

## Distribution of Metastatic Sites in Patients With Prostate Cancer: A Population-Based Analysis

Giorgio Gandaglia,<sup>1,2\*</sup> Firas Abdollah,<sup>1,2</sup> Jonas Schiffmann,<sup>1</sup> Vincent Trudeau,<sup>1</sup> Shahrokh F. Shariat,<sup>3</sup> Simon P. Kim,<sup>4</sup> Paul Perrotte,<sup>5</sup> Francesco Montorsi,<sup>2</sup> Alberto Briganti,<sup>2</sup> Quoc-Dien Trinh,<sup>6</sup> Pierre I. Karakiewicz,<sup>1,5</sup> and Maxine Sun<sup>1</sup>

<sup>1</sup>Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, Montreal, Canada

<sup>2</sup>Department of Urology, Urological Research Institute, Vita Salute San Raffaele University, San Raffaele Scientific Institute, Milan, Italy

<sup>3</sup>Department of Urology, Medical University of Vienna, Vienna, Austria

<sup>4</sup>Department of Urology, Yale University, New Haven, Connecticut

<sup>5</sup>Department of Urology, University of Montreal Health Center, Montreal, Canada

<sup>6</sup>Department of Surgery, Division of Urology, Brigham and Women's Hospital / Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts

**BACKGROUND.** There is few data on what constitutes the distribution of metastatic sites in prostate cancer (PCa). The aim of our study was to systematically describe the most common sites of metastases in a contemporary cohort of PCa patients.

**METHODS.** Patients with metastatic PCa were abstracted from the Nationwide Inpatient Sample (1998–2010). Most common metastatic sites within the entire population were described. Stratification was performed according to the presence of single or multiple ( $\geq 2$  sites) metastases. Additionally, we evaluated the distribution of metastatic sites amongst patients with and without bone metastases.

**RESULTS.** Overall, 74,826 patients with metastatic PCa were identified. The most common metastatic sites were bone (84%), distant lymph nodes (10.6%), liver (10.2%), and thorax (9.1%). Overall, 18.4% of patients had multiple metastatic sites involved. When stratifying patients according to the site of metastases, only 19.4% of men with bone metastases had multiple sites involved. Conversely, among patients with lymph nodes, liver, thorax, brain, digestive system, retroperitoneum, and kidney and adrenal gland metastases the proportion of men with multiple sites involved was 43.4%, 76.0%, 76.7%, 73.0%, 52.2%, 60.9%, and 76.4%, respectively. When focusing exclusively on patients with bone metastases, the most common sites of secondary metastases were liver (39.1%), thorax (35.2%), distant lymph nodes (24.6%), and brain (12.4%).

**CONCLUSIONS.** Although the majority of patients with metastatic PCa experience bone location, the proportion of patients with atypical metastases is not negligible. These findings might be helpful when planning diagnostic imaging procedures in patients with advanced PCa. *Prostate* 74:210–216, 2014. © 2013 Wiley Periodicals, Inc.

**KEY WORDS:** prostate cancer; metastatic disease; sites of metastases; bone metastases

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\*Correspondence to: Giorgio Gandaglia, MD, Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Center, 1058, rue St-Denis, Montreal (QC) H2X 3J4, Canada. E-mail: giorgio.gandaglia@gmail.com, giorgan10@libero.it

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## INTRODUCTION

Prostate cancer (PCa) represents the most common non-cutaneous malignancy for men, where an estimated 241,740 new cases will be diagnosed in 2013 in the United States [1]. Whereas most of those new diagnoses will be clinically localized, up to 17% of patients may experience metastatic disease, in which the risk of cancer-specific mortality is increased [2]. In this context, it is well established that, beyond regional lymph nodes, the skeleton represents the most common metastatic site [3–6]. Nonetheless, recent observations suggest that up to 15% of men with PCa might be affected by atypical metastases at diagnosis, defined as metastases located at sites other than bone and regional lymph nodes [7,8]. However, these findings were based on historical institutional series evaluating a small number of patients ( $N = 36$ – $1,589$ ). Consequently, they might not be generalizable to the United States population.

