CHARACTERIZATION OF SKELETAL METASTASES OF KNOWN AND UNKNOWN ORIGINS

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ABSTRACT

Background: There are limited epidemiologic studies characterizing skeletal metastasis, and fewer, if any, that comprehensively compare and contrast patients who are initially diagnosed with skeletal metastases of unknown primary (SMUP) to patients who have a known primary at the time that skeletal metastases are identified. Methods: This single-centered retrospective study provides a descriptive analysis of patient characteristics (demographics including but not limited to sex, age, and history of tobacco use), lesion characteristics (sites of primary lesion as well as number and location of metastatic lesions), and outcomes for patients identified as having SMUP compared to patients with a known primary cancer who have skeletal metastases. Results: In this study, 164 patients were identified as having bone metastases through record review of ICD-9 and ICD-10 codes. Of these patients, 65.9% had a known primary prior to identification of bone metastases while 34.1% were classified as having SMUP. Patients identified with SMUP were disproportionately male while patients with a known primary were disproportionately female. No other significant differences were identified for other patient characteristics. For patients with bone metastases with known primaries, the most common primary sites were lung, breast, and prostate carcinoma, in that order. However, the most common primary sites for patients with SMUP were, in order, lung, prostate, and breast carcinoma. The most common location for metastases, regardless of known or unknown primary was the spine, followed by the pelvis and the ribs. Lastly, with respect to long term prognosis, while there was a significant difference in patients’ survival time based on solely on SMUP status, there was no difference in survival once bone metastases were identified, regardless of whether the primary is known, as all bone metastases carried a poor prognosis. Conclusion: There are significant differences in the male to female ratio with respect to the initial presentation of bone metastases when comparing known primary to unknown primary malignancies. SMUP are more common in males than females, with 61% of males initially presenting with SMUP compared to only 39% of females presenting with SMUP. This finding warrants further evaluation of the etiology of this difference, which may potentially be clinically significant.

INTRODUCTION

Skeletal metastases, a common finding in metastatic disease, indicate the widespread dissemination of disease and poor prognosis [Kodaira, 2010]. Bone metastases are associated with an overall median survival of 5 months after diagnosis with 5% 5 year- and 1% 10 year-survival rates [Destombe, 2007]. Much of the pain experienced by patients with metastatic cancer, which is unfortunately very common, is caused by their bone metastases [Cleeland, 2006]. Current management techniques include a combination of surgeries, medications (narcotics, bone strengthening agents), radiopharmaceuticals, high intensity focused ultrasound, chemotherapy, and radiation [Kang, 2017; Mavrogenis, 2016]. Palliative care is instrumental for the preservation of quality of life for patients, with the hope for better and curative therapies on the horizon. Large scale epidemiologic studies on the prevalence and characteristics of bone metastases are sparse. There have only been three previous published studies to characterize bone metastases that
have included those with unknown metastases. A study in Japan and France only characterized SMUP, while a study performed in India included patients with SMUP and known primaries in their data collection but did not use that data to distinguish any potential differences between the two groups [Destombes, 2007; Takagi, 2015; Zacharia, 2018]. In addition to studies’ limitations, there is limited utility in generalizing the findings of these studies to a population in the United States. There are two studies from the United States characterizing bone metastases, illuminating the distribution of primary lesions responsible for bone metastases, but they do not include patients for whom a primary was unknown [Li, 2012; Hernandez, 2018]. This study of patient characteristics, lesion characteristics, and long-term outcomes in individuals with SMUP compared to those with known primaries will address a knowledge gap in the characteristics of bone metastases in the United States.

METHODS

Study population: This single-center retrospective study sought to characterize the disease course of patients identified with bone metastases at Carilion Clinic from 12/01/2007 to 02/28/2018. Records in that time frame associated with the ICD9 code 198.5 (secondary malignant neoplasm of bone and bone marrow), ICD10 code C79.51 (secondary malignant neoplasm of bone), or ICD10 code C79.52 (secondary malignant neoplasm of bone marrow) were extracted from the Carilion Clinic electronic medical record (EMR) by Dr. Yan Zhang. A second review was then conducted to ensure the identified cases met all of the inclusion criteria. Statistical analyses on these data were performed as defined below.

Data Collection: The information from the charts was extracted manually and subsequently placed into three categories: patient characteristics, lesion characteristics, and long-term outcomes. Patient characteristic information included the age and sex of the patient, history of tobacco and alcohol use, HIV status, use of immune suppression therapy, body mass index (BMI), and family history of cancer. Lesion characteristic information included the site of the primary lesion, the time between identification of primary malignancy and identified metastatic disease, the number of metastases, and the location of metastases. The presence of metastases was diagnosed using definitive radiologic findings. Determination of death was limited: death was identified either through the patient’s chart or through an obituary with identifying information (such as birthday, location, name of family members mentioned in the chart) which corresponded to the time that new notes stopped being recorded in the EMR. If no death date in the chart and no identifying obituary were noted, the patient was presumed to be alive.

