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Clinical predictors and recommendations for staging CT scan among men with prostate cancer

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Abstract

Objective—To identify clinical variables associated with a positive CT scan and estimate the performance of imaging recommendations in patients from a diverse sample of urology practices.

Materials and Methods—This study comprised 2,380 men with newly diagnosed prostate cancer seen at 28 practices in the Michigan Urological Surgery Improvement Collaborative (MUSIC) from March 2012 through September 2013. Data included age, prostate-specific antigen (PSA) level, Gleason score (GS), clinical T-stage, total number of positive biopsy cores, whether or not the patient received a staging abdominal/pelvic CT scan, and the CT scan result. We fit a multivariable logistic regression model to identify clinical variables associated with metastases detected by CT scan. We estimated the sensitivity and specificity of existing imaging recommendations.

Results—Among 643 men (27.4%) who underwent a staging CT scan, 62 (9.6%) had a positive study. In the multivariable analysis, PSA, GS, and clinical T stage were independently associated with the occurrence of a positive CT scan (all p-values<0.05). American Urology Association Best Practice recommendations for imaging when PSA >20 or GS ≥ 8 or locally advanced cancer had a sensitivity of 87.3% and specificity of 82.6%. Compared to current practice, implementing this recommendation in the MUSIC population was estimated to result in approximately 0.5% of positive studies being missed, and 26.1% fewer studies overall.

Conclusions—Successful implementation of CT imaging criterion of PSA >20 or GS ≥ 8 or clinical stage T3 would ensure that CT scans are performed for almost all men who would have positive studies while reducing the number of negative studies.

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Keywords

Prostate cancer; metastases; CT scans; verification bias; guidelines; current practice

INTRODUCTION

Computed tomography (CT) imaging of the abdomen or pelvis is commonly used as part of the staging process for men with newly diagnosed prostate cancer (PCa). However, there are numerous, and sometimes conflicting, recommendations published regarding use of this imaging modality that result in substantial variation in urologists' use of staging CT scans^{1, 2}. As a result, some patients who should be imaged are not, while others may undergo unnecessary imaging^{3, 4}.

Such differences in recommendations, and variations in practice, are due in part to the tradeoff between the potential benefits and harms of staging CT scans. On one hand, CT imaging provides greater certainty in staging. On the other hand, CT scans are costly, commonly result in incidental findings leading to follow-up imaging and biopsies, and expose patients to some risks associated with radiation^{5, 6}. Previous studies have found prostate specific antigen (PSA), Gleason score (GS), and clinical T-stage to be predictors of lymph node involvement at surgery; however, less is known about the degree to which these and other clinical variables correlate with the occurrence of radiographically-identifiable metastases, particularly among patients seen in both academic and community practices.^{6–11} Likewise, the degree to which existing CT imaging recommendations accurately distinguish patients who will have a positive study is also poorly understood. A greater appreciation of the performance of published recommendations among patients treated in diverse urology practices could lead to greater consistency in practice, and ultimately increase imaging among patients who are more likely to have a positive study, while reducing the number of potentially unnecessary staging evaluations.

In this context, we used data on CT imaging of men that were newly diagnosed with PCa from the statewide Michigan Urological Surgery Improvement Collaborative (MUSIC) to examine the association between routinely available clinical variables and the occurrence of metastatic disease interpreted as a positive CT scan.¹² We fit multivariable logistic regression models to identify predictors of a positive CT scan, and to evaluate the sensitivity and specificity of the published EAU guideline and the AUA Best Practice statement. We further estimated, for the MUSIC patient population, the mean number of positive studies missed and mean number of negative studies under each of these recommendations.

MATERIALS AND METHODS

Michigan Urological Surgery Improvement Collaborative

With financial support provided by Blue Cross Blue Shield of Michigan¹³, MUSIC was established as a statewide physician-led collaborative to improve the quality and cost effectiveness of prostate cancer care in Michigan. The collaborative now comprises a diverse group of 42 academic and community practices, covering nearly 90% of urologists

in the state. All men managed by a participating practice for a new diagnosis of prostate cancer are included in a web-based registry. The MUSIC registry maintains detailed clinical and demographic information, including patient age, PSA, biopsy Gleason score (GS), number of positive and negative biopsy cores, clinical T-stage as well as performance and results of imaging studies.

Patient Population

For this analysis, data were retrieved from the MUSIC registry for 2,515 men with newly diagnosed prostate cancer seen in 27 participating MUSIC practices from March 2012 to September 2013. Of these, 135 cases were excluded due to 42 patients missing PSA data, 34 patients missing GS data, 24 patients missing clinical T-stage data, 14 patients missing positive biopsy core data, 19 patients missing negative biopsy core data, 1 patient missing total biopsy cores taken, and 1 patient missing age. Thus, the final analytic cohort included 2,380 men with newly diagnosed prostate cancer from 27 MUSIC practices.

