The Role of Local Therapy for Oligometastatic Prostate Cancer

Should We Expect a Cure?

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KEYWORDS

• Prostate cancer • Oligometastatic disease • Radical prostatectomy • Radical radiotherapy
• PSMA-PET

KEY POINTS

- There are data to suggest that an oligometastatic state may confer a better outcome than higher-volume metastases.
- Such patients may be considered for aggressive approaches, including radical treatment of the primary cancer.
- The definition of oligometastatic state remains contentious, and superior imaging is challenging the traditional paradigm based on conventional imaging.
- Nonrandomized data suggest a survival benefit for patients who undergo treatment of the primary despite metastatic disease at diagnosis.
- Prospective trials are underway to assess this hypothesis, otherwise treatment of the primary in men with oligometastatic disease should be considered experimental.

INTRODUCTION

The so-called oligometastatic state is defined as limited metastatic burden amenable to aggressive local therapy in an attempt to achieve long-term survival. First described by Hellman and Weichselbaum in 1995,[1] these investigators postulated a theory that tumors, when in a state of oligometastasis, are at a transition point between localized disease and widespread metastases.[2,3] However, it remains contentious whether a truly oligometastatic state can be reliably identified, and therefore whether aggressive approaches directed toward such patients are warranted or reasonable.

Disclosures: None.
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Urol Clin N Am 44 (2017) 623–633
http://dx.doi.org/10.1016/j.ucl.2017.07.013

It is not known whether metastatic lesions in the oligometastatic state directly disseminate to other, distant sites of disease in the metastatic state, or whether the oligometastases facilitate disease progression by the primary tumor through the release of circulating growth factors.[4,5] Nevertheless, the treatment of the primary cancer in the oligometastatic state does seem to delay or interrupt the development of further metastatic disease in some, but not all, situations. This phenomenon has been observed in several cancer types, including renal cell carcinoma and colorectal, ovarian, and breast cancer.[6–8] In prostate cancer specifically, it is accepted that widespread metastatic disease accounts for more than 90% of prostate cancer–specific mortality,[9] and accordingly there is a conceptual argument that, by delaying this end stage of disease, perhaps at a point when the metastatic burden is low, clinicians can improve survival for men with prostate cancer. It was shown several years ago that there was a significant difference in overall survival in patients with prostate cancer who had fewer than 5 metastases at the time of diagnosis,[10] although the stratification of the number of metastases that should be considered oligo remains contentious.

The current standard of treatment of men with localized prostate cancer, with an otherwise expected longevity of more than 10 years, is curative therapy, achieved through radical prostatectomy or radiotherapy.[11] In contrast, when evidence of metastatic disease is present, albeit minimal metastatic disease (pelvic lymph node disease), the traditional treatment paradigm says that cure is no longer possible. Consequently, these patients have been commenced on systemic androgen deprivation therapy (ADT).[11–13] However, as alluded to earlier, there is emerging evidence that treatment of the primary tumor, and even metastatic deposits, in the context of metastatic and lymph node–positive prostate cancer may confer a survival benefit.[14–17]

However, not all men with metastatic prostate cancer benefit from potentially toxic local therapy, and as such the ability to accurately distinguish patients in the oligometastatic state, who may respond more favorably, is crucial before embarking on aggressive treatment.[18] With greater understanding of prostate cancer genomics, advances in imaging techniques, such as [11C] choline or prostate-specific membrane antigen (PSMA) PET, used in the diagnostic and surveillance setting,[19,20] and an increase in the number of clinical trials recruiting patients with prostate cancer, the detection of oligometastatic disease has increased. With this increase in detection has come an enthusiasm for treatment.

The foundation for successful treatment probably requires more than aggressive local control alone. It is likely that a multimodal approach to therapy is required, encompassing local consolidative therapy to the prostate, metastasis-directed therapy (including surgery or radiation), and systemic chemohormonal therapy.[21]

Current literature regarding both the diagnosis and treatment of oligometastatic disease remains limited. The definition of oligometastatic disease varies between studies and thus extrapolation of data in existing systematic reviews carries its own statistical prejudice. It is widely acknowledged that the data on treatment are drawn largely from nonrandomized trials, retrospective cohorts, and post-hoc analyses of prospective studies, all of which carry inherent bias, significantly limiting the findings. This article evaluates the available evidence in order to establish whether local treatment of oligometastatic prostate cancer is a feasible, safe, and beneficial strategy in an enlarging cohort of patients for whom traditional treatment paradigms are in a state of flux.

DEFINING OLIGOMETASTATIC PROSTATE CANCER

Most studies and trials have defined oligometastasis in prostate cancer according to the number of metastatic lesions. Most vary between 3 and 5 metastases,[2–9,11] although 1 study included patients with 10 or fewer lesions.[12] Other studies have defined the oligometastatic state according to site of lesions, with lymph node, bone, and extrapelvic metastases commonly used as site-specific criteria.[21] In addition, 1 previous study used the size of the metastases as part of their inclusion criteria, and defined oligometastasis in prostate cancer if there was only bone involvement, with each lesion less than half the size of the vertebral body.[22]

There is some validity to using either the number or site of metastases as the definition of oligometastasis in prostate cancer. A recent study by Sridharan and colleagues[23] showed that bone metastases contribute more than those of other sites to the development of widespread metastases, and that having more than 3 bone metastases had a major impact on prostate cancer–specific mortality.

However, the Achilles heel of all such strategies to define oligometastatic disease is that such a definition is a function of imaging sensitivity.[21,24] In prostate cancer, conventional imaging, typically using computed tomography (CT) scanning, or bone scintigraphy with technetium-99m, has very poor accuracy for identifying metastatic disease.

However, novel functional imaging techniques, such as 11C-choline and 18Ga-PSMA–PET/CT, has recently shown increased sensitivity to prostate cancer metastases.[20] As such, there seems