratification with next-generation imaging and the integration of genomic results may help determine exactly which patients with metastatic prostate cancer will benefit most from local therapy. . Now, for the first time in urologic cancer care, we are presented with a novel tumor-directed therapy based on enhanced imaging.

Conclusion

The oligometastatic prostate cancer is being increasingly viewed as a unique entity separate from widely spread metastatic disease. A growing body of evidence now supports a role for local ablative therapy to the primary tumor and metastatic sites to improve disease control and delay the progression of the disease to CRPC. Although our short term initial results are very much impressive, but overall result of this small cohort of prospective trial can not be concluded now. Long term follow-up and more case inclusion will may indicate the effect of the MMD in OMPC.

Key Points: Oligometastatic prostate cancer (OMPC), Cyto reductive Prostatectomy (CP), Androgen Deprivation Therapy (ADT) and Abirateron Acetate (AA) and Stereotactic Radiation Therapy (SBRT),

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