Since the knowledge of the sites of metastases is crucial for accurate staging of advanced tumors and for a prompt diagnosis of recurrence, our study aimed at describing the distribution of metastatic sites using a large contemporary population-based cohort representative of the United States. This descriptive exercise sought to determine the distribution of common metastatic sites.

## MATERIALS AND METHODS

### Population Source

Data were abstracted from years 1998 to 2010 of the US Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS). The NIS is a 20% stratified probability sample that encompasses approximately 8 million acute hospital stays per year from 1,045 hospitals in 46 states. It is the largest all-payer inpatient care observational cohort in the United States and in 2011 it represented approximately 97% of all hospital discharges.

### Study Cohort

Patients with a primary diagnosis of PCa were identified using the International Classification of Disease 9th Revision (ICD-9) diagnostic code: 185.0. Using secondary diagnostic codes, only patients with metastases were included in the study. For the purpose of the analyses, we excluded individuals with exclusively pelvic lymph node metastases (ICD-9: 196.6). Moreover, we excluded from our study patients younger than 18 years old. This resulted in a weighted estimate of 74,826 patients. For each patient, age, race,

year of admission, hospital region, and comorbidities were considered. The latter was classified according to the Charlson comorbidity index (CCI), which was derived using a commonly used algorithm [9,10].

### Metastatic Sites

Using previously described diagnostic codes [11], metastatic sites were categorized as follows: bone and bone marrow (198.5), distant lymph nodes (196.x, excluding intra pelvic lymph nodes [196.6]), liver (197.7), thorax (including lung [197.0], pleura [197.2], mediastinum [197.1], and other respiratory organs [197.3]), adrenal gland and kidney (198.7 and 198.0), brain and spinal cord (198.3), retroperitoneum and peritoneum (197.6), and digestive system (including large intestine and rectum [197.5], small intestine and duodenum [197.4], and other digestive organs and spleen [197.8]).

### Statistical Analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges were reported for continuously coded variables. The chi-square and *t*-tests were used to compare proportions and medians, respectively.

The analyses consisted of three steps. First, we examined the distribution of metastatic sites within the overall population, and stratified according to the number (1 vs.  $\geq 2$ ) of metastatic sites. Second, we examined the proportion of patients with  $\geq 2$  metastatic sites within the entire population, and according to site of metastases. Third, we focused on patients with bone metastases and evaluated the distribution of other concomitant metastatic sites. Finally, we examined the distribution of metastatic sites in patients without bone metastases.

All statistical tests were performed using performed using SPSS version 20 (SPSS, Chicago, IL).

## RESULTS

### Baseline Characteristics

Overall, a weighted estimate of 74,826 men with metastatic PCa was abstracted (Table I). Mean age at diagnosis was 74 years (median: 75, interquartile range [IQR]: 67–82). The majority of patients were Caucasian (52%) and had a CCI of 0 (69%). Respectively 82 versus 18% of patients had 1 versus  $\geq 2$  metastatic sites.

### Distribution of Metastatic Sites

Figure 1 represents the distribution of metastatic sites within the entire cohort. The majority of patients

*The Prostate*

**TABLE I. Descriptive Statistics of Patients Diagnosed With Metastatic Prostate Cancer (PCa) Within the Nationwide Inpatient Sample (NIS) Between 1998 and 2010**

