Review Article

Oligometastatic carcinoma prostate – An overview of the last decade

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ABSTRACT

Introduction: Oligometastatic prostate cancer (OMPC) has gained profound interest lately due to its different tumor biology and our ability to use multimodality therapy for cure or prolonged survival. Selecting the appropriate patient for treatment has become the aim of treating urologists, medical oncologists, and radiation oncologists. Through this review, we try to highlight the management of OMPC in light of recent literature.

Methods: Literature search was performed on Pubmed, Scopus and Embase using keywords "Oligometastatic", " Prostate Cancer" using operators such as "And" & "Or". Relevant articles were screened and all the latest articles on this emerging entity were included in this review.

Results: All trials relevant to oligometastatic prostate cancer defining the role of surgery, radiotherapy and systemic therapy were included and appropriate inferences were drawn. Relevant studies were compiled in tabular form for this article.

Conclusion: The current standard of care of management for OMPC remains systemic therapy on the lines of hormone-sensitive metastatic prostate cancer. The evolving role of surgery, and radiotherapy along with systemic therapy is highlighted in this article.

INTRODUCTION

In the last decade, oligometastatic prostate cancer (OMPC) has gained interest owing to the introduction of newer imaging modalities and literature supporting the role of multimodality approach. Citing these reasons, the possibility of a complete cure for this disease has led to debates regarding the appropriate selection of treatment options.[1] Despite having a variety of treatment options at our disposal, the difficulty lies in choosing the right patients to prevent overtreatment. The current guidelines recommend the treatment of oligometastatic disease in a trial setting. We undertook this review to identify the best evidence available for the classification of disease state, patient selection, and management options.

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DEFINITION, SPECTRUM, AND CLASSIFICATION OF OLIGOMETASTATIC PROSTATE CANCER

There is no single definition of OMPC. Most studies have kept 3–5 metastatic sites on conventional imaging as the cutoff limit.[2] In the spectrum of prostate cancer (PCa), OMPC encompasses three different disease scales: *De novo* OMPC (oligometastatic at presentation), oligorecurrent (after local treatment), and oligoprogression (after systemic treatment for metastatic disease). Each of these states may

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have a different biological potential and clinical behavior. According to the randomized androgen deprivation and radiotherapy trial, based on the biological behavior of OMPC, it can be defined as indolent and a state of low-metastatic potential.[3] This study concluded that cancer-specific mortality (CSM) was significantly higher in patients with >4 metastases than those with OMPC disease (P = 0.004).[3] To capture the spectrum of OMPC and to standardize the terminologies used, the European Organization for Research and Treatment of Cancer and the European Society of Radiation Therapy and Oncology have proposed a classification system.[4] This classification [Table 1.][4,5] identifies nine states of OMPC based on five questions:[5]

1. Is the patient having any history of polymetastatic disease?
2. Is the patient having any history of oligometastatic disease?
3. Time of diagnosis of OMPC from diagnosis of primary disease?
4. Whether systemic treatment is ongoing when the diagnosis of OMPC is made?
5. And whether the oligometastases are progressing on present imaging.

RATIONALE FOR THE MANAGEMENT OF THE PRIMARY AND METASTATIC SITES IN OLIGOMETASTATIC PROSTATE CANCER

As per the hypothesis, treating the primary as well as metastatic sites in OMPC leads to cytoreduction and a reduction of circulation of conventional tumor cells and disseminated tumor cells. This decreases the interactions between the primary tumor and the metastases mediated by cytokines, chemokines, and microRNAs.[6] The decrease in interaction may reduce the seeding of newer sites for metastases; reduce the progression of metastases and the reseeding of the primary site by tumor cells. Metastases-directed therapy (MDT) may produce an abscopal effect by immunomodulation whereby a systemic anti-tumor response is initiated to act on other distant tumor sites, Also, the treatment of the primary may prevent intratumoral adaptation and castration resistance.[7]

Table 1: Classification of the disease states of oligometastatic prostate cancer[4,5]

