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CONTEMPORARY TRENDS IN IMAGING TEST UTILIZATION FOR PROSTATE CANCER STAGING: DATA FROM THE CANCER OF THE PROSTATE STRATEGIC UROLOGIC RESEARCH ENDEAVOR

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ABSTRACT

Purpose: Previous investigators have reported widespread overuse of imaging tests for staging clinically localized prostate cancer. In this study imaging test utilization rates were analyzed in a contemporary group of patients, and clinical and demographic predictors of testing were identified.

Materials and Methods: Data were abstracted from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a longitudinal registry of men with various stages of prostate cancer. A total of 4,966 men met study inclusion criteria of available treatment and staging data. The rates of computerized tomography, magnetic resonance imaging and bone scans performed between the dates of diagnosis and primary treatment were analyzed in patients at 3 levels of clinical risk based on serum prostate specific antigen, Gleason sum and T stage. Time trends in test utilization were analyzed by linear regression. Contemporary rates were compared with those identified in a previous analysis of an earlier CaPSURE cohort. Demographic and clinical predictors of utilization were identified using generalized linear model analysis.

Results: Since June 1997, the overall use of staging tests has decreased 63%, 25.9% and 11.4% in patients at low, intermediate and high risk, respectively. The most precipitous decrease was noted for bone scan but the use of cross-sectional imaging also decreased in all groups. Utilization rates were lower in 2001 than in any other year studied in CaPSURE.

Conclusions: The rates of testing decreased significantly in all risk groups. However, in the absence of established clinical practice guidelines many patients at low and intermediate risk continue to undergo unnecessary testing, while a growing number of those at high risk are proceeding to treatment without previous imaging.

KEY WORDS: prostate, prostatic neoplasms, neoplasm staging, radionuclide imaging, diagnostic imaging

Imaging studies performed in men diagnosed with prostate cancer serve to enhance clinical staging before treatment and, thereby, facilitate optimal treatment planning. For example, early detection of tumor dissemination to pelvic lymph nodes or to bone may spare a patient local therapy that is unlikely to be curative and may prompt more rapid initiation of systemic therapy. However, all staging investigations are associated with low but definite risks to the patient and with significant costs to the health care system. While extant clinical practice guidelines do not include specific recommendations for pretreatment testing,[1] several studies done to identify appropriate indications for imaging have shown consistent overuse in patients with clinically low risk disease.[2]

Most of these studies used some combination of serum prostate specific antigen (PSA), biopsy Gleason sum and T stage to predict the likelihood of positive imaging results or occult advanced disease. For example, Oesterling demonstrated that a PSA of less than 10 ng./ml. has a negative predictive value of 99.5% for significant findings on bone scan and in fact only 0.8% of 2,064 patients with PSA as high as 20 ng./ml. had positive scans.[3] Levran et al reported that lymph node disease was detected on computerized tomography (CT) in only 1.5% of 861 patients and all positive images were noted in those with a PSA of greater than 20 ng./ml.[4] After extensive review of the available literature O'Dowd et al recommended that bone scan should only be performed in patients with PSA greater than 10 ng./ml., while cross-sectional imaging should be done only in those with PSA greater than 20 ng./ml., Gleason sum greater than 7 and/or clinical T stage 3 or 4 disease.[5]

Despite the promulgation of such recommendations studies to date have shown consistent patterns of overuse. In a 1997 survey of 1,500 urologists 52.4% of respondents stated that they ordered bone scans in all prostate cancer cases regardless of PSA and 28.6% ordered CT regardless of PSA.[6] In 1998 Kindrick et al compared staging test practice recommendations in the literature, particularly as identified by O'Dowd et al,[5] to actual practice patterns recorded between 1989 and June 1997 in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE), a national registry of patients with various stages of prostate cancer.[2] They observed a broad and consistent overuse of bone scan, CT and magnetic resonance imaging (MRI) with little change during the study period even as median PSA in their patient population decreased 25%. In the current study we present up-

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dated trends in imaging test utilization in a contemporary group of patients as well as an analysis of clinical and demographic predictors of testing.

MATERIALS AND METHODS

Description of data registry. CaPSURE is a longitudinal, observational database of men with biopsy proven prostate adenocarcinoma recruited from more than 35 urology practices across the United States, including academic and community based sites. Men are recruited consecutively into the study by urologists, who report complete clinical data and followup information on diagnostic tests and treatments. Patients are followed until death or study withdrawal. Additional details of the project methodology have been reported previously.[2, 7]

Subjects. Between June 1, 1995, when the database was opened, and August 31, 2001, 7,379 patients were invited to participate in the CaPSURE project and 7,199 agreed to participate. Of these patients 1,025 were excluded from analysis because the primary treatment classification was unknown or missing, while 1,166 were excluded because clinical staging information (PSA, Gleason sum, clinical T stage, and the dates of diagnosis and treatment) was incomplete. Another 42 men were excluded because they were diagnosed before 1989. The remaining 4,966 patients comprised the study population.