Primary Outcome

The primary outcome measure for this analysis was the occurrence of a staging CT scan (abdominal/pelvic or pelvic) that was determined to be positive for metastases. The treating clinicians in each practice were the final arbiters of whether or not a study was deemed positive. Data abstractors were instructed to review studies where there were questions about the results. In almost every case, classification of a study as positive was based on the finding of enlarged lymph nodes and/or other findings (e.g., bone lesions) identified by the radiologists as concerning for metastasis.

Statistical Analysis

We first performed univariate logistic regression analyses to evaluate the association between selected clinical variables and the occurrence of a positive CT scan. The clinical variables examined were age, PSA, GS, clinical T-stage, ratio of positive cores over total number of biopsy cores, in addition to whether or not the patient received an abdominal/pelvic CT scan and the CT scan result. After completing these univariate analyses, we then fit a multivariable logistic regression model to estimate the association between occurrence of a positive CT scan and the following clinical variables: PSA (continuous), categorical GS, categorical clinical T-stage, and the ratio of positive biopsy cores to total number of cores sampled (continuous). PSA was transformed to $\text{Ln}(\text{PSA}+1)$ to account for the skewed nature of the distribution. In addition, a GS of 7 was distinguished between 3+4 and 4+3, as prior literature has shown that patients with a GS 4+3 disease have a higher likelihood of cancer spread and a worse prognosis.¹⁴ In order to enhance the clinical applicability of our findings, we also fit a separate model with PSA specified as a categorical variable (i.e., <10, 10.1–20, >20 ng/mL).

Evaluation of Existing Clinical Recommendations

Next, we examined the sensitivity and specificity of existing imaging recommendations for the identification of positive studies in the MUSIC population. Based on the published literature, we determined that the EAU guidelines recommend a CT scan if asymptomatic

patients have a PSA >10 ng/mL or GS ≥ 8 or clinical T-stage $\geq T3$ ¹. The AUA Best Practice recommends a CT scan in asymptomatic patients with a biopsy GS ≥ 8 or a PSA >20 ng/mL or locally advanced disease².

We fit a logistic regression model to estimate for each patient the probability of a positive CT scan, based on their available clinical characteristics. To obtain a more accurate estimate of the sensitivity and specificity of the recommendations, we used the method of Begg and Greenes to mitigate the verification bias that exists because not all patients underwent radiographic staging with a CT scan¹⁵. The approach used is the same as that described for the evaluation of bone scan guidelines¹⁶. We then used the logistic regression model to estimate the expected number of positive CT scans that would be missed, and the expected number of negative CT scans, if the recommendations had been applied uniformly across the study sample. We also compared the expected number of CT scans ordered with each of the recommendations to actual practice patterns in MUSIC. All statistical analyses were two-sided, and performed at the 5% significance level using SAS version 9.3.

RESULTS

Table 1 presents the clinical characteristics of 2,380 patients included in the analytic sample. Among the 2,380 patients, 643 patients (27.0%) underwent a staging CT scan, and 62 (9.6%) of these studies were interpreted as positive for metastases. Patients who underwent CT imaging had significantly higher PSA levels, biopsy GS, and clinical T stages than those who did not receive a CT scan (all $p < 0.0001$).

Table 2 summarizes results from the univariate and multivariate logistic regression models, and presents the associations between clinical variables and a positive CT scan. The univariate analyses identified PSA, GS, clinical stage, and the ratio of positive cores as statistically significant predictors of a positive study (all p -values < 0.0001). In the multivariate analysis, PSA, GS ≥ 8 , and clinical stage $\geq T3$ were predictors of metastases (all $p < 0.05$) (Table 2). A separate model with PSA as a categorical variable revealed that PSA > 20 was a statistically significant cutoff. Illustrating this point, for the multivariate logistic regression model the odds ratio for PSA in the range 10.1 to 20 was 1.92 (95% CI: 0.82–4.49), compared to 5.37 (95% CI: 2.52–11.44) for PSA > 20.

