

Radiotherapy in the setting of Oligometastatic Prostate Carcinoma

DR NIRASHA CHIRANJAN



"I have lived through the effects of cancer on close family and friends. This first-hand experience inspired me to pursue my studies in Oncology.

Having walked this road, I am determined to give my patients the care they need, and so rightfully deserve. I remain steadfast in my dedication to my patients, their families and have long ago resolved to make this walk with them - my life's work." – Dr Nirasha Chiranjani.

Dr Chiranjani completed her MBChB at the University of Cape Town in 2006. Following two years of internship at McCord's Hospital in Durban, Dr Chiranjani completed a year of community service at Evander Hospital in Mpumalanga. In 2010, she joined the Radiation Oncology Department at the Charlotte Maxeke Johannesburg Academic Hospital.

Dr Chiranjani was successfully admitted as a Fellow of the College of Radiation Oncologists in early 2014 and joined DMO in August of the same year, where she is now a senior partner.

She consults at the Ahmed Kathrada Cancer Institute, Sandton Oncology and the West Rand Oncology Centre and is part of a team of eight Oncologists that consult at the DMO locations. Being available to the patient is of importance to us. Our Oncologists are available daily to our patients, throughout their treatment programme, and beyond for follow up care and are rostered on call, 24 / 7 - all year.

Dr Chiranjani treats a broad range of malignancies, with special interest in prostate, breast, gynaecological, head and neck, and central nervous system areas. She is an active participant in several multi-disciplinary forums related to cancer treatment and also has a keen interest in screening processes.

Prostate cancer is among the most common cancers in males worldwide. The spectrum of prostate cancers range from localised low and high risk tumours to metastatic hormone sensitive and hormone resistant disease. Radiation therapy is an important treatment modality in the management of prostate carcinoma and its role has evolved in the setting of oligometastatic disease.

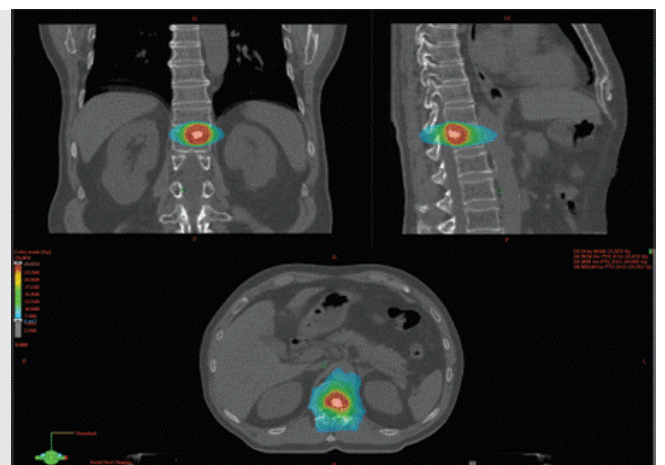
Oligometastatic prostate cancer (OMPC) can be defined as cancer with a limited number of metastases, typically fewer than 5 lesions. These patients have a better prognosis than patients with extensive metastatic disease.⁴

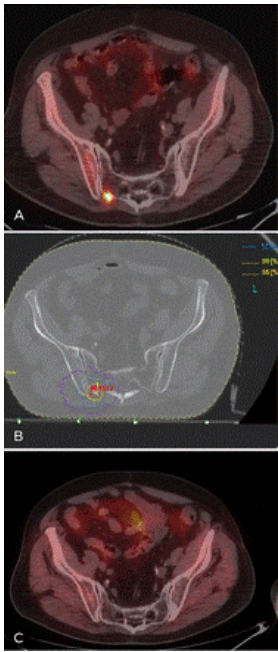
The concept of oligometastatic disease was first proposed by Sam Hellman and Ralph Weichselbaum at the American Society of Clinical Oncology (ASCO) over 20 years ago. It is derived from the Greek word "oligo" meaning "few." The concept involves controlling a primary tumor completely or controlling a single or limited number of metastatic lesions with local therapy, which can result in a cure. Oligometastatic disease is an intermediate biological state with a unique clinical picture within the spectrum of advanced disease, which has a favourable phenotype that is ideal for an intensive approach.³

