Beyond the Bone: Atypical Metastases in Prostate Cancer

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The bone represents the most common site of metastases in patients with prostate cancer (PCa). However, the proportion of men experiencing atypical metastatic sites, defined as the metastases localizing to sites other than bones or lymph nodes outside the pelvis or abdomen, is significant. For example, 10.6%, 10.2% and 9.1% of patients with metastatic PCa experience distant lymph nodes, liver, and thorax involvement, respectively. The knowledge of the distribution of metastatic sites can help provide physicians with better staging strategies, as well as follow-up protocols aimed at a prompt diagnosis of tumor recurrence after primary treatment. The involvement of atypical sites of metastases might also have a prognostic value, where individuals with visceral metastases experience shorter survival compared to their counterparts with exclusive bone involvement. Consequently, this parameter should be taken in account during the decision-making process in the treatment of PCa patients.


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Introduction

Prostate cancer (PCa) represents the most common non-cutaneous malignancy for men, where approximately 145,000 new cases will be diagnosed in the year 2013 in the United States alone[1]. The introduction of PSA-based screening policies led to a substantial decrease of the number of individuals with distant metastases. However, nowadays approximately 5% of patients present with metastatic PCa at diagnosis[2, 3].

The bone is generally considered the most common metastatic site in these individuals (Table 1)[4-8]. This was recently confirmed in a study conducted by our group evaluating a large contemporary cohort of patients with metastatic PCa representing the United States population (n=74,826). Particularly, we demonstrated that the bone represents the primary site of metastasis, with approximately 85% of individuals with metastatic PCa experiencing skeleton involvement[6]. Additionally, our results, together with those reported by previous investigations (Table 1), showed that the rate of atypical metastatic sites involvement, defined as the metastases localizing to sites other than bones or lymph nodes outside the pelvis or abdomen, is significant. For example, 10.6%, 10.2% and 9.1% of patients with metastatic PCa experience distant lymph nodes, liver, and thorax involvement, respectively[6].

Historically, the non-random homing of metastatic cells has been explained by the “seed and soil” hypothesis.
Table 1. Studies evaluating the distribution of metastatic sites in patients with prostate cancer (PCa).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Assessment of metastases</th>
<th>Distribution of metastatic sites</th>
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<tr>
<td>[8]</td>
<td>508 patients with newly diagnosed PCa evaluated at a single institution between January 1991 and June 1996</td>
<td>Computer tomography (CT) of the pelvis and abdomen</td>
<td>36 (7%) patients had atypical metastases</td>
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<td>CT of the thorax was performed in patients with evidence of disease above the diaphragm</td>
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<td>Brain CT or MRI was performed when clinically indicated</td>
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<td>[5]</td>
<td>1,589 men having either PCa or previously treated PCa</td>
<td>Autopsy</td>
<td>631 (39.7%) patients had lymphatic or hematogeneous metastases</td>
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<td>Hematogenous metastases were found in 556 (35%) patients</td>
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<td>The most common metastatic sites in these patients were the bone (90.1%), lung (45.7%), liver (25.0%), pleura (21.0%), and adrenals (12.8%)</td>
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<td>[7]</td>
<td>316 patients with metastatic PCa included in the M.D. Anderson Cancer Center tumor registry between 1994 and 1997</td>
<td>Information from diagnostic imaging, surgical findings, pathology reports, physician notes, and histologic and treatment information</td>
<td>283 (89.5%) patients had bone metastases</td>
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<td>46 (14.5%) patients had atypical lymph nodes metastases</td>
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<td>17 (5.4%) patients had lung metastases</td>
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<td>13 (4.1%) patients had liver metastases</td>
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<td>[4]</td>
<td>620 patients with newly diagnosed PCa evaluated at a single institution between 1999 and 2009</td>
<td>CT scan and bone scintigraphy</td>
<td>82 (13.2%) patients had atypical metastases</td>
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<td>The most frequent sites of atypical metastases were lung (40%), supradiaphragmatic lymph nodes (34%), and adrenal glands (15%)</td>
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<td>[6]</td>
<td>74,826 patients hospitalized for metastatic PCa included in the Nationwide Inpatient Sample (NIS) between 1998 and 2010</td>
<td>International Classification of Diseases 9th edition (ICD-9) diagnostic codes</td>
<td>63,134 (84.4%) patients had bone metastases</td>
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<td>7,912 (10.6%) patients had distant lymph node metastases</td>
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<td>7,615 (10.2%) patients had liver metastases</td>
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<td>6,782 (9.1%) patients had thorax metastases</td>
</tr>
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formulated by Paget in 1889\(^\text{[10]}\). The cells (“seeds”) acquire the ability to metastasize only in organs where they can survive and grow (“soils”)\(^\text{[9-12]}\). This process involves several steps, such as angiogenesis, local migration, invasion, intravasation, circulation, and extravasation of tumor cells, and the subsequent colonization of the target organ\(^\text{[11]}\). Consequently, the non-random homing of PCa cells is primarily related to the interaction between the tumor cells and the host organ microenvironment\(^\text{[12, 13]}\), which determines the directional migration down a chemotactic gradient to specific organs, their arrest in the capillary bed, and eventually their survival in the host organ microenvironment\(^\text{[9-13]}\). On the other hand, it has been hypothesized that the vascular blood flow might be in part responsible for the high prevalence of lower spine metastases in PCa patients\(^\text{[5,10,14,15]}\). In this context, Batson \textit{et al.} suggested that PCa cells might migrate to the lower spine because of a portal-like venous system between the prostatic region and the lower vertebrae\(^\text{[15]}\). An autopsy study by Bubendorf and colleagues in part confirmed this hypothesis showing a gradual decrease in the spine involvement from the lumbar to the cervical region, which could be related to an upward spread of PCa cells along spinal veins after initial lumbar involvement\(^\text{[15]}\).

