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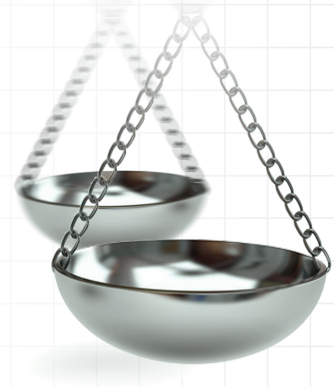

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Population-based validation of the National Comprehensive Cancer Network recommendations for baseline imaging for bladder cancer: a case for routine baseline bone scan?

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Aim: This study aims at evaluating the performance of some of the imaging recommendations of the National Comprehensive Cancer Network (NCCN) for initial evaluation of bladder cancer. **Methods:** Surveillance, epidemiology and end results program (2010–2015) was queried and patients with clinically (T1–T4) bladder cancer and complete information about clinical T/N (tumor/nodal) stage and metastatic sites were extracted. The following characteristics were evaluated in the current analysis: sensitivity, specificity, number needed to investigate (NNI), positive predictive value (PPV), negative predictive value and accuracy. **Results:** According to the current NCCN guidelines, PPV (for the recognition of lung metastases) is 4.7% and NNI to detect one case of lung metastasis is 21.2. Similarly, PPV (for the recognition of liver metastases) is 3.1% and NNI to detect one case of liver metastasis is 32.2. Using a different imaging threshold (i.e., routinely imaging all patients >T2N0), PPV (for the recognition of lung metastases) is 10.4% and NNI to detect one case of lung metastasis is 9.6. Similarly, PPV (for the recognition of liver metastases) is 7% and NNI to detect one case of liver metastasis is 14.2. The above two thresholds were also evaluated for routine bone scanning. PPV (for the detection of one case of bone metastasis) is 5.3% using the first threshold and 11.2% using the second threshold. **Conclusion:** Imaging per current NCCN guidelines results in few patients with undetected asymptomatic lung or liver metastases. A routine baseline bone scan should be additionally considered for some asymptomatic patients with muscle-invasive disease.

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Initial assessment of newly diagnosed patients with urinary bladder carcinoma should encompass the assessment of patient-related factors, disease-related factors and potential treatment-related factors [1]. Important patient-related factors would include age and comorbidity status, while important disease-related factors would include disease biology and disease extent [2]. In order to properly assess disease extent, baseline staging investigations are important to identify possible sites of metastatic disease [3,4].

Current national comprehensive cancer network (NCCN) recommendations for initial staging of bladder cancer propose a simplified risk-based approach whereby chest and abdominal/pelvic imaging is recommended for all patients >T1N0 disease. Bone imaging is, however, only recommended among patients with symptoms suggestive of bone metastasis [5]. These recommendations were echoed by a number of other international societies interested in streamlining urologic oncology practice (like the European Association of Urology and European Society of Medical Oncology) [6–8].

Given the prevalence of bladder cancer, there are huge medical and cost consequences of these recommendations [9]. It is thus important to assess the performance characteristics of these recommendations in a population-based setting and this is the aim of the current study. Such an assessment will hopefully outline the potential

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weaknesses and strengths of this approach and might lead to an improvement of the current staging algorithm for those patients. The current study hypothesizes that routine baseline bone scan might be warranted in some asymptomatic patients with locoregionally advanced bladder cancer.

Methodology

Study cohort selection

Within the Surveillance, epidemiology and end results (SEER) database, bladder cancer cases (T1–T4) diagnosed from 2010–2015 were selected. Cases with Ta or Tis disease were not included in the current cohort. This time period was selected because detailed information about metastatic sites was not available before these years. The selection criteria also included complete data about clinical T/N stage and sites of metastases (bone, brain, liver or lung). Surgical pathology T/N stages were not considered in the current analysis. SEER-18 registry was used to extract these data [10], and SEER*Stat software (Version 8.3.5) was used to perform this extraction. In this manuscript, all assessments of clinical staging as well as sites of distant metastasis refer to the status at diagnosis (i.e., at baseline).

Assessment of the NCCN baseline imaging recommendations

A number of analyses were considered in this study. These relate to the assessment of the performance characteristics of current NCCN bladder cancer recommendations for the detection of lung and liver metastases (i.e., routinely imaging all patients >T1N0 disease). Moreover, another imaging threshold was examined that entailed imaging all patients >T2N0.

