Downstream Studies Following the Use of Bone Scan in the Staging of Muscle-invasive Bladder Cancer

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OBJECTIVE To quantify the use of downstream studies following staging bone scans in patients with muscle-invasive bladder cancer. Bone scans may be obtained in high-risk bladder cancer patients prior to radical cystectomy to exclude bone metastases. However, false-positive bone scans can occur, resulting in the need for additional studies.

PATIENTS AND METHODS Using Surveillance, Epidemiology, and End Results (SEER)-Medicare data, we identified 4404 patients diagnosed with muscle-invasive bladder cancer from 2004 to 2011. We further identified those who underwent a bone scan prior to treatment within 6 months of diagnosis and prior to any treatment with cystectomy, radiotherapy, or chemotherapy. We determined the proportion of patients who underwent a subsequent study (bone X-ray, bone CT, bone MRI, and/or bone biopsy) within 3 months of the bone scan and prior to treatment.

RESULTS Among patients diagnosed with muscle-invasive bladder cancer, 1373 (31%) had a staging bone scan of whom 26% received a downstream study (n = 213). Overall, 61 patients (7%) received downstream bone-specific X-rays, more than 141 patients (>17%) received bone-specific CTs, and 28 patients (3%) received bone-specific MRIs. The use of bone biopsy was rare ($n < 11$; <1%). The total cost of all downstream studies was $103,468. Furthermore, there was a one-month delay in treatment for those who received a downstream study compared to those who did not ($P < 0.001$).

CONCLUSION Use of bone scan in the staging of muscle-invasive bladder cancer often results in the need for additional downstream studies. The delay in treatment and cost burden of downstream studies highlights a potential disadvantage of the routine use of this staging modality. UROLOGY 129: 74−78, 2019.

Bladder cancer is an aggressive disease with an estimated 10%-15% of patients presenting with metastatic disease at the time of diagnosis. Among patients with metastases, as many as 70% have bone involvement.[1] Thus, bone scintigraphy (bone scan) may be used to detect metastatic disease at the time of diagnosis, particularly in patients with high-risk disease (eg, those with advanced stage or atypical histology).

While bone scan is the most widely used modality for detecting of skeletal metastasis,[2] its value in preoperative staging of bladder cancer is unclear. On the one hand, bone scan is highly sensitive and can help detect early bone metastasis, thereby avoiding unnecessary surgery. On the other hand, this modality has a high false positive rate due to tracer uptake by many benign lesions, resulting in a specificity as low as 48%.[3] Furthermore, there is no correlation between precystectomy bone scan and clinical course of disease, even when using alkaline phosphatase to improve accuracy.[4] The majority of suspicious bone scan findings in one study were consistent with degenerative changes on radiographs and rarely altered patient treatment.[4] This ambiguity in the interpretation of bone scan may result in additional imaging, such as bone X-ray, bone computed tomography (CT), bone magnetic resonance imaging (MRI), and bone biopsy to further evaluate bone scan findings. Related to this, these additional tests increase costs. The burden of these additional studies has not been evaluated.

For this reason, we aim to quantify the use of downstream studies following staging bone scan in patients

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with muscle-invasive bladder cancer. Understanding the burden of these downstream studies may help refine preoperative bone scan use in this patient population.

MATERIALS AND METHODS

Data Sources and Study Population

Using Surveillance, Epidemiology, and End Results (SEER)-Medicare data, we identified patients diagnosed with muscle-invasive bladder cancer between 2004 and 2011. We included patients between the ages of 66 and 99 who were continuously enrolled in Medicare Parts A and B during the 12 months before and 9 months after diagnosis. We excluded patients participating in a health maintenance organization or Medicare Part C to ensure all health care was ascertained. We also excluded patients diagnosed at autopsy or death and those with another diagnosis of a nonurothelial malignancy prior to or at the time of diagnosis.