Types of OMPC	Sub-types
Genuine OMPC	
a. *de novo* OMPC	1. Synchronous (<6 months from diagnosis of primary lesion)
	2. Metachronous (>6 months from diagnosis of primary lesion)
	- Metachronous oligorecurrence
	- Metachronous oligoprogression
b. Repeat OMPC	1. Repeat oligorecurrence
	2. Repeat oligopersistence
	3. Repeat oligoprogression
Induced OMPC	1. Induced oligorecurrence
	2. Induced oligopersistence
	3. Induced oligoprogression

OMPC: Oligometastatic prostate cancer

APPROACH TO TREATMENT OF OLIGOMETASTATIC PROSTATE CANCER

The treatment of OMPC involves a three-tiered approach; systemic chemo-hormonal therapy, local consolidative therapy of the primary tumor (radiation therapy [RT] or radical prostatectomy [RP]), and metastases-directed therapy (MDT).

RADICAL PROSTATECTOMY IN OLIGOMETASTATIC PROSTATE CANCER SETTING

Surgical debulking as a part of the treatment approach in OMPC has been debatable. The role of surgical debulking in patients with OMPC has been criticized, owing to the complications associated with the procedure versus the marginal therapeutic role. The currently available literature is of low quality. The evidence includes retrospective studies, and subgroup analysis of clinical trials, with the risk of biases and confounders. Various theories have been proposed supporting the role of RP in OMPC patients as a part of a multimodality approach providing better therapeutic and oncological outcomes. As demonstrated by Tzelepi *et al*., even after 12 months of systemic treatment, clones of cells with potential for metastases are still present in the primary lesion.[8] Further, Rycaj and Tang reported that there is an alteration of the cellular signaling pathway which causes an increase in cell proliferation, dissemination, and angiogenesis. This is augmented by the molecular signals from the primary tumor site.[9]

The results of several studies reporting on the feasibility of RP in the setting of OMPC are described in Table 2.[10-20] At present, RP for metastatic disease is not standard of care (SOC) and should be attempted only in a clinical trial setting. Recent results from the prospective studies such as TRoMbone[13] trial have sought to research OMPC while SWOG S1802,[14] g-RAMMP[14] results are awaited which will further evaluate the role of surgery in OMPC.

TROMBONE TRIAL

This multi-institutional prospective randomized trial was conducted by Sooriakumaran *et al*[13] to assess whether RP with pelvic lymphadenectomy in addition to SOC (androgen deprivation therapy [ADT] ± docetaxel) is feasible in men with newly diagnosed synchronous OMPC. Fifty patients with <3 bone metastases were randomized and included in the study. The primary and secondary endpoints were the feasibility of randomization within 1 year and quality of life (QoL) respectively. The results showed that RP is feasible and safe to be further investigated in this

Table 2: Studies assessing feasibility and impact on oncological outcomes of radical prostatectomy in oligometastatic prostate cancer patients

Study	Objectives	Study design	Results
Culp *et al*., 2014[10]	To compare 5 year-OS and CSM rate in patients who underwent RP as local treatment versus no local treatment	Retrospective SEER-based study	5 years OS RP: 76.5% No LT: 30.6% CSM rate was decreased in patients treated with RP
Heidenreich *et al*., 2015[11]	To investigate the feasibility of RP in patients with OMPC	Single center Case–controlled study	RP group had better CSS (96% vs. 84%, *P*=0.043) and better OS (91% vs. 79%, 0=0.048 cPFS was also better (38.6 vs. 26.5 months, (*P*=0.032)
Sooriakumaran *et al*., 2016[12]	To study the safety of RP in patients with OMPC	Multi-institutional analysis	Overall complication rate was 20.8% 90 days continence rate was 64.4% CSS was 89% at 23 months follow-up
Gandaglia *et al*., 2017[15]	To assess the safety of RP in patients with OMPC	Single-center study	20% complications (CD Grade III or above) Increased intraoperative blood loss Increased need for BT Prolonged hospital stay
Parikh *et al*., 2017[16]	To evaluate the effects of local therapy (RP, RT) among patients with metastatic PCa	Retrospective NCDB based study	OS (5 years) 45.7% versus 17.1% Higher OS
Löppenberg *et al*., 2017[17]	To assess overall mortality in metastatic PCa patients receiving local versus no local treatment	Retrospective NCDB-based study	OM free survival rates (3 years): 63% versus 48%; *P*<0.001 No additional survival benefit observed amongst patients with >70% predicted mortality risk
Steuber *et al*., 2017[18]	To compare RP versus patients receiving standard systemic therapy in terms of local complications and castration resistant free survival	Single-center prospective	OS (*P*=0.25) and castration resistant-free survival (*P*=0.92) showed no significant difference RP group had lesser locoregional complications (*P*<0.01)
Preisser *et al*., 2019[19]	To compare open versus laparoscopic robotically assisted RP in OMPC patients	Retrospective analyses of NIS database	Overall complications (10.0% vs. 21.4%, *P*=0.001) including need for BT (2.6% vs. 11.2%, *P*=0.001), medical (4.1% vs. 8.3%, *P*=0.01) and surgical complications (2.2% vs. 4.9%, *P*=0.046) were higher in open group
Chaloupka *et al*., 2021[20]	To evaluate the effect of RP on postoperative HRQOL	Retrospective comparative study	No significant difference noted in terms of HRQOL between OMPC and localized disease patients after RP