The relatively slow proliferation rate of prostate cancer is reflected in a low α/β ratio between 1 and 4. Because the α/β ratio for prostate cancer is similar to or lower than the surrounding tissues responsible for most of the toxicity reported with radiation, radiation treatment fields and schedules using extremely hypofractionated regimens and stereotactic radiotherapy result in good cancer control rates without increased risk of late toxicity.^[1]

Stereotactic body radiotherapy (SBRT) is a form of real or near-real-time image guidance radiation therapy that uses high doses of radiation delivered in a precise and targeted method to the tumour, in a very limited number of fractions with low toxicity and excellent tolerance.

Example of a stereotactic body radiation therapy (SBRT) planning on a metastatic bone lesion





PET CT imaging shows right sacroiliac bone metastasis corresponding to the small focus of increased radiotracer uptake. (B) Metastasis-directed stereotactic body radiotherapy was administered at 40 Gy in 5 fractions; isodoses of 95%, 90%, 50%, and 30% (yellow, green, light blue, and violet lines, respectively) indicate the small irradiated volume (isodose of 95%) and the rapid fall of dose outside the target (isodose of 30%). (C) PET CT imaging showing no radiotracer uptake to the right sacroiliac bone metastasis after irradiation

De novo (synchronous) oligometastatic disease represents patients found to have metastatic disease at the time of initial diagnosis. **Oligorecurrent** (metachronous) disease are patients initially treated with definitive therapy to cure their malignancy who subsequently develop limited metastatic disease recurrence. The use of close PSA monitoring after primary treatment together with active incorporation of more sensitive and specific molecular imaging modalities such as PSMA-PET for local and systemic staging, has emerged as a crucial approach for early detection of oligorecurrence.

Finally, **oligoprogressive** disease represents patients with known metastatic disease who exhibit few isolated areas of progression in a background of otherwise stable disease. This oligometastatic state may be an apparent turning point between still-controllable regional disease that might be managed with local intervention, and diffuse disease for which systemic therapies are the mainstay. Oligorecurrent prostate cancer is now the preferred term for designating such relapses after primary curative-intent treatments.²

Metastasis-directed therapy for oligometastatic disease

Although promising, additional data from prospective studies are required to determine the role of metastasis-directed therapy (MDT) for males with oligometastatic disease, especially how it should be integrated with androgen deprivation therapy (ADT) and novel agents like androgen receptor pathway inhibitors.

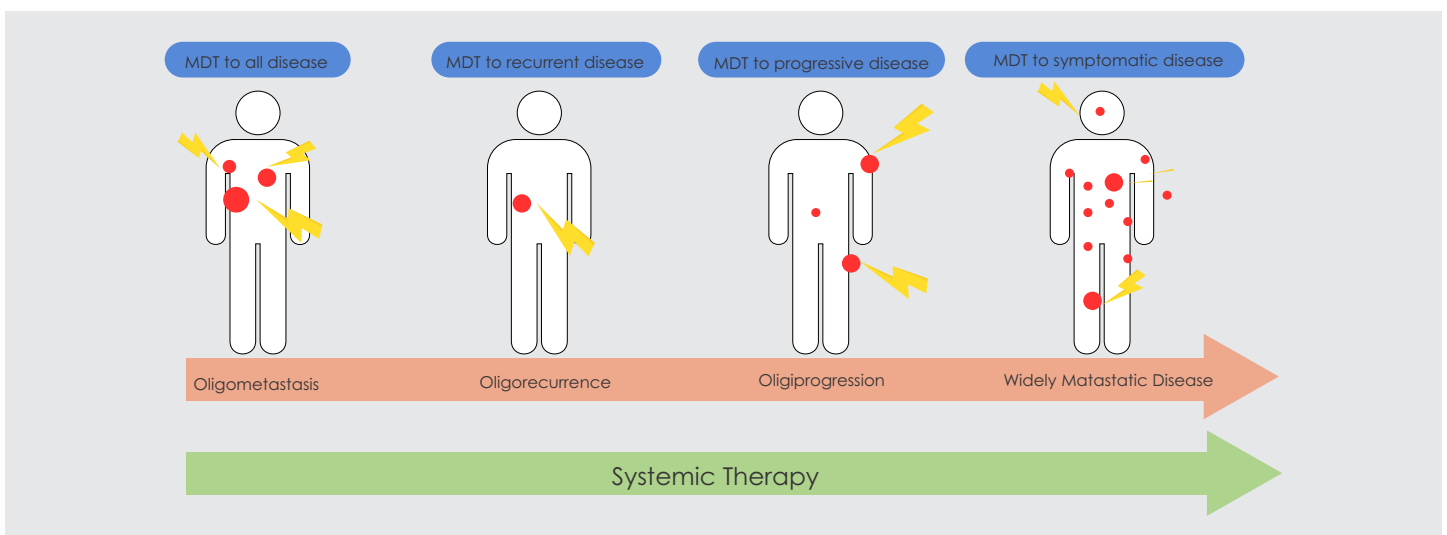
Decisions regarding treatment must be individualized, taking into account a wide range of factors (eg, site of metastasis, disease-free interval, patient age, PSA kinetics, patient comorbidities etc).