Patient demographic and pathological information was obtained using the SEER Patient Entitlement and Diagnosis Summary File (PEDSF).[1] As part of the demographic information, local census tract information (ie, percentage of ZIP code population with at least a high school education, population of the county of residence, and the median household income within the ZIP code) was obtained. Geographic region (northeast, south, central, west) was categorized based on SEER region at the time of the bladder cancer diagnosis that most closely preceded surgery. Tumor stage was based on the American Joint Committee on Cancer, 6th ed. TNM stage data derived through the SEER Collaborative Stage algorithm.[3,4]

Patients were included in the study if they completed a bone scan within 6 months of diagnosis and prior to any treatment with cystectomy, radiotherapy, or chemotherapy. Bone scan (including single-photon emission computed tomography [SPECT]) use was identified in the Medicare outpatient and carrier files by using Healthcare Common Procedure Coding System (HCPCS) codes 78300, 78305, 78306, 78315, and 78320. Treatment assignment was determined using relevant HCPCS codes in the outpatient and carrier files within 9 months of diagnosis. In the case where multiple treatments occurred following diagnosis, treatment was hierarchically assigned: cystectomy was preferred over radiotherapy, which was preferred over chemotherapy.

Outcomes

The primary outcome was completion of a downstream study within 3 months of the bone scan and prior to any treatment. We define a downstream study to include bone computed tomography (CT), bone X-ray, bone MRI, and bone biopsy (Supplemental Table). Medicare payments for each study were identified using the outpatient and carrier files.

Statistical Analysis

The study population was stratified by completion of a downstream study. Demographic, socioeconomic, and pathologic characteristics of the study population were compared between groups using chi-square tests.

The number and proportion of patients who underwent each downstream study was determined and the total number of each study was recorded. The average number of studies per patient and cost of each study per patient were calculated. Payments were standardized to 2012 dollars using the Medicare Economic Index for Part B claims to account for changes in price inflation and rounded to the nearest dollar. The median time in months was calculated from the data of diagnosis to the date of treatment (cystectomy, radiation, or chemotherapy) for those who received downstream studies and those who did not.

Statistical analyses were performed using R (version 13.2)[7] using the packages dpylr[8] for data management and compareGroups[9] for descriptive tables. Statistical significance was defined as $P < 0.05$. The University of Pittsburgh institutional review board deemed that this study was exempt from review.

RESULTS

The demographic, clinical, and pathological information for the cohort is summarized in Table 1. We identified 4404 patients diagnosed with muscle-invasive bladder cancer between 2004 and 2011, of whom 835 patients received a bone scan. Of those who completed a bone scan, 213 (26%) patients had a downstream study. Patients who had a downstream study had greater comorbidity, resided in less densely populated counties, and lived in ZIP codes with higher median household income (all $P < 0.05$). There were also regional differences in use of downstream studies ($P = 0.04$). Patients who underwent downstream studies were less likely to receive cystectomy or radiation and more likely to have metastatic disease at diagnosis ($P < 0.001$). The time from diagnosis to treatment among those who received a downstream study was 1 month longer compared to those who did not have a downstream study ($P < 0.001$).

The frequency and costs of downstream studies in patients are summarized in Table 2. Of the 835 patients who received a bone scan, 61 (7%) had a subsequent bone radiograph, more than 141 (>17%) had a bone CT, 28 (3%) had a bone MRI, and less than 11 (<2%) had a bone biopsy. In 35.7% of cases (n = 76), more than one downstream study was required for a given patient. In total, there were 101 bone radiographs, 188 bone CTs, 39 bone MRIs, and less than 11 patients had bone biopsies. The total cost of all downstream studies in this analysis was $103,468. The cost of downstream bone CTs was $57,829. The total costs of bone X-ray and bone MRI were $19,122 and 21,925, respectively. The total cost of bone biopsies was $4,591. This corresponded to a cost per-patient of approximately $300 for bone radiograph and $800 for bone MRI.

DISCUSSION

In this population-based cohort, almost one-third of patients completed a bone scan at the time of diagnosis. Of these patients, 26% had a downstream study (ie, bone radiograph, bone CT, bone MRI, or biopsy). Patients who had downstream studies were less likely to receive cystectomy or radiation (as opposed to chemotherapy) and more likely to have metastatic disease at diagnosis.