HRQOL: Health-related quality of life, RP: Radical prostatectomy, OMPC: Oligometastatic prostate cancer, RT: ion therapy, CSM: Cancer-specific mortality, OS: Overall survival, PCa: Prostate cancer, cPFS: Conventional criteria, CSS: Cancer- specific survival, LT: Local treatment

cohort of patients. In terms of urinary continence, 16.7% were still incontinent after 6 months but these rates were comparable to those of standard surgery. Furthermore, the QoL in the intervention group was comparable to the control group. Progression-free survival (PSA <1 ng/mL at 6 months after surgery, Gleason 8–10, pT3, and positive margin rate were seen in 82.6%, 82.6%, 87.5%, and 41.7%, respectively. Despite promising results, a randomized controlled trial (RCT) with a larger cohort is needed to assess the treatment effectiveness in the OMPC setting as a part of a multimodality approach.

RADIATION THERAPY IN OLIGOMETASTATIC PROSTATE CANCER SETTING

Culp *et al*. looked at a SEER database retrospectively to study the role of local therapy (RP/RT) in patients with OMPC. The results showed better OS and CSM rates in comparison to patients not receiving local therapy.[10] There is evidence to support the role of RT as a part of multimodality treatment but the concept behind its application is still a matter of debate. It is unclear whether the role of RT in this setting is as a part of a multimodality curative approach or only to delay the start of ADT.[1] There are two prospective RCTs and a meta-analysis highlighting results for RT to the primary tumor in a metastatic setting.

STOPCAP meta-analysis

This meta-analysis used prospective framework for adaptive meta-analysis to include three studies – PEACE 1 (ongoing), HORRAD, and STAMPEDE-H. In unselected patients, prostatic radiotherapy did not show any benefit in overall survival (hazard ratio [HR] 0.92%–95% confidence interval [CI] 0.81–1.04; *P* = 0.195). However, in the subgroup of men with fewer than five bone metastases, the 3-year survival showed a 7% improvement, supporting a role of local therapy in oligometastatic disease.[21]

HORRAD trial

This was a multi-center RCT that included 432 patients (1:1) with PSA >20 ng/dL and metastases on bone scan. The intervention was RT with ADT (70 Gy in 35 fractions or 57.5 Gy in 19 fractions) to the prostate: pelvic lymph nodes were not included. The control group received only ADT. There was no survival benefit in the RT group (45 months - 95% CI 40–49.9 vs. 43 months - 95% CI 32.6–53.4; HR 111.95% CI 0.87–1 43:0 = 0.4). There were important limitations in the study as the assessment of metastases was by bone scan alone, and visceral metastases were not assessed. The pool of patients probably had a much higher burden of disease and the RT given was much lower (70 Gy to prostate not including the LN). However, the 2-year survival began to separate for the subset of patients

with PSA <142 ng/dL, <5 bone metastases, and Gleason score <8.[22]