Statistical Analysis: Of the 207 patients identified from Carilion’s EMR, 164 were eligible for inclusion in this study. Most patients were excluded because they either were never diagnosed with bone metastases (having other diagnoses such as degenerative bone changes, primary bone cancer, and bone islands) or were diagnosed with bone metastases outside of the time frame of the study. Four patients with bone metastases were excluded from study as it was unknown from the chart review when the skeletal metastases occurred with respect to identification of the primary malignancy. Descriptive statistics were performed on the data sorted by patient characteristics and lesion characteristics discussed above.

Additionally, descriptive statistics were used to distinguish bone metastases with a known primary site (SMUP = no) from bone metastases with no known primary (SMUP = yes). A chi-square analysis was performed to identify if the following demographic and medical history variables changed between SMUP = no and SMUP = yes: gender, multiple metastases, tobacco, alcohol, immunosuppressant use, history of cancer, and death. Kaplan Meyer curves were created to compare survival times in patients with SMUP = no and SMUP = yes.

RESULTS

Patient Characteristics: This study found that there was no statistically significant difference between SMUP = no and SMUP = yes with respect to the following patient characteristics: age, tobacco use, alcohol use, illicit drug use, previous use of immune suppression therapy, BMI, family history of cancer, and HIV status. Interestingly, a higher percentage of men were found to have SMUP (60.7%) when compared to the known primary group (42.6%) with a p-value of 0.0277.

Lesion Characteristics

Primary malignancies associated with metastases: Primary sites were eventually identified in 97.6% of patients (Figure 1). In patients with a known primary when bone metastases were identified, the most common primary sites were lung (26.8%), breast (24.1%), and prostate (15.7%). The distribution of primary sites for patients initially presenting with SMUP was different, with lung (36.5%), prostate (17.3%), and breast (9.6%) having the highest incidence respectively. The primary lesions listed in the ‘other’ column include cholangiocarcinoma, neuroblastoma, rectal cancer, laryngeal cancer, gastrointestinal stromal tumor, bladder cancer, ovarian cancer, ureteral cancer, anaplastic large cell lymphoma, parotid adenoid cystic carcinoma, Hodgkin’s lymphoma, and several others with each of these diagnoses only having one accompanying patient.

![Figure 1](image.png)

Figure 1. The most common primary diagnoses in patients with bone metastases, further delineated on whether the primary was known (blue) or unknown (red) at time bone metastases were found. The three most common in both groups were lung, breast and prostate in various orders. For SMUP yes, “Other” is not counted as one of the most common as it comprises of a number of different primary types listed in the text above.

Number of metastatic lesions: A majority of patients in both SMUP yes and no presented with multiple metastases (Figure 2). A greater proportion of patients with SMUP (12.5%) presented with a single metastasis when compared to patients with known primary disease (8.3%). An ANOVA test showed no significance in these values.
It is important to note that a patient presenting with metastases in multiple bones had each site included in the analysis (for example, if a patient presented with metastases to the spine and ribs, then a count was given to the spine in addition to the ribs). This is the reason that the number of occurrences do not add up to the number of patients, as most patients presented with multiple sites.

**Long-term Outcomes:** Data about the survival time for each tumor type were collected and stratified according to SMUP status. Kaplan-Meyer analysis found no statistical significance in the overall survival between the groups. This analysis was then taken a step further, looking at whether there was a difference in survival time if the primary tumor had been diagnosed prior to the bone metastasis being found. In Figure 4, the Kaplan-Meyer curve depicts a statistically significant difference in the survival times between SMUP yes versus no, with patients having their primary site for cancer diagnosed prior to the discovery of bone metastasis demonstrating a longer survival time compared to those who received their primary diagnosis after the bone metastases were discovered.

**DISCUSSION**

**Patient Characteristics:** In this study population males are statistically significantly more likely to have an SMUP compared to females. This finding is in alignment with prior studies performed in Japan and France which investigated patients with SMUP only and found a male predominance. This male predominance is most likely due to a multifactorial process. This difference could be related to the fact that prostate cancer was more prevalent for patients presenting with SMUP than breast when compared to the known primary malignancy group. Another reason for this finding could be the differences in the known impacts between male and female specific screenings. This finding also leads to the question however of whether there is something inherent in men that predispose them to bone metastasis more quickly before a primary diagnosis can be made or whether there is a social factor in that men may not go to the doctor as quickly for symptoms.