Data analysis. Demographic factors extracted from CaPSURE included patient age at diagnosis, race, education, income, treatment site location and type (academic or community), and type of insurance. Clinical factors included PSA at diagnosis, Gleason score of diagnostic biopsy and pretreatment clinical T stage. These data were combined to stratify patients into clinical risk groups, including low risk—PSA less than 10 ng./ml., Gleason sum less than 7 and clinical stage T1 or T2a; intermediate risk—PSA between 10.1 and 15 ng./ml., Gleason sum 7 or clinical stage T2b; and high risk—PSA greater than 15 ng./ml., Gleason sum greater than 7, or clinical stage T3 or T4. Primary treatments were grouped as prostatectomy, radiotherapy (external beam or interstitial), cryotherapy, hormonal ablation only and watchful waiting. Imaging tests were included if they were performed during the staging interval, defined as the period between the date of diagnostic biopsy and the date of primary treatment. Only bone scans and abdominal or pelvic CT and MRI were analyzed.

The primary outcome variable in all analyses was test utilization, defined as the percent of patients receiving a given test during the staging interval. To contrast contemporary testing patterns with those reported by Kindrick et al[2] utilization rates were compared in patients in each risk group diagnosed before and after June 30, 1997 with the significance of differences assessed by the chi-square test. Overall linear trends in test use in patients at low and intermediate risk were assessed by plotting test utilization in these patients against the year of diagnosis. The significance of trends was tested by multiple linear regression to control for the decrease in median PSA during the study period.

Demographic and clinical predictors of test utilization were first assessed via univariate chi-square analysis except for the ordinal variables risk and age, which were assessed by the Mantel-Haenszel chi-square test for trend. Factors showing a significant univariate predictive value were included in a multivariate generalized linear model (a modification of analysis of variance which is more robust with respect to variable sample sizes across groups). The significance of the contribution to the multivariate model was tested using the F statistic. Imaging testing frequencies at the various levels of the variables with significant predictive value in the multivariate model were compared using Duncan's multiple comparisons analysis. All analyses were performed using commercially available software.

RESULTS

Patient and physician characteristics. Table 1 lists patient clinical and demographic characteristics. Mean age at diagnosis plus or minus standard deviation was 67.4 ± 8.3 years. Mean serum PSA was 15.6 ± 21.1 ng./ml. (median 8.1). The mean Gleason sum was 6.0 ± 1.4 (median 6). Compared with the group analyzed by Kindrick et al[2] the average patient in CaPSURE was almost 4 years younger. Median PSA decreased more than a whole point from 9.2 ng./ml., while Gleason sum increased slightly from 5.8. As in the earlier data set, more than 91% of patients had clinical T stage T1 or T2 disease and a staging interval of 6 months or less. About a third of the patients were in each risk group.

Time trends in staging test use. We compared test utilization in the study data set of Kindrick et al through June 1997[2] and in patients entered into CaPSURE since July 1997. Table 2 shows utilization trends stratified by patient risk groups. Since June 1997, the proportion of patients re-