In terms of the performance of existing recommendations in the MUSIC population, the EAU guideline had the highest sensitivity (90.2%) and the lowest specificity (74.7%) for recommending imaging among patients with positive studies, largely reflecting its recommendation to scan patients with GS ≥ 7 cancers. Comparatively, the AUA Best Practice recommendations had a sensitivity and specificity of 87.3% and 82.6%, respectively. Table 3 compares the performance of the EAU and AUA recommendations with respect to the expected number of positive CT scans that would be missed, and the expected number of negative CT scans that would be ordered, if these guidelines had been implemented across the MUSIC population analyzed herein. We estimated that uniform implementation of the AUA and EAU recommendations would result in a 0.5% and 0.4% missed positive scan rate, respectively. The EAU recommendation would result in 27.7% of all patients being imaged, with 88.1% of these patients having a negative study. Conversely, if the AUA Best

Practice recommendations were implemented uniformly, only 20% of the study population would be scanned, with 84% of the imaged patients having a negative study.

Figure 1 compares the total number of CT scans that would have been recommended based on EUA and AUA recommendations with the actual number of studies obtained for patients managed by MUSIC urologists. Assuming perfect adoption of the guidelines, the EAU guideline would result in an increase in the total number of CT scans compared with current practice in Michigan, while implementation of recommendations from AUA would result in 26.1% fewer studies.

DISCUSSION

Patients with newly diagnosed prostate cancer all have some probability of metastatic disease, and may in theory benefit from a staging CT scan to assess for evidence (and extent) of metastatic disease. However, there are also potential harms associated with routine use of CT scans, including the cascade of diagnostic and therapeutic interventions associated with follow-up of incidental findings unrelated to the prostate cancer, health risks from radiation exposure, and potentially unnecessary costs to patients and the health care system.¹⁷ Illustrating this point, Orme et al reported that abdominal CT scans have the highest number of incidental findings among all imaging modalities. Although incidental findings may benefit some patients, in many cases they yield anxiety, discomfort and costs without improvements in health outcomes¹⁸. Accordingly, many are calling for recommendations and care pathways that facilitate more judicious use of CT imaging, particularly for the radiographic staging of men with newly diagnosed prostate cancer.

The protocols and interpretations for each CT scan were performed by local radiologists in accordance with standard practice in the MUSIC collaborative. The treating clinicians in each practice were the final arbiters of whether or not a study was deemed positive. As such, the results are generalizable to a large and diverse population of urologists and patients.

We found that PSA levels >20 ng/mL, biopsy GS 8, and clinical T stage T3 were independently associated with a positive staging CT scan. Moreover, we determined that—among published recommendations for CT imaging—the AUA Best Practice statement, which suggests CT imaging for patients with PSA >20, or GS 8 or locally advanced disease (interpreted as cT3/4), performs most efficiently. In particular, while both the AUA recommendations and the EAU CT guidelines had high sensitivity (i.e., were very likely to recommend imaging for patients who had a positive study), the criteria proposed by the AUA had much greater specificity (i.e., were less likely to recommend imaging in patients with negative studies). When applied to this sample of patients from the MUSIC registry, both recommendations resulted in <1% of positive studies missed. However, because of the large differences in specificity, uniform application of the EUA guidelines (versus the AUA Best Practice recommendations) would have resulted in the performance of more than three times as many CT scans compared to actual practice in the MUSIC population. Conversely, with uniform adoption of the AUA Best Practice recommendations, we estimate that the total number of CT scans would be reduced by more than 25% compared to current imaging practices.

A potential limitation of this study includes the fact that we did not have test results for all patients that did not receive a CT scan; however, we adjusted for this potential source of bias (i.e., verification bias) using the method of Begg and Greenes to obtain more accurate estimates of sensitivity and specificity than have appeared in the literature thus far. This method uses information from the entire population by fitting a logistic regression model to calculate the imputed probability of a positive CT scan for patients that were not imaged. Another possible limitation is that there could be correlation among clinical practices for selecting patients for CT scans in MUSIC. We investigated this issue by fitting separate models that account for clustering of patients within urology practices (i.e., generalized estimating equations), and we found no evidence of such correlations.

These limitations notwithstanding, this study provides a framework for adopting changes in clinical practices that enhance the efficiency of CT imaging for staging of patients with newly-diagnosed prostate cancer. Specifically, a policy that recommends performance of a CT scan if the patient has a PSA >20 ng/mL or GS 8 or clinical T-stage T3, can be anticipated to lead to more scans in patients who benefit from such imaging (i.e., those who have identifiable metastases that change clinical decision making), and fewer imaging studies in patients who are unlikely to benefit. At the same time, the total number of CT scans would be reduced significantly, thereby reducing concerns related to incidental findings, costs, and radiation exposure associated with such studies. Moving forward, therefore, these data will serve as the cornerstone of our efforts to implement evidence-based imaging appropriateness criteria across MUSIC practices in Michigan.