Additionally, assessment of hypothetical recommendations for bone imaging using either one of the above two thresholds was conducted (i.e., either imaging all patients >T1N0 or imaging all patients >T2N0).

Data collection & statistical calculations

The following data were collected from each case within the study cohort: age, race, gender, histology, grade, subsite within the bladder, clinical stage, treatments offered (including surgery, radiotherapy and/or chemotherapy), bone, brain, liver and lung metastases. Descriptive analyses were then performed to illustrate the frequencies and proportions of different baseline characteristics. Performance characteristics for different imaging thresholds among different metastatic sites were then evaluated. These performance characteristics included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), number needed to investigate (NNI) and accuracy. SPSS statistics 20.0 (IBM, NY, USA) was used to perform all the calculations (Table 1).

Results

Patient characteristics

After excluding patients with insufficient data sites of distant metastases and clinical T/N stage, a total of 38,561 patients were included in the study. Urothelial carcinoma represented the majority of cases (92.6%) and age group ≥70 years represented the majority of cases (64.6%). The white race represented 87.8% and males represented 76.2% of the study population. Most patients have high-grade disease according to International society of urologic pathology (ISUP) grading system (76.7%). Details of clinical stages, as well as subsites, were summarized in Table 2. In this cohort of patients, bone metastases were reported in 2.4% of patients, liver metastases in 1.5% of patients, lung metastases in 2.2% of patients and brain metastases in 0.2% of patients.

Assessment of NCCN baseline imaging recommendations for chest & abdominal imaging

Among included patients in this analysis, 23,652 patients (61.3%) have a T1N0 disease (thus, chest and abdominal imaging should not be recommended as per the NCCN recommendations), while 14,909 (38.7%) have a more advanced disease (i.e., routine imaging would be recommended).

Using NCCN guidelines, 152 patients (0.3%) with lung metastases would have been missed, and 104 patients (0.2%) with liver metastases would have been missed. Meanwhile, 14,205 patients (36.8%) would have chest imaging in the absence of lung metastases, and 14,451 patients (37.4%) would have abdominal imaging in the absence of liver metastases.

This means a PPV (for the recognition of lung metastases) of 4.7% and NNI to detect one case of lung metastasis of 21.2. Similarly, this results in a PPV (for the recognition of liver metastases) of 3.1% and NNI of 32.2 to

Table 1. Baseline characteristics of included patients in the study (n = 38,561 patients).

Parameter	N (%)
Race	
White	33,849 (87.8%)
Black	2648 (6.9%)
Others	1794 (4.7%)
Unknown	270 (0.6%)
Sex	
Females	9159 (23.8%)
Males	29,402 (76.2%)
Age	
<40 years	156 (0.4%)
40–69 years	13,492 (35%)
≥70 years	24,913 (64.6%)
Subsite	
Trigone	2242 (5.8%)
Dome	1642 (4.3%)
Lateral wall	6957 (18%)
Anterior wall	1036 (2.7%)
Posterior wall	3364 (8.7%)
Bladder neck	1386 (3.6%)
Ureteric orifice	880 (2.3%)
Urachus	32 (0.1%)
Overlapping lesion	4857 (12.6%)
Bladder, NOS	16,147 (41.9%)
ISUP grade	
Low grade	3558 (9.2%)
High grade	29,569 (76.7%)
Unknown	5434 (14.1%)
Histology	
Urothelial carcinoma	35,684 (92.6%)
Nonurothelial carcinoma	2877 (7.4%)
Clinical stage	
T1N0	23,652 (61.3%)
T2N0	10,888 (28.2%)
>T2N0	4021 (10.4%)
Radical surgery	
No	36,863 (95.6%)
Yes	1650 (4.3%)
Unknown	48 (0.1%)
Chemotherapy	
Yes	12,087 (31.3%)
No/unknown	26,474 (68.7%)
Radiotherapy	
Yes	4166 (10.8%)
No/unknown	34,395 (89.2%)
Bone metastases	
Yes	941 (2.4%)
No	37,620 (97.6%)
Brain metastases	
Yes	67 (0.2%)
No	38,494 (99.8%)
Liver metastases	
Yes	562 (1.5%)
No	37,999 (95.8%)
Lung metastases	
Yes	856 (2.2%)
No	37,705 (97.8%)

ISUP: International society of urologic pathology; N: Number; T/N: Tumor/nodal.

detect one case of liver metastasis. Additional performance characteristics including sensitivity, specificity, NPV and accuracy were detailed in Table 2.