TABLE 1. *Patient demographic and clinical characteristics*

	No. Before 1997 (%)	No. After 1997 (%)	Total No. (%)
Age at diagnosis:			
Younger than 60	575 (16.5)	321 (21.7)	896 (18.1)
60–69	1,455 (41.8)	566 (38.2)	2,021 (40.7)
70–79	1,259 (36.1)	478 (32.3)	1,737 (35.0)
80 or Older	195 (5.6)	116 (7.8)	311 (6.3)
Race:			
White	2,957 (84.9)	1,286 (86.8)	4,243 (85.4)
Black	388 (11.1)	130 (8.8)	518 (10.4)
Latino	72 (2.1)	23 (1.6)	95 (1.9)
Other	67 (1.9)	43 (2.9)	110 (2.2)
PSA (ng./ml.):			
Less than 4	334 (9.6)	204 (13.8)	538 (10.8)
4–10	1,620 (46.5)	872 (58.8)	2,492 (50.2)
10.01–20	794 (22.8)	251 (16.9)	1,045 (21.0)
Greater than 20	736 (21.1)	155 (10.5)	891 (17.9)
Gleason sum:			
2–4	602 (17.3)	43 (2.9)	645 (13.0)
5–6	1,764 (50.6)	931 (62.8)	2,695 (54.3)
7	693 (19.9)	358 (24.2)	1,051 (21.2)
8–10	425 (12.2)	150 (10.1)	575 (11.6)
Clinical T stage:			
T1	753 (21.6)	673 (45.4)	1,426 (28.7)
T2	2,390 (68.6)	744 (50.2)	3,134 (63.1)
T3	316 (9.1)	55 (3.7)	371 (7.5)
T4	25 (0.7)	7 (0.5)	32 (0.6)
Risk group:			
Low	1,113 (32.0)	647 (43.7)	1,760 (35.4)
Intermediate	1,071 (30.7)	517 (34.9)	1,588 (32.0)
High	1,300 (37.3)	318 (21.5)	1,618 (32.6)
Staging interval (mos.):			
6 or Less	3,369 (96.7)	1,450 (97.8)	4,819 (97.0)
7–12	115 (3.3)	32 (2.2)	147 (2.96)
Primary treatment:			
Prostatectomy	1,560 (44.8)	637 (43.0)	2,197 (44.2)
Hormonal only	792 (22.7)	465 (31.4)	1,257 (25.3)
External beam radiotherapy	636 (18.3)	259 (17.5)	895 (18.0)
Watchful waiting	340 (9.8)	91 (6.1)	431 (8.7)
Cryotherapy	147 (4.2)	13 (0.9)	160 (3.2)
None/other	9 (0.3)	17 (1.2)	26 (0.5)
Insurance type:			
Medicare/supplemental	2,664 (76.5)	992 (66.9)	3,656 (73.6)
Medicare alone	654 (18.8)	302 (20.4)	222 (19.3)
Veterans Affairs	61 (1.8)	71 (4.8)	132 (2.7)
Other	105 (3.0)	117 (7.9)	222 (4.5)
Geographic region:			
East	1,700 (48.8)	519 (35.0)	2,219 (44.7)
South	919 (26.4)	211 (14.2)	1,130 (22.8)
Midwest	312 (9.0)	520 (35.1)	832 (16.8)
West	553 (15.9)	232 (15.7)	785 (15.8)
Site type:			
Community	3,176 (91.2)	1,281 (86.4)	4,457 (89.8)
Academic	308 (8.8)	201 (13.6)	509 (10.2)
Totals	3,484	1,482	4,966

TABLE 2. *Staging test utilization rates in groups before and after June 1997*

Risk Group	Before 1997	After 1997	p Value
Low:			
Bone scan	58.5	18.6	<0.0001
CT	24.6	10.4	<0.0001
MRI	3.0	0.9	0.0039
Any cross-sectional test	27.4	11.6	<0.0001
Any staging test	61.3	22.7	<0.0001
Intermediate:			
Bone scan	67.5	50.9	<0.0001
CT	29.9	15.3	<0.0001
MRI	5.0	1.4	0.0004
Any cross-sectional test	34.0	16.3	<0.0001
Any staging test	71.0	52.6	<0.0001
High:			
Bone scan	77.5	68.9	0.0013
CT	35.9	25.1	0.0003
MRI	5.9	2.5	0.0164
Any cross-sectional test	40.5	27.4	<0.0001
Any staging test	79.5	70.4	0.0005

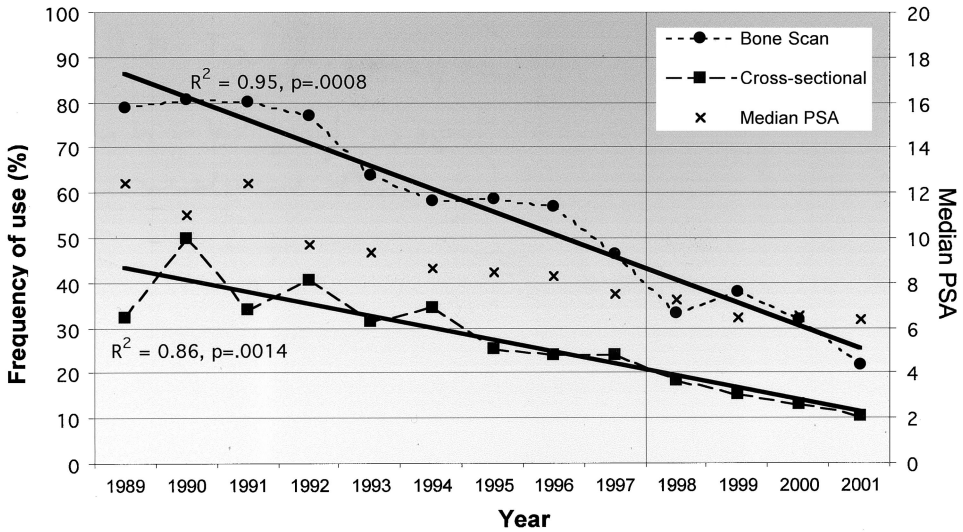
ceiving any staging imaging test decreased by 63% in those at low risk, by 25.9% in those at intermediate risk and by 11.4% in those at high risk. The most precipitous decreases occurred in bone scan utilization rates, which decreased 68.2%, 24.6% and 11.1% in the low, intermediate and high risk groups, respectively. Cross-sectional imaging decreased in all groups by 57.7%, 52.1% and 32.3%, respectively. This decrease was consistent for CT and MRI.