	Overall (N = 74,826)	Patients with bone metastases (N = 63,135)	Patients without bone metastases (N = 11,694)	P-value
Year of diagnosis				
1998–2000	19,838 (26.5)	16,637 (26.5)	3,201 (27.4)	0.03
2001–2003	18,685 (25.0)	15,777 (25.0)	2,908 (24.9)	
2003–2007	21,911 (29.3)	18,597 (29.5)	3,313 (28.3)	
2008–2010	14,396 (9.2)	12,124 (19.2)	2,272 (19.4)	
Age at diagnosis				
Mean (median)	74 (75)	71.0 (75)	71.4 (72)	<0.001
Interquartile range	67–82	67–82	63–80	
Race (%)				
Caucasian	38,682 (51.7)	32,271 (51.1)	6,412 (54.8)	<0.001
African-American	11,980 (16.0)	10,414 (16.5)	1,566 (13.4)	
Hispanic	4,724 (6.3)	4,045 (6.4)	679 (5.8)	
Other <sup>a</sup>	2,338 (3.1)	1,997 (3.2)	341 (2.9)	
Unknown	17,104 (22.9)	14,409 (22.8)	2,695 (23.0)	
CCI (%)				
0	51,619 (69.0)	43,136 (68.3)	8,483 (72.5)	<0.001
1	17,449 (23.3)	14,994 (23.7)	2,455 (21.0)	
2	4,852 (6.5)	4,184 (6.6)	667 (5.7)	
≥3	910 (1.2)	821 (1.3)	89 (0.8)	
No. of metastatic sites (%)				
1	61,095 (81.6)	50,873 (80.6)	10,221 (87.4)	<0.001
≥2	13,734 (18.4)	12,262 (19.4)	1,472 (12.6)	
Site of metastases (%)				
Bone	63,134 (84.4)	63,134 (100)	0 (0)	
Distant lymph nodes	7,912 (10.6)	3,015 (4.8)	4,897 (41.9)	
Liver	7,615 (10.2)	4,796 (7.6)	2,819 (24.1)	
Thorax	6,782 (9.1)	4,322 (6.8)	2,460 (21.0)	
Brain	2,354 (3.1)	1,516 (2.4)	837 (7.2)	
Digestive system	2,038 (2.7)	751 (1.2)	1,287 (11.0)	
Retroperitoneum	1,382 (1.8)	621 (1.0)	761 (6.5)	
Kidney and adrenal gland	757 (1.0)	434 (0.7)	324 (2.8)	

<sup>a</sup>Includes Asian, Pacific Islander, Native American, and other unspecified.

had bone metastases (84%). Other common sites of metastases were distant lymph nodes (10.6%), liver (10.2%), thorax (9.1%), brain (3.1%), and digestive system (2.7%).

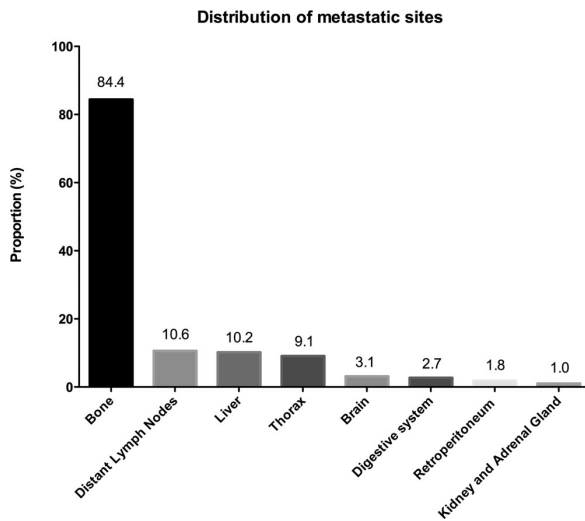
Of all patients with a single metastatic site involved (N = 61,095), most had bone metastases (83%, Fig. 2A). Conversely, distant lymph nodes, liver, thorax, and brain metastases were observed in 7.3%, 3.0%, 2.6%, and 1.0% of patients, respectively.

Amongst patients with ≥2 metastatic sites involved (N = 13,734), 89%, 42%, 38%, 25%, and 12.5% of patients had bone, liver, thorax, distant lymph nodes, and brain metastases, respectively (Fig. 2B). Figure 3 describes the proportion of patients with ≥2 metastatic sites, stratified according to the site of metastases. For example, amongst patients with exclusively bone metastases (N = 63,135), only 19% had other concomi-