Table 2. Recommendations for chest and abdominal imaging according to National comprehensive cancer network bladder cancer guidelines.

	Reference: Lung metastases as shown on chest imaging		NNI (1/PPV) 21.2
Lung metastases (856 patients)	**No lung metastases (37,705 patients)**		
Chest imaging recommended (14,909 patients)	TP N = 704 patients	FP N = 14,205 patients	PPV = TP/(TP+FP) 4.7%
Chest imaging not recommended (23,652 patients)	FN N = 152 patients	TN N = 23,500 patients	NPV = TN/(TN+FN) 99.4%
	Sensitivity = TP/TP+FN 82.2%	Specificity = TN /FP+TN 62.3%	Accuracy (TN+TP/All) 62.7%
Reference: Liver metastases as shown on abdominal imaging		**NNI (1/PPV) 32.2**	
Liver metastases (562 patients)	**No liver metastases (37,999 patients)**		
Abdominal imaging recommended (14,909 patients)	TP N = 458 patients	FP N = 14,451 patients	PPV = TP/(TP+FP) 3.1%
Abdominal imaging not recommended (23,652 patients)	FN N = 104 patients	TN N = 23,548 patients	NPV = TN/(TN+FN) 99.6%
	Sensitivity = TP/TP+FN 81.5%	Specificity = TN /FP+TN 62%	Accuracy (TN+TP/All) 62.2%

FN: False negative; FP: False positive; NNI: Number needed to investigate; NPV: Negative predictive value; PPV: Positive predictive value; TN: True negative; TP: True positive.

Table 3. Modified recommendations for chest and abdominal imaging (excluding T2N0 cases from routine imaging).

	Reference: Lung metastases as shown on chest imaging		NNI (1/PPV) 9.6
Lung metastases (856 patients)	**No lung metastases (37,705 patients)**		
Chest imaging recommended (4021 patients)	TP N = 419 patients	FP N = 3602 patients	PPV = TP/(TP+FP) 10.4%
Chest imaging not recommended (34,540 patients)	FN N = 437 patients	TN N = 34,103 patients	NPV = TN/(TN+FN) 98.7%
	Sensitivity = TP/TP+FN 48.9%	Specificity = TN /FP+TN 90.4%	Accuracy (TN+TP/All) 89.5%
Reference: Liver metastases as shown on abdominal imaging		**NNI (1/PPV) 14.2**	
Liver metastases (562 patients)	**No liver metastases (37,999 patients)**		
Abdominal imaging recommended (4021 patients)	TP N = 280 patients	FP N = 3741 patients	PPV = TP/(TP+FP) 7%
Abdominal imaging not recommended (34,540 patients)	FN N = 282 patients	TN N = 34,258 patients	NPV = TN/(TN+FN) 99.2%
	Sensitivity = TP/TP+FN 49.8%	Specificity = TN /FP+TN 90.2%	Accuracy (TN+TP/All) 89.5%

FN: False negative; FP: False positive; NNI: Number needed to investigate; NPV: Negative predictive value; PPV: Positive predictive value; TN: True negative; TP: True positive.

Assessment of modified baseline imaging threshold for chest & abdominal imaging

A proposed alternative imaging threshold would exclude patients with T1N0/T2N0 from a routine chest and abdominal imaging. Among included patients in this analysis, 34,540 patients (89.5%) have T1N0/T2N0 disease (thus, chest and abdominal imaging should not be recommended as per the alternative threshold), while 4021 (10.5%) have a more advanced disease (i.e., routine imaging would be recommended).

Using this alternative threshold, 437 patients (1.1%) with lung metastases would have been missed, and 282 patients (0.7%) with liver metastases would have been missed. Meanwhile, 3602 patients (9.3%) would have chest imaging in the absence of lung metastases, and 3741 patients (9.7%) would have abdominal imaging in the absence of liver metastases.

This means a PPV (for the recognition of lung metastases) of 10.4% and NNI to detect one case of lung metastasis of 9.6. Similarly, this results in a PPV (for the recognition of liver metastases) of 7% and NNI of 14.2 to detect one case of liver metastasis. Additional performance characteristics including sensitivity, specificity, NPV and accuracy were detailed in Table 3.