Over a quarter of patients who received a bone scan had a downstream study. There are several potential reasons for this high frequency. First, the precision of bone scan is poor because benign diseases can mimic metastasis.[5-8] In such instances, additional imaging is required to characterize these equivocal bone scan findings.[9] Second, bone scan requires osteoblastic activity to detect abnormalities; therefore low-volume lesions confined to the marrow can go undetected.[10,11] Third, due to this lack of

Table 1. Demographic, socioeconomic, and pathological characteristics of the study population

Characteristics	No Downstream Procedure (*N* = 622)	Downstream Procedure (*N* = 213)	*P* Value*
Age at diagnosis (%)			0.10
66-69	115 (19)	37 (18)	
70-74	142 (23)	60 (29)	
75-79	143 (23)	57 (27)	
80 or more	219 (35)	57 (27)	
Sex (%)			0.75
Male	411 (66)	144 (68)	
Female	211 (34)	69 (32)	
Race (%)			0.25
White	529 (85)	188 (88)	
Non-white	93 (15)	25 (12)	
Comorbidity (%)			0.03
0	343 (56)	95 (45)	
1	160 (26)	66 (31)	
2	55 (9)	30 (14)	
3 or more	58 (9)	20 (9)	
Marital status (%)			0.04
Married	351 (56)	137 (64)	
Not married/unknown	271 (44)	76 (36)	
*Education level (%)***			0.78
Low (<75% with high school education)	76 (12)	28 (13)	
High (>75% with high school education)	541 (88)	181 (87)	
County of residence population (%)			0.04
1,000,000 or more	352 (57)	110 (52)	
250,000-999,999	127 (20)	36 (17)	
Less than 250,000	143 (23)	67 (32)	
*Median household income (%)***			0.03
$45,000 or less	200 (32)	83 (40)	
$45,001-$60,000	1152 (31)	564 (33)	
More than $60,000	1191 (32)	593 (35)	
U.S. geographic region (%)			0.03
Northeast	189 (30)	66 (31)	
South	118 (19)	31 (15)	
Central	66 (11)	38 (18)	
West	249 (40)	78 (37)	
Year of diagnosis (%)			0.63
2004	82 (13)	31 (15)	
2005	95 (15)	30 (14)	
2006	66 (11)	33 (16)	
2007	85 (14)	28 (13)	
2008	79 (13)	28 (13)	
2009	62 (10)	21 (10)	
2010	88 (14)	24 (11)	
2011	65 (11)	18 (8)	
Treatment (%)			<0.001
Cystectomy	311 (50)	94 (44)	
Radiation	241 (39)	70 (33)	
Chemotherapy	70 (11)	49 (23)	
Months from diagnosis to treatment (IQR)	2 (1.3-3)	3(2-5)	<0.001
T stage (%)			0.59
T2	426 (69)	146 (69)	
T3	125 (20)	38 (18)	
T4	71 (11)	29 (16)	
N stage (%)			0.63
N0/NX	512 (82)	172 (81)	
N+	95 (15)	29 (14)	
M stage (%)			<0.001
M0/MX	592 (92)	181 (85)	
M+	30 (5)	32 (15)	

Percentages might not sum to 100 because of rounding.
* *P* values determined using Chi-square tests.
** Education level and median household income of the ZIP code of residence

Table 2. Frequency and cost of downstream procedures among 835 patients who underwent a bone scan following diagnosis of muscle-invasive bladder cancer

Downstream Procedure	Patients (*N* = *835*)	Procedures	Procedures per Patient	Total Cost* ($)	Cost per Patient ($)
Bone radiograph	61 (7)	101	1.7	19,122	313
Bone CT	>141 (>17)	>183	>1.2	57,829	**
Bone MRI	28 (3)	39	1.4	21,926	783
Bone biopsy	<11 (<2)	<11	<1.0	4,591	**
Any	213 (26)	334	1.6	103,468	486

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging
Total Medicare payments obtained from outpatient and carrier files. Payments were standardized to 2012 dollars using the Medicare Economic Index for Part B claims to account for changes in price inflation and rounded to the nearest dollar. Percentage is calculated from number of downstream procedures divided by total number of patients (835).
** Exact numbers not shown to be compliant with SEER-Medicare guidelines.