After prior definitive therapy, patients will occasionally present with metachronous oligometastatic disease, which most of the time is diagnosed using positron emission tomography (PET CT) with more sensitive prostate-specific radiotracers.

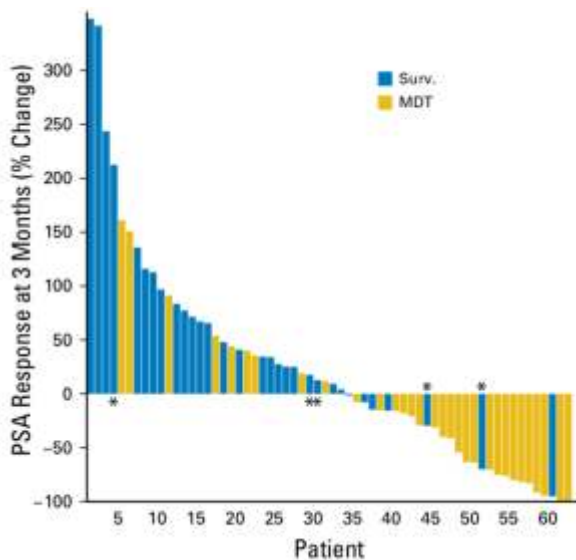
The following data are available regarding the benefit of metastasis-directed therapy for males with oligometastatic prostate cancer:

- In an early phase II trial (**STOMP**), 62 asymptomatic patients with a biochemical recurrence after primary definitive treatment, one to three metastases on conventional (not PET-based) imaging, and a serum testosterone >50 ng/mL were randomly assigned to observation alone or to metastasis-directed therapy.

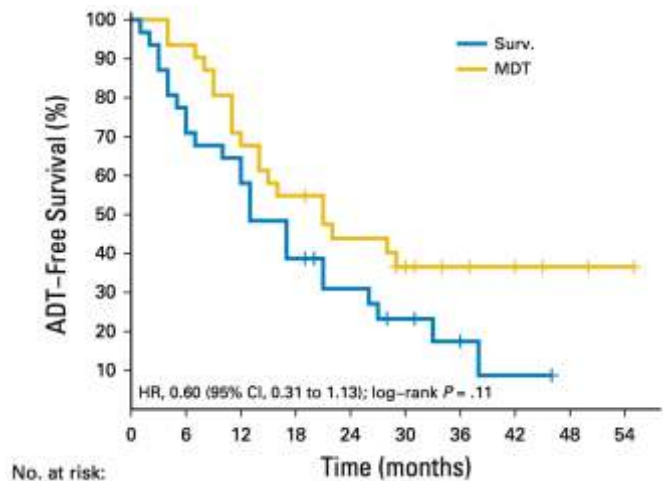
In the latest analysis, presented at the 2020 American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium, the time to initiation of ADT based on progression of symptoms, progression to more than three metastases, or progression of known lesions was significantly longer in patients who received initial metastasis-directed therapy (five-year ADT-free survival 34 versus 8 percent, HR 0.57, 95% CI 0.38-0.84), although five-year overall survival was similarly high in both groups (85 percent)⁸