Table 4. Hypothetical recommendations for routine bone imaging (first rows: excluding T1N0 from routine imaging; second rows: excluding T1N0/T2N0 from routine imaging).

	Reference: Bone metastases as shown on bone scan		NNI (1/PPV) 18.8
Bone metastases (941 patients)	No bone metastases (37,620 patients)		
Bone imaging recommended (14,909 patients)	TP N = 796 patients	FP N = 14,113 patients	PPV = TP/(TP+FP) 5.3%
Bone imaging not recommended (23,652 patients)	FN N = 145 patients	TN N = 23,507 patients	NPV = TN/(TN+FN) 99.4%
	Sensitivity = TP/TP+FN 84.6%	Specificity = TN /FP+TN 62.5%	Accuracy (TN+TP/All) 63%
Reference: Bone metastases as shown on bone scan		NNI (1/PPV) 8.9	
Bone metastases (941 patients)	No bone metastases (37,620 patients)		
Bone imaging recommended (4021 patients)	TP N = 450 patients	FP N = 3571 patients	PPV = TP/(TP+FP) 11.2%
Bone imaging not recommended (34,540 patients)	FN N = 491 patients	TN N = 34,049 patients	NPV = TN/(TN+FN) 98.6%
	Sensitivity = TP/TP+FN 47.8%	Specificity = TN /FP+TN 90.5%	Accuracy (TN+TP/All) 89.5%

FN: False negative; FP: False positive; NNI: Number needed to investigate; NPV: Negative predictive value; PPV: Positive predictive value; TN: True negative; TP: True positive.

Assessment of hypothetical baseline imaging thresholds for routine bone imaging

Current NCCN guidelines recommend bone scan only if there are suggestive clinical findings. Based on the observation that bone metastases were reported in this cohort at a frequency higher than liver and lung metastases, it was reasonable to explore the performance characteristics of two hypothetical imaging thresholds for a routine bone scan. These two imaging thresholds include either doing a routine bone scan for all cases, except T1N0 patients or routine bone scan for all cases, except T1N0/T2N0.

Using the first threshold (all patients except T1N0), PPV (for the detection of one case of bone metastasis) is 5.3% and NNI to detect one case of bone metastasis is 18.8. Likewise and using the second threshold, PPV (for the detection of one case of bone metastasis) is 11.2% with NNI to detect one case of bone metastasis of 8.9. Other performance characteristics of both thresholds (including sensitivity, specificity, NPV and accuracy) are detailed in Table 4.

Discussion

Overall, the current analysis suggests that the current NCCN baseline imaging recommendations for bladder cancer provide a reasonable paradigm to the initial evaluation of bladder cancer patients. In a population-based setting, adherence to these guidelines would lead to few patients with undetected asymptomatic lung or liver metastases. These findings are reassuring to the oncologists and urologists managing bladder cancer. On the other hand, the current analysis shows that routine bone scan might be considered among patients with muscle-invasive disease (especially those with ≥T3 and/or node-positive disease).

Current NCCN guidelines also do not support routine brain imaging in the initial staging of asymptomatic patients. Given the overall low incidence of brain metastases in the current population-based cohort, this recommendation seems reasonable and should not be altered.

Accurate assessment of the true extent of disease is a fundamental step in the evaluation of newly diagnosed bladder carcinoma cases. A balanced approach to the initial staging of bladder cancer is important in order to ensure that cases with metastatic disease are not offered unnecessary and overly morbid radical surgeries, and meanwhile to ensure that cases with early-stage disease are not overwhelmed with unnecessary over investigations.

A number of weaknesses have to be noted in the current analysis. Foremost, the current study is based on cases diagnosed and treated within the USA. Thus, the generalizability of the results of the current analysis to other jurisdictions needs to be done with caution. Second, there is no detailed information about the type and extent of investigations that helped to decide local stage of the disease in each patient as well as whether he/she does or does not have a distant metastatic disease. However, it is expected that the vast majority of patients diagnosed and treated within community/academic centers in the USA would have been adequately staged and assessed prior to starting treatment. Third, the SEER database does not include information on symptoms. Patients with bone

metastases who are technically (according to the NCCN guidelines) not candidates for staging imaging studies may have symptoms, which would mandate imaging studies.

