The Egyptian Journal of Hospital Medicine (July 2025) Vol. 100, Page 3957-3959

Oligometastatic Bladder Cancer Management: Current Evidence and Future Directions

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ABSTRACT

Background: Metastatic bladder cancer has long been considered a terminal disease with a poor outcome. Now, evidence suggests that there is an in-between stage called oligometastatic disease, where a patient has only a limited number of metastatic sites. This specific condition challenges the traditional approach of providing only palliative care.

Objective: This review discusses the current methods for diagnosing and managing oligometastatic bladder cancer, emphasizing how crucial advanced imaging techniques like PET-CT are for accurately detecting this state. The main strategy for treatment involves combining multiple types of treatment. This includes using chemotherapy and immune checkpoint inhibitors, along with aggressive, targeted treatments for each specific tumor site. These targeted options, including surgery or stereotactic body radiotherapy, show promise for improving patients' survival. We look at the evidence for these treatments, stress the importance of having a team of different specialists make decisions, and treatment plan.

Methods: We searched PubMed and Google Scholar for bladder cancer, oligometastatic disease, metastasis-directed therapy, metastasectomy, systemic therapy, and immunotherapy. Only the most current or comprehensive study, which covered the years 2004–2025, was considered. The authors also assessed pertinent literature references. Ignored are documents written in languages other than English. Dissertations, oral presentations, and conference abstracts were among the papers that were not considered to be significant scientific research.

Conclusion: Oligometastatic bladder cancer should be viewed as a distinct clinical entity that presents a unique opportunity for curative-intent therapy. Better research from future clinical trials is urgently needed to confirm the effectiveness of this strategy.

Keywords: Oligometastatic disease, Bladder cancer, Urothelial carcinoma, Metastasis-directed therapy, SBRT.

INTRODUCTION

Bladder cancer poses a substantial health burden globally, with urothelial carcinoma representing the most prevalent histology. Approximately one-quarter of patients diagnosed with muscle-invasive bladder cancer will either present with or ultimately progress to metastatic urothelial carcinoma [1]. Traditionally, metastatic urothelial carcinoma has been associated with dismal prognosis. When managed exclusively with palliative systemic therapy, the five-year overall survival rate is only about 5% to 15% [2].

Traditionally, cancer metastasis was understood as an all-or-nothing event: either it was in one place, or it had spread everywhere. However, in 1995, a new concept was introduced by **Hellman and Weichselbaum** called the "oligometastatic state." They defined this as a distinct intermediate stage of cancer with only a few metastatic sites, typically one to five [3]. This theory suggests that some primary tumors are not able to spread widely throughout the body. For these patients, aggressively treating every metastatic site with what is called metastasis-directed therapy could potentially offer long-term control of the disease or even a cure. This idea has become popular in treating various cancers like prostate, lung, and colorectal cancer, and now it is being seriously studied for bladder cancer. Finding and treating oligometastatic bladder cancer is now a real possibility by using better imaging technology and more effective drugs [4]. This review will discuss the current state of oligometastatic bladder cancer treatment, looking at how it's diagnosed, the importance of local and systemic therapies, and what the future holds.

Defining and Diagnosing Oligometastatic Bladder Cancer

There is still no standard, agreed-upon definition for oligometastatic bladder cancer. In practice, most research defines it by the number of metastatic sites (usually three to five or fewer) and how many organs are affected (typically just one or two) [5].

A crucial differentiation exists between two presentations of oligometastatic bladder cancer. Synchronous oligometastatic bladder cancer is identified when metastasis is present at the initial diagnosis of muscle-invasive bladder cancer. Conversely, metachronous oligometastatic bladder cancer describes metastasis that manifests after a period of remission following the definitive treatment of the primary tumor. Metachronous disease is generally associated with a more favorable prognosis, particularly when preceded by a long disease-free interval [6].

To ensure a patient truly has oligometastatic disease, accurate staging is critical. The standard approach uses contrast-enhanced CT scans of the chest, abdomen, and pelvis, but this approach is not very good at finding small lesions, and it misses the full extent of the disease in 20-30% of patients. New technologies, which are improving metastatic sites detection are needed. For this reason, fluorodeoxyglucose positron emission tomography (FDG PET/CT) scans have emerged as a key

Received: 30/04/2025
Accepted: 30/06/2025

tool. These scans are more sensitive and better at finding hidden metastatic sites that traditional imaging misses. This helps differentiate patients with limited diseases from those with more widespread diseases [7]. Supporting this, a large study showed that radiation therapy (SBRT) planned to use a PET/CT scan was highly effective, controlling the tumor locally in 88% of cases over two years [8]. Liquid biopsies, which test blood for tumor DNA (ctDNA) or new urine markers, are promising tools for detecting early cancer recurrence and determination of treatment effectiveness [8].

Systemic Therapy: The Foundation of Management

The main treatment for oligometastatic bladder cancer is systemic therapy. This is essential for killing tiny cancer cells that are too small for any current scan to detect. Therefore, targeted treatments for specific tumors (metastasis-directed therapy) should not be used on their own. Instead, they should consider reinforcing therapy that is combined with the main systemic treatment [9].

1- Platinum-based chemotherapy

The standard initial treatment for patients with metastatic bladder cancer who are fit enough to receive it is chemotherapy, that includes cisplatin (such as gemcitabine/cisplatin or dose dense-methotrexate/vinblastine/adriamycin and cisplatin (MVAC) combinations). When treating oligometastatic bladder cancer specifically, chemotherapy is often used as induction chemotherapy. Patients with stable or responsive disease after 3-4 cycles of chemotherapy are then considered as the best candidates for targeted therapy (metastasis-directed therapy). This is because responding well to the initial chemotherapy is a good indicator for selecting patients who are most likely to benefit from more aggressive treatment [9].