ADT-free survival



Surveillance: 35% of pts have a PSA decline
MDT: 75% of pts have a PSA decline



ITT: median ADT-free survival 13 months vs 21 months
HR: 0.60 [95% CI: 0.31 – 1.13], log-rank p=0.11

Ost et al. JCO 2018

- Additional information is available from two uncontrolled phase II trials, both of which used prostate-specific PET scanning:
- In one trial 72 patients with a rising PSA after definitive local therapy and negative conventional imaging, who all then underwent prostate-specific membrane antigen (PSMA)-PET/CT to detect and localize oligometastatic disease. Overall, 38 were found to have a PSMA-detected oligometastatic recurrence that was thought amenable to metastasis-directed therapy, 92 percent of which were nodal only, the remainder skeletal.

At a median follow-up of 15.9 months, 22 percent of the 37 patients who were treated with SBRT (n = 27) or surgery (n = 10) normalized their PSA. Median time to PSA progression (freedom from ADT) was 17.7 months.

- The OLIGOPELVIS GETUG P076 trial studied high-dose salvage radiotherapy plus short-term androgen deprivation therapy in 67 patients with isolated oligometastatic pelvic node relapse detected by PET CT after treatment for localized disease.

35 had previously received prostate radiotherapy. After a median follow-up of 49 months, median biochemical relapse-free survival was 25.9 months, 58 percent remained progression free at three years.⁹⁻¹⁰

The benefits of stereotactic body RT (SBRT) for treatment of oligometastatic disease can be illustrated by the following reports:

- The phase II Observation versus Stereotactic Ablative Radiation for Oligometastatic Prostate

Cancer trial (The **ORIOLE** Phase 2 Randomized Clinical Trial) randomly assigned 54 males with recurrent, hormone-sensitive, oligometastatic prostate cancer (three or fewer lesions as determined by conventional imaging) to observation and no further treatment for six months or to SBRT to the metastatic sites outside of the prostate that were detected by conventional imaging.

Six months after randomization, progression (defined as a PSA increase, radiographic progression on conventional imaging, or symptomatic decline) was observed in 19 percent of those undergoing SBRT versus 61 percent of the control group.

The patients randomized to SBRT all underwent PET CT using highly sensitive, prostate cancer-specific PSMA-based radionuclides at baseline and at six months.

- In another randomized phase II study (SABR-COMET) of 99 patients with cancer of a variety of primary tumors (16 with prostate cancer) and up to five metastatic lesions to any site (65 had bone metastases), when compared with palliative care alone (which included standard-fractionation RT with or without systemic chemotherapy), the use of SBRT for treatment of oligometastatic disease was associated with a significant improvement in five-year overall survival (42 versus 18 percent, p = 0.006)
- A meta-analysis of 23 observational studies of SBRT for oligometastatic prostate cancer recurrence concluded that local control was excellent, with minimal severe or late toxicity, and among the five studies reporting this outcome, the average duration of ADT-free survival was approximately 20 months.⁵⁻⁶

Study	N	Nodal Recurrence	Number of mets	Treatment arms	Type of treatment	Type of imaging	Media follow-up	Results
STOMP	62	55%	<3 extra-cranial	Observation vs. metastases-directed therapies	SBRT (n=25) sLND (n=6)	Choline PET/CT	5.3 years	Improved ADT-free survival (HR: 0.53; p,0.05)
ORIOLE	54	61%	≤3	Observation vs. metastases-directed therapies	SBRT	Conventional imaging (for study inclusion) = PSMA PET/CT	18.8 months	SBRT improved progression-free survival
SABE-COMET	16	4	1-5	SOC vs. SOC+ SABR	SBRT	Conventional imaging + PET	51 months	SBRT improved overall survival

Genetic and genomic classification, DNA biomarkers and circulating tumor DNA may add to the management pathway of oligometastatic prostate carcinoma.