**Lesions:** Only 34.1% of patients in this study presented with SMUP. Comparatively, the population in the bone metastasis study in India had 55% of patients identified with SMUP, highlighting the vast differences between the two populations studied and the importance of continuing these characterization studies in multiple locations. In the current study, the most frequent primary sites for patients with SMUP were lung, prostate, and breast carcinoma, as was found in French and Indian studies. The most frequent primary sites for patients with metastases of a known primary were lung, breast, and prostate – results that differ when compared to the results of the two large US studies which found breast, prostate, and lung cancer to be the most frequent cause of metastases of known primaries, respectively [Li, 2012; Hernandez, 2018]. This could be due to the geographical area in which this study was performed. As noted in a previous section, the variation in primary cancer between groups by SMUP status could also be a factor as to why more males were diagnosed with SMUP. This study also found that only 10.4% of patients were identified with a single bone metastasis, with the remaining patients having multiple metastases. It appeared that SMUP may more frequently present with an isolated metastases when compared to metastases from a known primary, however this was not a statistically significant finding.

**Site of metastases:** The most common location for metastases regardless of SMUP status was the spine, followed by the pelvis and the ribs (Figure 3). This distribution did not change when data were further stratified based on single or multiple metastases for SMUP status.
When looking at the location of metastases, this study is in alignment with previous studies in that the spine, followed by the pelvis, were the most common sites of location for bony metastases regardless of SMUP status and the number of metastases. This seems to suggest that for any type of cancer with bone metastases, there seems to be a preference for the spine and pelvis when the cancer is metastasizing to bone. It may be worthwhile in future research to investigate whether there are certain characteristics of these locations that make it more likely for a cancer to metastasize to these areas and whether there is something that can be done to mitigate this risk of metastasis.

**Long-Term Outcomes:** This study analyzed the survival time of the patients whereas the other studies on SMUP did not include this information. The general trend showed that those who were SMUP = yes had a shorter survival time from the time of diagnosis of their primary lesion when compared to those who were SMUP = no. This is a reflection of the reality that patients with a known primary site have interventions prior to the onset of the bone metastases. As a result, patient’s presenting with SMUP have a shorter survival time. However, there was no statistical difference in survival time from the time of diagnosis of the bone metastasis, showing that whether or not the primary lesion is known, the diagnosis of bone metastasis carries a poor prognosis.

**Limitations:** One of the limitations of this study is the process of death determination. There were inconsistencies in the reporting and there was also the assumption that if there was no notification in the chart nor was there an obituary that the patient was still alive, which could potentially be untrue. Obituaries are not required announcements of death so a patient’s family could plausibly not have submitted their loved one for that announcement. Additionally, this study only applies to patients who present at Carilion Clinic. Therefore, conclusions should not be drawn from our statistics about larger populations. Lastly, some of the groups included had such low numbers that there was no possibility determining any statistical significance to those findings. The limitations of this study make our study an exploratory analysis. We are interested in identifying signs of potential associations that might be useful in guiding future research for potential patient identification and diagnostic guidelines in similar areas with rural patient populations.

**Conclusions**

Overall, this study showed that men were found to have SMUP more often than women. The data also showed that the most common primary cancers in the study’s population with bone metastases were lung, breast, and prostate; however, this does change when stratified based on SMUP status. Bone metastases most commonly present in multiple locations with the preferred location being the spine, pelvis, and ribs regardless of SMUP status. Additionally, it was found that when the primary diagnosis is identified prior to metastases, the survival time is longer. Once bone metastases are identified, there is no difference in survival, regardless of whether the primary lesion is known.

**Future Directions**

Currently, having bone metastasis is a very poor prognostic factor for those with cancer [Kodaira, 2010]. As we have gathered more data characterizing the features of bone metastasis with known and unknown primaries, future work can be geared towards investigating why males more commonly present with SMUP. Another interesting study would be to investigate why there is preferential location for bone metastases to the spine. Expanding this study to include other institutions would be beneficial as well so the findings could represent a larger population.

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**Key Points**

- Male predominance in the skeletal metastasis of unknown primary group that was statistically significant. The implications of this finding are uncertain at this time, requiring further investigation.
- Most common known primaries with metastases were lung, breast, and prostate cancer, differing from previous US data.
- Most common unknown primaries with metastases were lung, prostate, and breast cancer, mirroring data in France and India.

**Glossary of Abbreviations**

- **BMI** = body mass index
- **EMR** = electronic medical record
- **SMUP** = skeletal metastasis of unknown primary

**REFERENCES**


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