2- Immune checkpoint inhibitors (ICIs)

The emergence of immune checkpoint inhibitors has completely changed the treatment for metastatic bladder cancer. Drugs like pembrolizumab, atezolizumab, and nivolumab are now approved treatments in different situations. The JAVELIN Bladder 100 trial, set a new standard of care. Now, patients who have stable disease on chemotherapy are switched to avelumab as ongoing "maintenance" therapy [10]. This maintenance strategy is highly relevant for oligometastatic bladder cancer patients who have completed induction chemotherapy and metastasis-directed therapy. Also, there is a substantial preclinical and clinical basis for combining radiotherapy with immunotherapy. The irradiation of a tumor can induce immunogenic cell death, leading to the release of tumor antigens and generating an in-situ vaccination effect. This localized immune stimulation can potentiate a systemic anti-tumor immune response, potentially causing the regression of non-irradiated tumors—a phenomenon identified as the abscopal effect [11]. This synergy makes the combination of SBRT and immune checkpoint inhibitors a particularly attractive strategy in oligometastatic bladder cancer.

Local therapy for primary tumor

1- Radical cystectomy

A large analysis of nearly 1,381 patients from the SEER cancer database found that the benefit of cystectomy in oligometastatic bladder cancer depends on sites of metastasis. The study showed a clear survival advantage for patients whose metastasis was in their bones or in distant lymph nodes. However, the surgery did not provide a significant benefit for patients whose cancer had spread only to the liver or lungs [12].

2- Bladder preservation strategies

Trimodality therapy (maximum transurethral resection of bladder tumor + chemoradiation) can lead to five-year survival rate of 75% in some patients with muscle-invasive bladder cancer. For those who also have a few metastases elsewhere, this approach is possible only if the main bladder tumor responds to treatment and there are no other contraindications for bladder preservation protocol [13].

Metastasis-directed therapy (MDT)

The aim of metastasis-directed therapy is to use precise, powerful treatments to wipe out all visible signs of cancer spread. The treatment is chosen based on the tumors' location, size, and number, as well as factors specific to each patient [14].

1- Surgical Metastasectomy

Surgery to resect metastasis is the most traditional and well-known type of metastasis-directed therapy. For bladder cancer patients, this approach is most often used to treat a small number of recurring lymph nodes in the pelvic or abdominal area, or to remove a few isolated tumors in the lungs. Retrospective analysis has documented five-year overall survival rates between 30% and 60% for highly selected patients who underwent metastasectomy. The most favorable outcomes were observed in individuals with a prolonged disease-free interval prior to recurrence and in whom a complete surgical resection (R0) was achieved [14,15]. However, patient selection is critical, and surgery is often limited by the anatomical location of the metastasis and patient comorbidities [14,15].

2- Stereotactic Body Radiation Therapy (SBRT)

SBRT is an effective, non-surgical treatment that serves as an alternative to surgery. It works by delivering very precise, high-dose radiation over just a few sessions (one to five) to destroy tumors. This technique can accurately target cancer sites almost anywhere in the body—including bones, lungs, and lymph nodes—with very little damage to the surrounding healthy areas. Multiple studies looking back at bladder cancer cases have shown that SBRT is extremely effective, with success rates between 80% and 95% [16].

The success of SBRT in controlling individual tumors may translate into decrease tumor progression and prolong overall survival. For example, In the multicenter analysis oligometastatic bladder cancer patients staged with either conventional or molecular imaging, treated with a median SBRT BED10 dose of 78 Gy, **Franzese *et al.*** reported 2-year overall survival and progression free survival rates of 50% and 38%, respectively. The local control at 2 years was 88%. No grade 3 adverse event was reported. These outcomes are significantly better than what has been historically seen in patients who only receive systemic treatments like chemotherapy [17].

An Integrated Multimodal Treatment Strategy

Treating oligometastatic bladder cancer effectively requires a team of specialists including urologists, medical oncologists, and radiation oncologists, working together on a clear plan. Getting a precise diagnosis using high-quality scans, ideally including a PET/CT is the first step. Then reviewing the performance status of the patient to make sure that the patient will tolerate an aggressive treatment approach. Next, the patients receive an initial course of systemic therapy. After this, they are scanned again to assess response. If the disease progresses, then the patient continues with standard treatment. However, if tumor response or stable disease is detected, the next step is to use targeted treatments like surgery or SBRT, while also ensuring the original bladder tumor is fully treated. After all this, the patient may receive ongoing immunotherapy as a "maintenance" treatment to decrease the cancer recurrence [18].

CONCLUSION AND FUTURE DIRECTIONS

The therapeutic paradigm for oligometastatic bladder cancer is experiencing a significant evolution, shifting from a historically nihilistic viewpoint to a more proactive strategy targeting long-term disease control. Current evidence, though predominantly retrospective, strongly supports a multimodal approach that integrates systemic therapy with aggressive metastasis-directed therapy to improve outcomes in carefully selected patients. Future progress requires addressing critical questions through well-designed clinical trials. It is imperative to prospectively validate the overall survival benefit of adding metastasis directed therapy to systemic therapy through randomized controlled trials. Additionally, research must establish the optimal sequencing of these modalities and develop molecular and imaging biomarkers to refine patient selection. The integration of novel, highly active agents, such as antibody-drug conjugates and FGFR inhibitors, also needs systematic investigation. In summary, oligometastatic bladder cancer should be viewed as a distinct clinical entity that presents a unique opportunity for curative-intent therapy, the full potential of which can only be realized through a multidisciplinary, evidence-based, and patient-centered approach.

Conflict of interest: The authors declared no conflicts of interest.

Funding: No funds.

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