CONCLUSIONS

Implementation of criterion for CT imaging that include PSA >20, or GS 8 or locally advanced disease (interpreted as cT3/4) would ensure that CT scans are performed for almost all men who would have studies positive for metastases, with an estimated missed positive rate of less than 1%, while at the same time reducing the total number of staging evaluations by more than 25%.

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Figure 1.

Total number of CT scans performed for the 2,380 men in the study population compared to the projected number of CT scans if the recommendations from the EAU guidelines or the AUA Best Practice statement were implemented for the same population.

Table 1

Patient characteristics

Variables	All patients without CT (n=1,737)	All patients with CT (n=643)	p value
Age at diagnosis (years)			0.1734
Mean (median)	63.8 (64)	66.0 (66)	
Range	40.4–95	40–99	
Clinical Stage, No. (%)			<0.0001
T1	1,386 (79.79)	359 (55.83)	
T2	339 (19.52)	246 (38.26)	
T3/T4	12 (0.69)	38 (5.91)	
PSA, ng/mL			<0.0001
Mean (median)	8.60 (5.20)	49.91 (7.74)	
Range	0.23–1,008.90	0.40–6,873.40	
PSA, ng/mL, No. (%)			<0.0001
10	1,576 (90.73)	377 (58.63)	
10.01–20	124 (7.14)	146 (22.71)	
20.01–50	20 (1.15)	64 (9.95)	
>50	17 (0.98)	56 (8.71)	
Biopsy Gleason score, No. (%)			<0.0001
6	747 (43.01)	62 (9.64)	
3 + 4	671 (38.63)	174 (27.06)	
4 + 3	212 (12.20)	97 (15.09)	
8–10	107 (6.16)	310 (48.21)	
Biopsy cores taken, No.			0.3859
Mean (median)	12.47 (12.00)	12.73 (12.00)	
Range	2–82	1–78	
Positive cores, No.			<0.0001
Mean (median)	3.26 (3.00)	6.18 (6.00)	
Range	1–20	1–16	

Variables	All patients without CT (n=1,737)	All patients with CT (n=643)	p value
Positive cores, %			<0.0001
Mean (median)	27.02 (23.08)	50.39 (50)	
Range	2.44 – 100	3.13 – 100	

Table 2
Univariate and multivariate logistic regression models predicting the occurrence of a positive CT scan.

Factors	Univariate logistic regression model			Multivariate logistic regression model		
	OR (95% CI)	p value	Overall p value	OR (95% CI)	p value	Overall p value
Age at diagnosis (years)	1.02 (0.99 – 1.05)	0.17	(0.17)	1.00 (0.96–1.03)	0.83	(0.83)
Clinical T stage						
T1	Reference		(<0.0001)	Reference		(0.0005)
T2	2.05 (1.09–3.86)	0.03		1.32 (0.63–2.76)	0.47	
T3/4	21.05 (9.52–46.56)	<0.0001		6.18 (2.36–16.19)	0.0002	
PSA	2.79 (2.21 – 3.54)	<0.0001	(<0.0001)	2.16 (1.65 – 2.84)	<0.0001	(<0.0001)
Biopsy Gleason sum						
3+4	Reference		(<0.0001)	Reference		(0.005)
4+3	15.49 (1.84 – 130.48)	0.01		8.13 (0.91–72.94)	0.06	
8–10	50.69 (6.96 – 369.16)	<0.0001		19.72 (2.62–148.39)	0.004	
Positive Cores, %	35.08 (12.06 – 102.03)	<0.0001	(<0.0001)	1.82 (0.47–7.01)	0.39	(0.39)

OR = odds ratio; PSA = prostate specific antigen; CI = confidence interval; PSA was transformed to Ln(PSA+1)

Table 3

Performance of published imaging recommendations in the MUSIC population

Guidelines	Patients with CT (n=643)			Patients without CT (n=1,737)			Entire Population (n=2,380)		
	No. of patients to be scanned, (%)	No. of positive CT missed, (%)	No. of negative CT, (%)	No. of patients to be scanned, (%)	Expected no. of positive CT missed, (%)	Expected no. of negative CT, (%)	No. of patients to be scanned, (%)	Expected no. of positive CT missed, (%)	Expected no. of negative CT, (%)
EAU	429 (66.7)	1 (0.2)	213 (33.1)	231 (13.3)	7 (0.4)	212 (12.2)	660 (27.7)	9 (0.4)	581 (24.4)
AUA	355 (55.2)	2 (0.3)	286 (44.5)	120 (6.9)	8 (0.5)	103 (5.9)	475 (20.0)	11 (0.5)	399 (16.8)