Another possible way of spread might be represented by the so-called “cava-type pathway”. Particularly, some cells might directly invade the systemic circulation, and eventually visceral sites, through the inferior vena cava \(^\text{[5, 10]}\). Of note, in order to be able to invade and survive in visceral sites such as lung, liver, and brain, PCa cells acquire a more aggressive phenotype, which may eventually result in faster tumor progression and lower survival rates\(^\text{[16-18]}\). In this regard, Pond \textit{et al.} recently
showed that the metastatic site is significantly associated with the risk of dying in patients with castration-resistant PCa\textsuperscript{[16]}. Particularly, men with liver and lung metastases had a substantially shorter median survival compared to their counterparts with skeletal involvement\textsuperscript{[16]}. Similarly, Armstrong et al. showed that the presence of liver metastases represented an independent prognostic factor in men with metastatic castration-resistant PCa\textsuperscript{[18]}. Taken together, these observations can help provide physicians with better prognostic tools in the context of metastatic PCa.

Finally, it should be highlighted that approximately 10% of patients with metastatic PCa have distant lymph nodes invasion. In this context, previous studies showed that the involvement of distant lymph nodes might depend on the lymphatic spread throughout regional station\textsuperscript{[19]}. Consequently, it might be hypothesized that tumor cells invading the lymph nodes did not acquire yet the ability to spread through the haematogenous pathways to the bone and visceral sites\textsuperscript{[6, 10, 19]}. This less aggressive tumor phenotype would ultimately lead to a better prognosis in patients with exclusive lymph node involvement\textsuperscript{[16]}. In this context, previous investigations reported that the survival of patients with node-positive disease is not invariably poor\textsuperscript{[20]}. This is true even when considering patients who experience disease recurrence after primary treatment\textsuperscript{[21, 22]}. For example, it has been hypothesized that patients with nodal recurrence after surgery might benefit from local tumor control, such as salvage lymph node dissection, in terms of clinical-recurrence free survival\textsuperscript{[22, 23]}. Well-designed prospective randomized trials are still needed to better clarify this issue.

From a clinical standpoint, these observations highlight that the site of metastases has important implications on patient prognosis. Indeed, while individuals with lymph node metastases are not invariably affected by systemic disease, those with bone and visceral involvement harbor a worse prognosis\textsuperscript{[22]}. Particularly, the presence of atypical sites of metastases should help physicians to better stratify patients for the administration of systemic therapies. Indeed, since men with visceral involvement have the worst survival, they are less likely to respond to conventional treatment approaches, such as androgen deprivation therapy\textsuperscript{[24]}. Consequently, they might deserve more aggressive therapies. In this context, it should be noted that previous randomized trials assessing the oncologic efficacy of novel molecules such as sipuleucel-T, abiraterone acetate, and radium-223 did not include this sub-cohort of patients. Therefore, well-designed prospective studies are needed to assess the impact of these systemic treatments on survival in patients with atypical sites of metastases.

Concluding, although the bone represents the most common site of metastasis in PCa patients, the proportion of individuals experiencing atypical sites of metastasis is non-negligible. From a clinical standpoint, the knowledge of the distribution of metastatic sites can help provide physicians with better staging strategies, as well as follow-up protocols for a prompt diagnosis of tumor recurrence after primary treatment. Additionally, since the site of metastasis has an impact on survival, this parameter should be considered during the decision-making process in the treatment of patients with metastatic PCa\textsuperscript{[16–18]}.

Conflict of interests

The authors declare that there is no conflict of interests.

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