These weaknesses should be viewed in the context of the strengths of the current study. Most importantly, the utilization of such a large dataset which is derived from the SEER database with its well-known rigorous quality assurance process is a major point of strength. Another relevant strength is the ability of the SEER database to provide adequate information about the type of initial staging approach of each patient (i.e., clinical or pathological or pathological after neoadjuvant treatment). This is in contrast to the majority of other institutional or population-based datasets, which report only surgical pathology staging. Reliance on clinical staging in the current analysis would allow the proper simulation to real-life clinical situations where bladder cancer patients present initially with cystoscopic and pelvic imaging findings and cases are then discussed in the multidisciplinary team to evaluate future staging and treatment options.

It has to be noted also that although the main reason behind the chest and abdominal imaging is to identify lung and liver metastases (respectively), other distant sites of metastases might be identified through the chest and abdominal imaging (including distant lymph nodes and adrenal metastases). Moreover, abdominal imaging for urothelial carcinoma of the bladder might serve as a screening investigation for possible second primary urothelial carcinoma as well as concurrent urological or vascular abnormalities. Unfortunately, it is not possible to quantify accurately the number of cases with adrenal or distant abdominal/ thoracic lymph nodes within the current SEER dataset. Thus, it is not possible to assess the added benefit of these imaging investigations in terms of recognizing these additional sites of metastases. It has to also be noted that because of the common risk factors between lung and bladder cancer, routine chest imaging in those cases might work as a screening test for potential second primary lung cancer.

An important question that remains unanswered within the current study is whether we should accept the current threshold proposed by the NCCN guidelines (i.e., imaging all patients >T1N0)? This is particularly relevant given the improvement in specificity and PPV with excluding T2N0 from routine investigations (at the expense of worsening sensitivity).

While improving performance characteristics of the current staging approach of bladder cancer is a legitimate end point, other important end points need also to be considered.

These include the economic costs associated with routinely investigating all patients with a muscle-invasive disease, the rare – but possible – dangers from excessive radiation exposure and contrast administration from contrast-enhanced imaging as well as the psychological burden entailed within each new investigation/procedure that the patient is exposed to [11]. Another important point to be considered might be related to the impact of metastatic disease finding on therapeutic decision making in bladder cancer. Discovery of one site of metastatic disease would most probably lead to exclusion of radical cystectomy as a potential therapeutic option. This also has important cost and quality considerations both to individual patients as well as the whole healthcare system.

Another important aspect of the current NCCN approach for bladder cancer imaging might be related to the suboptimal performance of current pelvic imaging technologies to identify local/nodal extent of bladder cancer. This is another area of improvement in the future that needs to be considered.

In conclusion, imaging per current NCCN guidelines results in few patients with undetected asymptomatic lung or liver metastases. On the other hand, routine bone scan should be additionally considered for asymptomatic patients with muscle-invasive disease (particularly those with >T2N0 disease).

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This article does not contain any studies with human participants or animals performed by the author.

Informed consent: As this study is based on a publicly available database without identifying patient information, informed consent was not needed.

Summary points

- This study aims at evaluating the performance characteristics of some of the imaging scans recommended by the National comprehensive cancer network (NCCN) guidelines for initial evaluation of bladder cancer.
- Surveillance, epidemiology and end results program (2010–2015) was queried and patients with clinically (T1–T4) bladder cancer and complete information about clinical T/ N stage and metastatic sites were extracted.
- The following characteristics of performance evaluated in the current analysis included sensitivity, specificity, number needed to investigate (NNI), positive predictive value (PPV), negative predictive value and accuracy.
- According to the current NCCN guidelines, PPV (for the recognition of lung metastases) is 4.7% and NNI to detect one case of lung metastasis is 21.2.
- Similarly, PPV (for the recognition of liver metastases) is 3.1% and NNI to detect one case of liver metastasis is 32.2.
- Using a different imaging threshold (i.e., routinely imaging all patients >T2N0), PPV (for the recognition of lung metastases) is 10.4% and NNI to detect one case of lung metastasis is 9.6.
- Similarly, PPV (for the recognition of liver metastases) is 7% and NNI to detect one case of liver metastasis is 14.2. The above two thresholds were also evaluated for routine bone scanning.
- PPV (for the detection of one case of bone metastasis) is 5.3% using the first threshold and 11.2% using the second threshold.

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