In the first 2 years of the study (1989 to 1990) risk group had no bearing on utilization rates, which were 80.6%, 81.8% and 82.1% in patients at high, intermediate and low risk, respectively (Mantel-Haenszel chi-square test $p = 0.806$). However, in the last 2 years (2000 to 2001) risk had a strong bearing on utilization with rates of 68.4%, 49.2% and 20.2%, respectively ($p < 0.0001$). Utilization rates were lower in 2001 than in any other year included in CaPSURE. Figure 1 shows long-term trends in the use of bone scan and cross-sectional pelvic imaging in patients at low and intermediate risk. The use of bone scan and cross-sectional imaging decreased significantly during the study period. These findings persisted after correcting for decreasing median PSA (multiple linear regression $p < 0.001$).

Factors predictive of test utilization. Table 3 lists demographic and clinical factors predicting test utilization. On univariate analysis treatment type, risk group, race, geographic location and insurance type were significantly associated with test utilization. On multivariate analysis controlling for the year of diagnosis all variables except age persisted as significant predictors. The overall R^2 for the multivariate model was 0.224 ($p < 0.0001$). By analysis multiple comparisons, patients undergoing cryotherapy had the highest utilization rates, those followed by watchful waiting had the lowest rate and differences among other treatment types were not significant. Patients in the Veterans Affairs system had lower utilization rates than those with other

TABLE 3. *Demographic and clinical factors predictive of test utilization*

Factor	%	SD	Univariate p Value (chi-square test)	Multivariate p Value (F)
Treatment:				
Watchful waiting	30.2	45.9	<0.0001	<0.0001
Prostatectomy	63.3	48.2		
External beam radiotherapy	73.6	44.1		
Cryotherapy	87.5	33.2		
Hormonal only	62.8	48.4		
Risk:				
Low	47.1	49.9	<0.0001	<0.0001
Intermediate	65.0	47.7		
High	77.7	41.7		
Age:				
Younger than 60	59.0	49.2	0.169	Not applicable
60–69	65.3	47.6		
70–79	62.5	48.4		
80 or Older	58.8	49.3		
Race:				
White	62.3	48.5	0.014	0.023
Black	68.7	46.4		
Latino	52.6	50.2		
Other	61.8	48.8		
Practice type:				
Community	62.9	48.3	0.524	Not applicable
Academic	61.5	48.7		
Location:				
West	52.1	50.0	<0.0001	<0.0001
East	75.4	43.1		
Midwest	45.0	49.8		
South	58.5	49.3		
Insurance type:				
Medicare/supplemental	63.6	48.1	<0.0001	0.0004
Medicare alone	61.9	48.6		
Veterans Affairs	44.7	49.9		
Other	64.4	48.0		



Time trends in imaging test utilization rates in patients at low and intermediate risk showing percent that underwent bone scan or cross-sectional imaging per year of diagnosis with linear regression lines. Median PSA per year is shown with R^2 and p corrected for median PSA.

types of insurance and Latino patients had lower rates than those in other racial groups. All differences among geographic regions were significant. Patients treated in the East were most likely to undergo imaging, followed in order by those in the South, West and Midwest. As expected, on multivariate analysis patients at high risk underwent the most staging tests and those at low risk underwent the fewest tests. There was wide variation among individual practice sites. For those accruing at least 10 patients to CaPSURE the overall rates ranged from 18.1% to 86.1%.