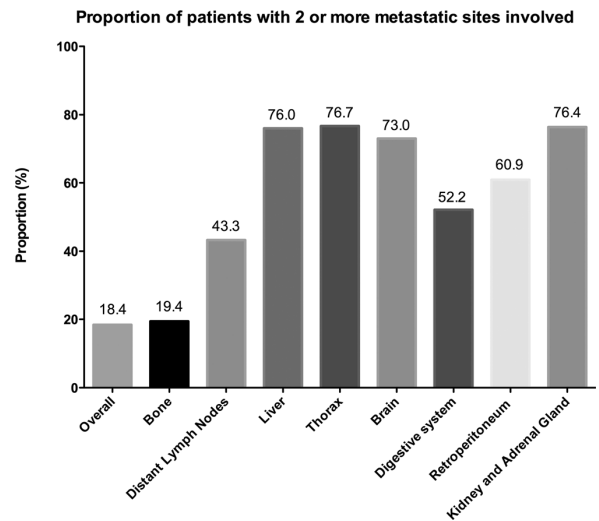
tant metastatic sites. Conversely, amongst patients with exclusively liver metastases (N = 7,911), 76% had other concomitant metastatic sites.

### Bone Metastases

Overall, a weighted estimated of 63,135 patients had bone metastases and 11,694 presented without bone metastases (Table I). When patients were stratified according to the presence of bone metastases (bone metastases vs. no bone metastases), statistically significant differences were observed with regard to year of admission, age, race, CCI, and number of metastatic sites involved (all  $P \leq 0.03$ ). Of all patients with bone metastases, the most common sites of metastases were liver (39%), thorax (35%), distant lymph nodes (25%), and brain (12.4%; Fig. 4A). In



**Fig. 1.** The distribution of metastatic sites in patients with prostate cancer included in the Nationwide Inpatient Sample between 1998 and 2010.



**Fig. 3.** Proportion of patients with two or more metastatic sites involved overall and stratified according to the metastatic sites.

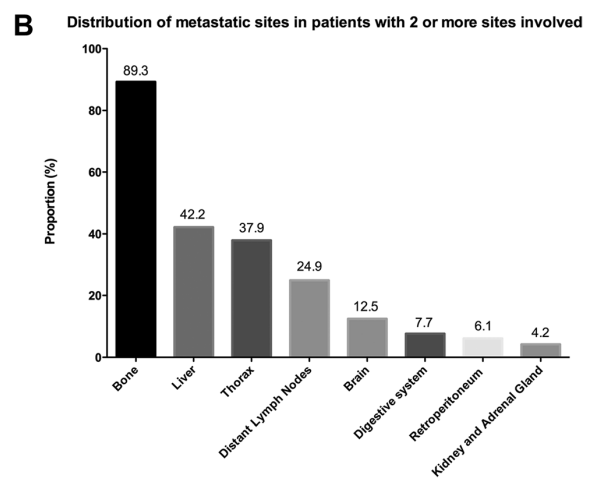
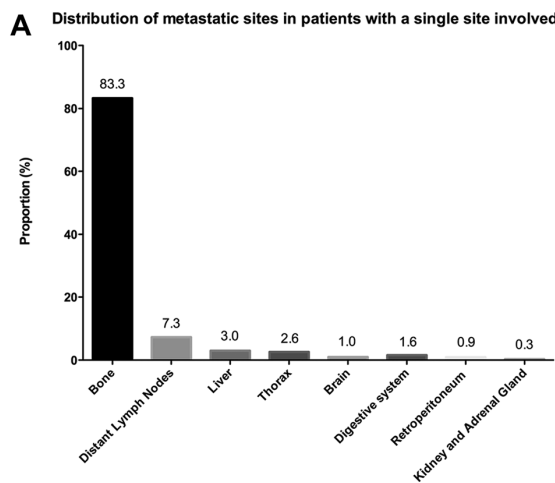
contrast, among those without bone metastases (N=11,694), the most common sites of metastases were distant lymph nodes (41.9%), liver (24.1%), thorax (21.0%), and the digestive system (11.0%, Fig. 4B).

