Health Services Research

Clinical Predictors and Recommendations for Staging Computed Tomography Scan Among Men With Prostate Cancer

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OBJECTIVE	To identify clinical variables associated with a positive computed tomography (CT) scan and estimate the performance of imaging recommendations in patients from a diverse sample of urology practices.
MATERIALS AND METHODS	This study comprised 2380 men with newly diagnosed prostate cancer seen at 28 practices in the Michigan Urological Surgery Improvement Collaborative 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 and/or pelvic CT scan, and CT scan result. We fit a multivariate 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 men (9.6%) had a positive study. In the multivariate analysis, PSA, GS, and clinical T stage were independently associated with the occurrence of a positive CT scan (all P values <.05). The American Urological Association's Best Practice Statements' recommendations for imaging when PSA level >20 ng/mL or GS $\geq$8 or locally advanced cancer had a sensitivity of 87.3% and specificity of 82.6%. Compared with current practice, implementing this recommendation in the Michigan Urological Surgery Improvement Collaborative population was estimated to result in approximately 0.5% of positive study results being missed, and 26.1% of fewer study results overall.
CONCLUSION	Successful implementation of CT imaging criterion of PSA level >20, GS $\geq$8, or clinical stage $\geq$T3 would ensure that CT scans are performed for almost all men who would have positive study results while reducing the number of negative study results. UROLOGY ■: ■−■, 2014. © 2014 Elsevier Inc.

C omputed 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 the 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, whereas others may undergo unnecessary imaging.[3,4]

Such differences in recommendations, and variations in practice, are due in part to the trade off 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 resulting 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) level, 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 result 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 result, while reducing the number of potentially unnecessary staging evaluations.

In this context, we used data on CT imaging of men who 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. We fit multivariate logistic regression models to identify predictors of a positive CT scan, and to evaluate the sensitivity and specificity of the published European Association of Urology (EAU) guidelines and the American Urological Association's (AUA) Best Practice Statements. We further estimated, for the MUSIC patient population, the mean number of positive study results missed and mean number of negative study results under each of these recommendations.

MATERIALS AND METHODS

Michigan Urological Surgery Improvement Collaborative

With financial support provided by the Blue Cross Blue Shield of Michigan,[12] MUSIC was established as a statewide physician-led collaborative to improve the quality and cost effectiveness of PCa 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 PCa are included in a Web-based registry. The MUSIC registry maintains detailed clinical and demographic information, including patient age, PSA level, biopsy GS, number of positive and negative biopsy cores, and 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 2515 men with newly diagnosed PCa seen in 27 participating MUSIC practices from March 2012 to September 2013. Of these, 135 patients were excluded because of 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 2380 men with newly diagnosed PCa from 27 MUSIC practices.

Primary Outcome

The primary outcome measure for this analysis was the occurrence of a staging CT scan (abdominal and 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 in which there were questions about the results. In almost every case, classification of a study result as positive was based on the finding of enlarged lymph nodes and/or other findings (eg, 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 level, 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 and pelvic CT scan, and the CT scan result. After completing these univariate analyses, we then fit a multivariate logistic regression model to estimate the association between occurrence of a positive CT scan and the following clinical variables: PSA level (continuous), categorical GS, categorical clinical T stage, and the ratio of positive biopsy cores to the total number of cores sampled (continuous). PSA was transformed to ln(PSA + 1) to account for the skewed nature of the distribution. In addition, a GS of 7 was distinguished between GS of 3 + 4 and 4 + 3 as prior literature has shown that patients with a GS of 4 + 3 disease have a higher likelihood of cancer spread and a worse prognosis.[13] To enhance the clinical applicability of our findings, we also fit a separate model with PSA specified as a categorical variable (ie, <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 study results 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 level of >10 ng/mL, GS of ≥8, or clinical T stage ≥T3.[1] The AUA's Best Practice Statements recommend a CT scan in asymptomatic patients with a biopsy GS of ≥8, PSA level of >20 ng/mL, or locally advanced disease.[2]

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[14] to mitigate the verification bias that exists because not all patients underwent radiographic staging with a CT scan. The approach used is the same as that described for the evaluation of bone scan guidelines.[15] 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 2 sided, and performed at the 5% significance level using SAS (SAS Institute Inc, Cary, NC), version 9.3.