STAMPEDE trial H-arm

This multicenter RCT conducted in 117 hospitals in the UK and Switzerland included 2016 patients with newly detected metastases (1:1 randomization). The intervention group received EBRT to the prostate (36 Gy as 6 weekly cycles or 55 Gy as 20 daily fractions over 4 weeks. The control group received ADT (early docetaxel chemotherapy was permitted after 2015-18% received chemotherapy). Median PSA was 97 ng/dL, and 40% had low-volume metastatic disease as per CHAARTED criteria. There was no overall survival advantage in the RT group. RT was well tolerated, and 5% developed RTOG grade 3-4 adverse events after RT. A prespecified analysis of the low-volume metastatic patients showed a better 3-year survival (73% for control vs. 81% for the RT group).[23]

METASTASIS-DIRECTED TREATMENT

Treatment of M1 lesions can hypothetically decrease the further occurrence of distant metastatic lesions. This in turn can improve survival and therapeutic oncological outcomes. However, available data is still in the nascent stages, especially as regards surgery which includes salvage lymph node dissection (sLND) limited to the retroperitoneal nodes.

SALVAGE LYMPH NODE DISSECTION

Several studies have reported satisfactory outcomes in terms of recurrence-free survival (RFS) after sLND (±ADT). Fossati *et al*. proposed risk stratification model to identify patients who may be benefited after sLND. The model included variables such as the number of nodal metastases, site involved, Gleason Grade, time to biochemical recurrence, and PSA levels at the time of sLND.[24] In the last decade, only one retrospective study reported RFS of 38% after 8 years follow-up amongst patients undergoing sLND.[25] Data are limited to say whether sLND is effective for managing OPMC. Prospective randomized trials are needed to validate its role in this setting.

STEREOTACTIC BODY RADIATION THERAPY

The applications of stereotactic body radiation therapy (SBRT) have been well-documented for bone, nodal as well as visceral metastases. Several prospective RCTs and one meta-analysis have reported on the role of SBRT as a part of MDT in the OMPC setting.[26-31] The summary of various reported and ongoing trials is shown in Table 3.

Stereotactic ablative radiotherapy for the comprehensive treatment of oligometastases trial

This prospective RCT included patients with <5 metastases and randomized them to receive systemic therapy alone or in addition to SBRT. The phase II results showed better OS and PFS rates in patients of the SBRT arm.

STOMP trial

This multicentric, phase II study randomized patients having recurrent hormone-sensitive OMPC in a 1:1 ratio between surveillance and MDT (SBRT/surgery) of all lesions identified on choline PET/CT. On median follow-up of 36 months, patients who received MDT showed better ADT-free survival (21 vs. 13 months).[26] On 5-year follow-up, the ADT-free survival was 34% and 8% for MDT and surveillance groups, respectively.[32]

ORIOLE trial

This prospective Phase II RCT included 54 patients with recurrent oligometastatic hormone-sensitive prostate cancer based on conventional imaging. They were randomized then to receive SBRT versus observation. At 6 months follow-up, PFS was better in the intervention arm as progression was seen in only 19% of patients as compared to 61% in the control group.

Viani *et al*. conducted a meta-analysis comprising more than 20 observational studies reporting on the role of SBRT in recurrent metastatic setting. The authors concluded that SBRT was safe and a feasible option in this cohort of patients with minimal acute toxicity (<1.5%) with rates of PFS, local control, and ADT-free survival were 0.413, 0.976, and 20.1 months, respectively.[31] Awaited phase III results may provide robust data on whether MDT actually has any significant impact on OS.

SYSTEMIC THERAPY

Systemic therapy in form of ADT with chemotherapy (docetaxel)[33-35] or ADT + Abiraterone[36,37] or ADT + Enzalutamide[38,39]/Apalutamide[40] remains the SOC for OMPC. The choice of systemic therapy depends on patient characteristics, age and comorbidities, disease characteristics (pattern of metastases), and patient choice. It should be noted that the primary subject of interest in majority of the trials was not OMPC. Furthermore, as OMPC population was not the primary target of these studies, the subanalysis performed in this context had methodological drawbacks.[1]