**DISCUSSION**

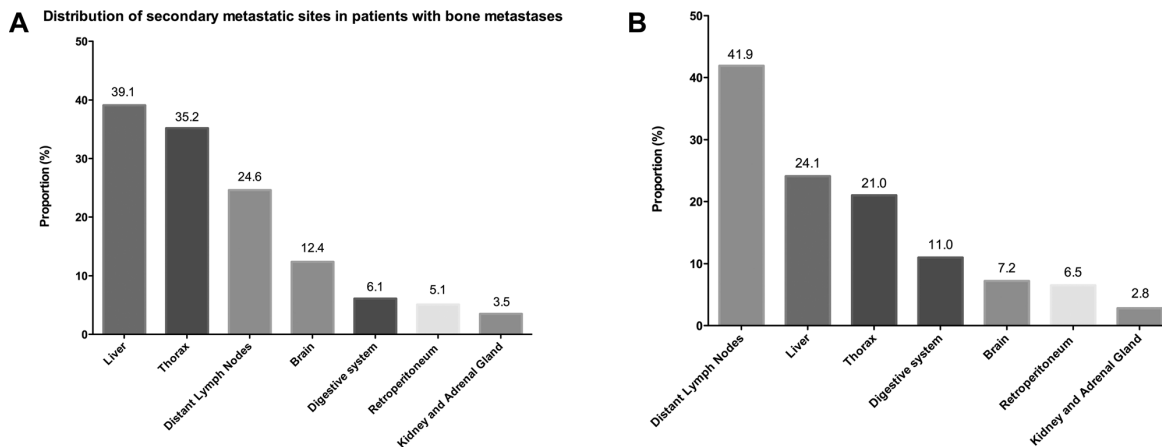
Although PCa has a well-recognizable pattern of spread, most often to regional lymph nodes and to the skeleton [6], many patients might present with atypical metastases at diagnosis [12]. An accurate knowl-

edge of the sites of metastases in patients presenting with PCa is crucial to properly plan staging and additional diagnostic procedures. Currently, only few studies have described in-depth the sites of metastasis in PCa patients. However, these reports were based on small institutional cohorts [7,12], or referred to historical populations [6,12]. Hence, a more accurate assessment of the sites of metastases in PCa patients utilizing a cohort that is more generalizable and representative of the United States is needed.

Several findings were noteworthy. First, we confirmed that the bone represents the most common site



**Fig. 2.** The distribution of metastatic sites in patients with a single site involved (A) and in those with two or more sites involved (B).



**Fig. 4.** The distribution of metastatic sites when evaluating exclusively patients with (A) and without bone involvement (B).

of metastasis in PCa patients [3,5]. Particularly, up to 85% of patients included in our study had bone involvement. The reasons for such a high prevalence of bone and skeleton metastases might reside in tumor biology [12,13]. Although the exact mechanism of PCa metastasizing to the bone is relatively unknown, different hypotheses have been proposed. Historically, the existence of specific metastatic sites for PCa has been explained with the “seed and soil” hypothesis. Over a hundred years ago, Paget et al. [14] hypothesized that the development of metastases depends on the interaction between the “seeds” (i.e., the characteristics of metastatic cells) and the “soil” (i.e., the characteristics of the target organ microenvironment): the “seeds” of PCa metastatic cells preferentially settle in the “soil” of bone matrix. Recently, in addition to this theory it has also been hypothesized that specific target organ might have the ability to attract cancer cells through the release of chemotactic factors (homing theory) [15,16]. Moreover, Batson et al. [17] proposed that PCa cells frequently migrate to the skeleton, and particularly the lower spine, because of a portal-like venous system between the prostate and the lower vertebrae. Although we were not able to identify the specific skeletal sites of metastases, the results of our study clearly confirm that metastatic PCa cells have a high affinity to the bone and the skeleton. As a clinically relevant consequence, this provided a therapeutic target for the development of new molecules, such as zoledronic acid, denosumab, and radium-223 [18,19].

Second, distant lymph nodes represented the most common metastatic sites, besides the bones. Overall, 10.6% of patients presented with distant lymph node metastases. Additionally, approximately 42% of patients without bone metastasis experienced distant lymph

node involvement. In this regard, previous studies showed that distant lymph nodes do not represent primary PCa lymphatic landing sites, but their involvement depends on the lymphatic spread through pelvic stations [20]. For example, Briganti et al. [20] recently showed that PCa lymphatic spread ascends from the pelvis up to the retroperitoneum invariably through common iliac lymph nodes. In this context, it has been hypothesized that cancer cells that metastasize to the lymph nodes still do not have acquired phenotypic changes that confer them the ability to invade the systemic circulation. Therefore, distant lymph node metastases might harbor a different malignant potential compared to bone or visceral metastases. Unfortunately, due to the nature of our observations we were not able to compare oncologic outcomes according to the site of metastasis. In this regard, further studies are needed to clarify this issue.