RESULTS

Table 1 presents the clinical characteristics of 2380 patients included in the analytic sample. Among the 2380 patients, 643 patients (27.0%) underwent a staging CT

Table 1. Patient characteristics

Variables	All Patients Without CT (N = 1737)	All Patients With CT (N = 643)	P Value
Age at diagnosis, y			.1734
Mean (median)	63.8 (64)	66.0 (66)	
Range	40.4-95	40-99	
Clinical stage, n (%)			<.0001
T1	1386 (79.79)	359 (55.83)	
T2	339 (19.52)	246 (38.26)	
T3/T4	12 (0.69)	38 (5.91)	
PSA, ng/mL			<.0001
Mean (median)	8.60 (5.20)	49.91 (7.74)	
Range	0.23-1008.90	0.40-6873.40	
PSA, ng/mL, n (%)			<.0001
≤10	1576 (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, n (%)			<.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, n			.3859
Mean (median)	12.47 (12.00)	12.73 (12.00)	
Range	2-82	1-78	
Positive cores, n			<.0001
Mean (median)	3.26 (3.00)	6.18 (6.00)	
Range	1-20	1-16	
Positive cores, %			<.0001
Mean (median)	27.02 (23.08)	50.39 (50)	
Range	2.44-100	3.13-100	

CT, computed tomography; PSA, prostate-specific antigen.

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	1.02 (0.99-1.05)	.17	.17	1.00 (0.96-1.03)	.83	.83
Clinical T stage						
T1	Reference		<.0001	Reference		.0005
T2	2.05 (1.09-3.86)	.03		1.32 (0.63-2.76)	.47	
T3/4	21.05 (9.52-46.56)	<.0001		6.18 (2.36-16.19)	.0002	
PSA	2.79 (2.21-3.54)	<.0001	<.0001	2.16 (1.65-2.84)	<.0001	<.0001
Biopsy Gleason score sum						
≤3 + 4	Reference		<.0001	Reference		.005
4 + 3	15.49 (1.84-130.48)	.01		8.13 (0.91-72.94)	.06	
8-10	50.69 (6.96-369.16)	<.0001		19.72 (2.62-148.39)	.004	
Positive cores, %	35.08 (12.06-102.03)	<.0001	<.0001	1.82 (0.47-7.01)	.39	.39

CI, confidence interval; OR, odds ratio; other abbreviation as in Table 1.
PSA was transformed to ln (PSA + 1).

scan, and 62 (9.6%) of these study results 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 values <.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 T stage, and the ratio of positive cores as statistically significant predictors of a positive study result (all P values <.0001). In the multivariate analysis, PSA, GS ≥8, and clinical stage ≥T3 were predictors of metastases (all P values <.05; Table 2). A separate model with PSA as a categorical variable revealed that PSA level >20 ng/mL was a statistically significant cutoff. Illustrating this point, for the multivariate logistic regression model the odds ratio for PSA in the range of 10.1-20 ng/mL was 1.92 (95% confidence interval, 0.82-4.49) compared with 5.37 (95% confidence interval, 2.52-11.44) for PSA level >20 ng/mL.

In terms of the performance of existing recommendations in the MUSIC population, the EAU guidelines had the highest sensitivity (90.2%) and the lowest specificity

Table 3. Performance of published imaging recommendations in the MUSIC population

Guidelines	Patients With CT (N = 643)			Patients Without CT (N = 1737)			Entire Population (N = 2380)		
	No. of Patients to Be Scanned, n (%)	No. of Positive CT Missed, n (%)	No. of Negative CT, n (%)	No. of Patients to Be Scanned, n (%)	Expected No. of Positive CT Missed, n (%)	Expected No. of Negative CT, n (%)	No. of Patients to Be Scanned, n (%)	Expected No. of Positive CT Missed, n (%)	Expected No. of Negative CT, n (%)
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)

AUA, American Urological Association; EAU, European Association of Urology; MUSIC, Michigan Urological Surgery Improvement Collaborative; other abbreviation as in Table 1.
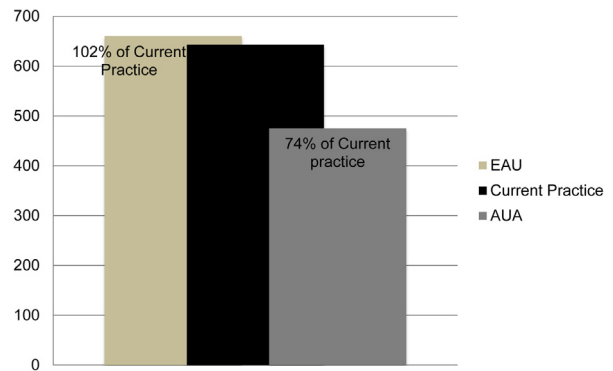

Figure 1. Total number of computed tomography scans performed for the 2380 men in the study population compared with the projected number of computed tomography scans if the recommendations from the European Association of Urology guidelines or the American Urological Association's Best Practice Statements were implemented for the same population. AUA, American Urological Association; EAU, European Association of Urology. (Color version available online.)