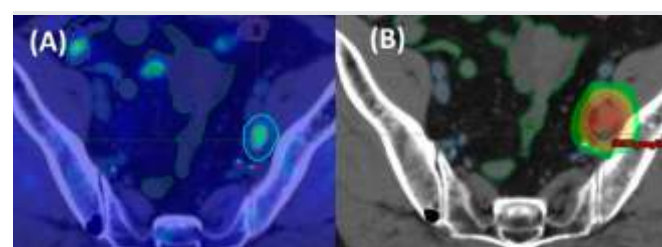
A sub-analysis was conducted on pooled data from STOMP and ORIOLE trials to assess the effectiveness of a high-risk mutational signature in stratifying outcomes after MDT, which was defined as the presence of pathogenic somatic mutations within ATM, BRCA1/2, Rb1, and TP53.

Long-term results showed that metastasis directed therapy (MDT) benefitted both patients with and without a high-risk mutation, although those individuals without a high-risk mutation treated with MDT had superior outcomes (median PFS 13.4 months versus 7.5 months).¹¹

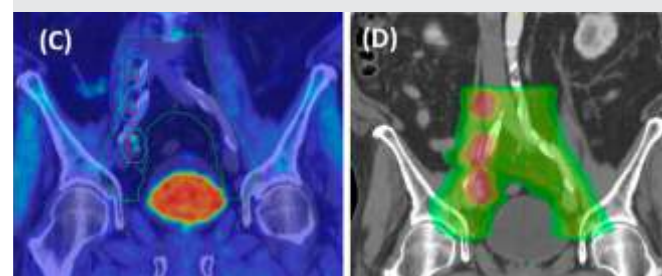
These findings suggest that selected patients with oligometastatic or oligorecurrent disease lacking a high-risk mutation could potentially de-escalate treatment using MDT alone. Conversely, patients with high-risk mutations should be contemplated for an intensified targeted approach.

Currently, several phase II and phase III studies recruit patients with recurrent OMPC to assess combinations of MDT and systemic therapy options, such as ADT plus abiraterone + apalutamide.¹² POSTCARD will determine the effect of durvalumab in addition to MDT¹³ and Stereotactic Body Radiotherapy with or without darolutamide for OligoRecurrent Prostate Cancer (DART), which will study the combination of darolutamide with SBRT.¹⁴ A phase III trial will test the role of apalutamide alone or in combination with MDT in patients with recurrent hormone sensitive prostate cancer.¹⁵

Common SBRT recommended fractionations used are 35 Gy in 5 fractions for spinal lesions and 30 Gy in 3 fractions for extra spinal bone metastases. For the treatment of nodal disease, elective nodal irradiation (45 Gy in 25 fractions) with a boost to suspicious lymph nodes (2.2-2.7Gy per fraction) or SBRT doses of 35 Gy in 5 fractions are recommended.¹⁶⁻¹⁷



Example of (A) a patient with solitary oligorecurrent pelvic nodal relapse detected via PSMA-PET and (B) the corresponding imaging matched SBRT plan capture (30 Gy in 3 fractions)



C) a patient with multiple (3) oligorecurrent pelvic and low paraaortic nodal disease in PSMA-PET and (D) the matched radiotherapy to the extended field pelvic nodes (45 Gy in 25 fractions) with a simultaneous integrated boost to 65 Gy

In conclusion, oligometastatic prostate cancer should be viewed as an opportunity to alter the disease trajectory of prostate carcinoma. These patients should be managed jointly in a multidisciplinary team setting for best outcomes. Radiotherapy has a proven role to offer cure and delay disease progression.

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