Third, a non-negligible proportion of patients had visceral metastases without bone involvement. Particularly, the most common sites of visceral metastases in patients without bone and distant lymph nodes involvement were liver and thorax. This observation highlights the possibility of a third metastatic pathway: the onset of visceral metastases in the absence of skeleton involvement might be related to the spread of PCa cells directly through the inferior vena cava, the so-called “cava-type pathway” [12].

Finally, approximately one out of five patients included in the current study presented with multiple metastatic sites involved at diagnosis. This held true even when evaluating only patients with bone metastases. Particularly, the most common secondary metastatic sites in patients with bone metastases were the liver, thorax, and distant lymph nodes. Taken together, these observations highlight the need for additional

staging procedures even in patients presenting with metastatic disease.

From a clinical standpoint, the results of our study lead to important considerations. Although the skeleton is the most common site of PCa metastasis [3,4], a non-negligible proportion of men with advanced PCa might experience metastases in atypical sites. Specifically, more than 15% of patients with metastatic PCa have visceral metastases without bone involvement at presentation. According to the National Comprehensive Cancer Network (NCCN) guidelines, bone scan and pelvic CT or MRI are indicated for staging in patients at high risk of metastases (i.e., high prostatic-specific antigen [PSA], high Gleason score, or rapid PSA progression) [21]. However, our findings indicate that these diagnostic procedures might not be sufficient for properly staging all metastatic patients. For example, a considerable proportion of patients present with thoracic metastases at the time of diagnosis (9.1%). Specifically, 2.3% of patients included in our cohort experienced metastases to the thorax in the absence of any other site involved. This becomes crucial since the current guidelines do not routinely indicate thorax imaging at PCa presentation [21,22]. Therefore, it is possible that a substantial proportion of men might be falsely classified as non-metastatic at diagnosis. Additionally, even when the skeleton is the primary metastatic site, up to 20% of patients will harbor metastases in additional (atypical) sites. Since accurate staging through imaging is an integral part of PCa management, our findings suggest that supplementary tests beyond bone scan and pelvic imaging should be considered in metastatic PCa patients [23].

It should be pointed out that the current study represents the largest of similar reports describing the distribution of metastatic sites in PCa patients identified in the literature [6–8,12]. The second largest report is based on 316 patients included in a single-center tumor registry [6]. Moreover, our findings are more clinically relevant compared to what observed in large contemporary autoptic series of metastatic PCa patients [12].

Despite these strengths, our study is not devoid of limitations. First, the NIS focuses primarily on hospitalized patients. This prevented us to evaluate the distribution of metastatic sites in men with metastatic PCa who never required a hospital stay. Thus, we could not exclude that the nature of the database introduced a selection bias toward patients with larger burden of disease and more metastatic sites. Second, we could not determine the exact location of metastases. For example, although it is well known that the majority of patients with bone metastases have the lower spine involved [12,24], we could not verify this observation in our cohort. Third, detailed data on

oncologic history were not available. This prevented us to investigate the association between serum PSA and the distribution of metastases or the number of metastatic sites. On the other hand, previous studies failed to show an association between PSA levels and disease distribution in patients with metastatic PCa [7]. Finally, the NIS relies on ICD-9 codes for assessment of secondary diagnostic codes, which might be subject to potential coding biases. Nonetheless, the NIS estimates are considered to be precise and accurate [25].

## CONCLUSIONS

Although the majority of patients with metastatic PCa present with bone metastases, the proportion of patients with atypical metastases is not unimportant. Particularly, the most common metastatic sites besides the bone were distant lymph nodes, liver, and lung. These findings might be helpful when planning diagnostic imaging procedures in patients with advanced PCa.

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