(74.7%) for recommending imaging among patients with positive study results, largely reflecting its recommendation to scan patients with GS 7 cancers. Comparatively, the AUA's Best Practice Statements' 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 rates, respectively. The EAU recommendation would result in 27.7% of all patients being imaged, with 88.1% of these patients having a negative study result. Conversely, if the AUA's Best Practice Statements' recommendations were implemented uniformly, only 20% of the study population would be scanned, with 84% of the imaged patients having a negative study result.

Figure 1 compares the total number of CT scans that would have been recommended based on the EAU and AUA recommendations with the actual number of study results 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 although implementation of recommendations from AUA would result in 26.1% fewer study results.

COMMENT

Patients with newly diagnosed PCa 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 the routine use of CT scans, including the cascade of diagnostic and therapeutic interventions associated with follow-up of incidental findings unrelated to the PCa, health risks from radiation exposure, and potentially unnecessary costs to patients and the health care system.[16] Illustrating this point, Orme et al[17] 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 outcomes. 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 PCa.

The protocols and interpretations for each CT scan were performed by local radiologists in accordance with standard practice in the MUSIC. The treating clinicians in each practice were the final arbiters of whether or not a study result 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's Best Practice Statements, which suggest CT imaging for patients with PSA level >20 ng/mL, GS ≥8, or locally advanced disease (interpreted as cT3/4), perform most efficiently. In particular, although both the AUA recommendations and the EAU CT guidelines had high sensitivity (ie, were very likely to recommend imaging for patients who had a positive study result), the criteria proposed by the AUA had much greater specificity (ie, were less likely to recommend imaging in patients with negative study results). When applied to this sample of patients from the MUSIC registry, both recommendations resulted in <1% of positive study results missed. However, because of the large differences in specificity, uniform application of the EAU guidelines (vs the AUA's Best Practice Statements' recommendations) would have resulted in the performance of >3 times as many CT scans compared with actual practice in the MUSIC population. Conversely, with uniform adoption of the AUA's Best Practice Statements' recommendations, we estimate that the total number of CT scans would be reduced by >25% compared with current imaging practices.

A potential limitation of this study includes the fact that we did not have test results for all patients who did not receive a CT scan; however, we adjusted for this potential source of bias (ie, 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 who were not imaged. Another possible limitation is that there could be a 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 (ie, generalized estimating equations), and we found no evidence of such correlations.

Notwithstanding these limitations, 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 PCa. Specifically, a policy that recommends performance of a CT scan if the patient has a PSA level >20 ng/mL, GS ≥8, or clinical T stage ≥T3 can be anticipated to lead to more scans in patients who benefit from such imaging (ie, those who have identifiable metastases that change clinical decision making), and fewer imaging study results 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 study results. 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.

CONCLUSION

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

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EDITORIAL COMMENT

The authors reporting on behalf of the Michigan Urological Surgery Improvement Collaborative reviewed the computed tomography (CT) staging findings in 643 men who were newly diagnosed with prostate cancer. Typical clinical parameters for prostate cancer were collected. Only 9.6% of CT scans were positive for metastatic disease (enlarged lymph nodes). The authors then analyzed what would the impact have been if CT scans were obtained either according to the American Urological Association (AUA) Best Practice Statements' recommendations (prostate-specific antigen level >20 ng/mL, Gleason score 8-10, and cT3-4) or per European Association of Urology (EAU) guidelines (prostate-specific antigen level >10 ng/mL, Gleason score 8-10, and cT3-4). The AUA's or EAU's approach would have missed a positive CT scan result in only 0.5% and 0.4% of cases, respectively. However, the EAU's vs AUA's approach would have resulted in a higher rate of imaging and a higher negative study result rate (27.1% and 88.1% vs 20% and 84%, respectively).

The findings in this simple and intelligently designed study are clinically relevant and show that the more limited use of CT scans obtained nearly the same sensitivity for metastatic disease detection while sparing the cost and radiation exposure of the imaging in an additional 7% of patients. Perhaps, equally important to the data collected are the model and methods themselves. It is remarkable that the Michigan Urological Surgery Improvement Collaborative voluntary effort includes nearly 90% of the urologists in Michigan. This type of clear headed and proactive cooperative thinking and pooling of data, which combines best patient guidelines or recommendations with health system financial considerations for medical practice patterns should serve as a model for emulation across the whole span of clinical practice issues.

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