specificity, there can be difficulty in the interpretation of bone scan results, and in fact, such uncertainty has been observed in prior studies.[9,10,12] For these reasons, additional correlative imaging may often be required following bone scan. Despite this, we have shown that bone scan continues to be frequently used in the preoperative setting, with significant provider and regional variation.[13] Several studies have suggested that bone scan may not even be the optimal test for detection of bone metastasis. MRI was found to detect bone metastasis when bone scan failed to do so, and may offer greater sensitivity.[10,14,15,16]

There was variation in the type of downstream study used. MRI may offer increased sensitivity; however, CT scan was used more frequently than MRI as a downstream study (17% vs 3%) in our study. Spiral CT scan allows for imaging of the entire skeleton while minimizing superposition effects.[17] While CT is highly sensitive for cortical deformities, it is more difficult to detect tumors within the marrow space.[17] With a combination of positron emission tomography and CT, PET/CT offers both pharmacokinetic characteristics and anatomic localization, potentially increasing its accuracy in bone metastasis detection. In a meta-analysis examining imaging modalities for screening of bone metastasis, MRI and PET/CT were found to be more accurate compared to CT and bone scan.[18] These findings were recapitulated in a study of metastatic breast cancer.[17,19] While we are unable to discern the rationale for choosing a particular downstream study, CT scan may be more common given its general availability, low cost, and routine use in cancer staging. Furthermore, detection of bone metastasis using MRI generally requires a whole body scan, which can be costly, less accessible, and not always covered by insurance.[20]

Timely treatment is critical for muscle-invasive bladder cancer. Studies have shown that delaying cystectomy more than 3 months can result in pathologic upstaging and decreased survival.[21,22] In this study, we found that those who underwent a downstream study had a delay of 1 month from time of diagnosis to any treatment, including cystectomy. Studies examining delays in care have identified interdisciplinary coordination, staging studies, preoperative evaluations, and scheduling as common causes of delay.[23] Some steps in this process may be unnecessary or inefficient, and therefore offer opportunities to optimize our diagnostic pathways and improve outcomes. For instance, more stringent guidelines regarding indications for bone scan use may help avoid unnecessary imaging and downstream studies, ultimately preventing delay in definitive therapy.

Utilization of diagnostic imaging has been increasing dramatically over the years, resulting in an estimated cost of 100 billion dollars annually.[24,25] In our analysis, additional downstream studies resulted in an added cost of $486 per patient, totaling just over $100,000 throughout the study period. This suggests that bone scan often comes with an unrecognized cost in addition to the cost of the bone scan itself. Although modest, these costs may actually be unnecessary and even avoided if there was better standardization leading to more prudent bone scan use. A similar analysis performed in prostate cancer revealed additional spending of 2 million dollars per year from downstream studies after bone scan.[26] These additional costs must be considered in relation to the overall costs of treating muscle-invasive bladder cancer, which includes $39,651 in direct 90-day hospital costs per radical cystectomy performed.[27]

These findings should be considered in the context of several limitations. First, we used Medicare hospitalization claims, which may limit the generalizability of our findings. However, the majority of patients with bladder cancer are in the seventh decade of life or older and have Medicare coverage. Second, due to limitations in the use of claims data, the analysis could not include details about the indications or results of the downstream studies. However, bone biopsy was the least prevalent downstream study, which may suggest that the other less invasive downstream studies were likely to clarify presence of metastatic bone disease. Lastly, this is a retrospective observational study, and therefore is limited by unmeasured variables, including availability of imaging facilities and patient travel distance. However, since these studies are billable events, we feel we are adequately capturing patients who underwent downstream studies.

The use of bone scan in the staging of muscle-invasive bladder cancer often results in the need for additional downstream imaging. The cost burden of this downstream imaging and delay to treatment highlight potential disadvantages of the routine use of this staging modality. Further studies examining the utility of bone scan in the staging setting would be useful to help avoid potentially unnecessary cost to our health system.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.04.009.

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