NEWER APPROACHES

Theranostics refers to the use of radionuclide agents for the purpose of diagnosis as well as therapeutics. This helps in the selection of patients in whom this radionuclide agent can be used for treatment as well as monitoring response to treatment. Among various radionuclides available, the most used is Lutetium-177 (177 Lu). Other agents are Actinium-225 and Iodine-131. In a pilot study including 10 patients with <10 metastases with no surgery or RT and with significant PSMA uptake, metastases were targeted

Table 3: Summary of trials reporting on metastases-directed therapy in oligometastatic prostate cancer setting

Study	Objective	Study design	Results
Ost *et al*.[26] (STOMP)	Surveillance versus MDT (SBRT/surgery) for oligorecurrent patients identified on choline PET-CT (≤3 metastases)	Prospective, RCT	ADT-free survival (5 years): 8% versus 34% for the surveillance and MDT group respectively
Palma *et al*.[27] (SABR-COMET)	SOC alone versus SOC + SBRT in OMPC patients (≤5 metastases)	Prospective, RCT	PFS and OS improved overall in SBRT+SOC arm
Phillips *et al*.[28] (ORIOLE)	Observation versus SBRT in oligorecurrent setting identified on conventional imaging (≤3 metastases)	Prospective, RCT	Follow-up (6 months): Progression in 19% versus 61% in SBRT and observation group respectively SBRT group showed improved median PFS (not reached vs. 5.8 months)
Siva *et al*.[29] (Popstar)	To assess feasibility of SBRT in castrate sensitive and castrate resistant oligorecurrent OMPC	Prospective, RCT	Treatment completion: 97% distant PFS at 1 year: 58% Distant PFS at 2 years: 39% Local PFS at 1 year: 97% Local PFS at 2 years: 93%
Preisser *et al*.[30] (STAMPEDE arm-M)	To assess if addition of SBRT to M1 sites improves survival after RT/surgery	Prospective, RCT	Awaited
Peace V-Storm trial[44]	Combined whole pelvic radiotherapy and MDT versus MDT alone	Prospective RCT	Awaited
Postcard trial[45]	Durvalumab plus SBRT versus SBRT alone	Prospective, RCT	Awaited
DART trial[46]	Darolutamide plus SBRT versus SBRT alone	Prospective, RCT	Awaited

SOC: Standard of care, RT: Radiation therapy, SBRT: Stereotactic body RT, RCT: Randomized controlled trial, ADT: Androgen deprivation therapy, PFS: Progression-free survival, OS: Overall survival, OMPC: Oligometastatic prostate cancer, PET-CT: Positron emission tomography-computed tomography

with 177-Lu-PSMA-617. The results showed a decline in tumor volume and PSA velocity stabilized after 2 cycles of 177 Lu therapy. Complete biochemical response was observed in one patient after 24 weeks while decline in S. PSA was noted in three patients.[41] Various trials are ongoing to study the efficacy and effectiveness of theranostic approach as a part of combination with SOC. Currently, theranostics is considered only in the clinical trial setting.

It has already been established that germline mutations in DNA repair genes are present in 8%–12% of patients with M1 PCa and this prevalence is significantly greater than compared to localized cases (5%). Up to 23% of patients with M1 disease have been shown to have somatic lineage mutations. At present, FDA has approved the use of olaparib, niraparib, rucaparib, and pembrolizumab for these patients. The first three drugs target the mutations in DNA repair genes while the latter is approved for tumors with MSI-H in M1 patients.[42,43]

Limitations of the current literature

The current literature available on OMPC has lacunae in certain areas such as detailed biological and genetic classification, risk stratification and patient selection. The appropriateness of MDT within the context of tumor-related molecular factors and clinical variables like comorbidities are not clearly addressed. Further genetic and biological classification will not only help in achieving an accurate definition for this subset of patients but also help identify the molecular features which predict response. Future trials can focus on surveillance strategies, optimization of RT and systemic protocols, and include biomarkers and liquid biopsy for better risk stratification.

CONCLUSIONS

The SOC of management for OMPC is still systemic therapy either in the form of chemotherapy or androgen receptor-targeted agents along with ADT. There is exciting ongoing research in this field which shall clarify the role of multimodality approach in improving survival and QoL in patients with OMPC. Although the role of local treatment (surgery/RT) and MDT appears to be promising, data are needed to validate their role.

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