DISCUSSION

The advent of widespread PSA screening produced a sharp increase in the yearly incidence of prostate cancer and concomitant downward stage migration with more early detection of localized disease. These trends have created a situation in which rates of heath care expenditures for prostate cancer staging tests have increased dramatically. Analysis of CaPSURE data through 1997 showed widespread and consistent overuse even as the patient disease burden at diagnosis decreased throughout the 1990s.[2]

Since 1998, others have confirmed the lack of value for staging tests in patients at low risk. A number of instruments based on multivariate regression or neural network analysis have been increasingly well validated, further corroborating the low likelihood of extensive disease in patients with favorable clinical prognostic factors.[8] In fact, CT does not consistently identify the extent of disease. O'Dowd et al reviewed 18 studies and reported only 35.7% sensitivity, prompting them to argue that the only patients who should undergo CT are those in whom pelvic lymphadenectomy is planned.[5] In another review Reckwitz et al reported only 55% to 75% sensitivity for detecting local extension and 25% to 45% sensitivity for detecting lymph node metastases, while for MRI sensitivity was only 20% to 70% and 0% to 15%, respectively.[8] Hunchareck and Muscat estimated that eliminating unnecessary CT alone could produce a cost saving of $20 to $50 million yearly in direct costs.[9]

The overuse of imaging tests is not restricted to the United States. In fact, the problem may be worse internationally. In a recent report Quinn et al from an academic center in Australia stated without justification that only 2 of a consecutive cohort of 834 patients with prostate cancer treated in 13 years did not undergo pretreatment pelvic CT.[10] After 1996 routine bone scans were not performed in patients with a PSA of less than 10 ng./ml.[10]

We describe trends in staging test utilization in the last 12 years with particular focus on changes since our last analysis of CaPSURE data 4 years ago. Our major finding is that since the previous analysis, utilization rates decreased dramatically by 63%, 25.9% and 11.4% in patients at low, intermediate and high risk. All decreases were statistically significant. That the lowest rates in all studies occurred in patients diagnosed in 2001 suggests that these trends are ongoing. It is important to emphasize that men who have been diagnosed but have not yet undergone treatment were not included in this analysis. Therefore, rates in recently diagnosed patients were not lowered artificially by a lag in the completion of pretreatment testing.

While we identified significantly higher utilization rates in patients undergoing cryotherapy, since 1996 fewer than 10 (less than 5%) yearly have received this treatment. From 1999 onward only 3 of these 10 men underwent bone scan and none underwent cross-sectional imaging. As expected, patients following by watchful waiting had the lowest utilization rates. It is interesting that these rates did not vary significantly with risk. Otherwise treatment type did not predict utilization rates. We noted significant variation by geographic site with highest utilization rates in the East and the lowest in the Midwest, while at the single practice site level there was almost a 5-fold variation in testing rates across the country.

The decrease in utilization in men at low and intermediate risk is quite encouraging. Even more so is the fact that risk now predicts utilization at a statistically significant level, whereas it did not in the earlier data set. The decrease in rates in high risk cases may be explained in part by a change in treatment patterns in the 2 periods. Before July 1997 52.1% of patients at high risk received definitive local therapy (prostatectomy, radiation therapy or cryotherapy) and 40.2% received hormonal therapy as primary treatment. Since July 1997, only 36.8% of patients at high risk have received local therapy, while 57.2% have received hormonal therapy. Presumably staging tests would not change the treatment plan in men planning to undergo systemic therapy only. However, utilization rates in those at high risk who underwent local therapy decreased from 88.5% to 80.3% ($p = 0.015$), suggesting that a growing number may in fact be receiving treatment without adequate staging.

A great strength of CaPSURE is that it tracks utilization and outcome patterns in actual practice without the strictures imposed by clinical trial protocols. The practice sites from which CaPSURE patients are recruited represent a broad range of geographic locales, and a mix of academic and community practices. Data are collected irrespective of any particular research question. Thus, they are free of any bias that may be introduced when data are collected to address a specific hypothesis.

Because data on patients accessioned before June 1, 1995 were entered retrospectively, they may be vulnerable to reporting bias. However, previous analysis has shown no difference in staging test utilization in men diagnosed before this date and those diagnosed between June 1995 and June 1997.[2] A perennial caveat with respect to the interpretation of CaPSURE data is that only staging tests ordered by urologists are included. Tests ordered by primary physicians before referral, or by medical or radiation oncologists after diagnosis would be missed. Furthermore, in the cited studies CT but not MRI utilization was evaluated, although MRI and CT are not necessarily interchangeable staging modalities. However, MRI utilization rates in CaPSURE are highly heterogeneous by practice site with 2 sites accounting for almost 40% of scans. Due to this skew in the data and because our data set does not distinguish endorectal from body coil MRI, which is an important distinction when addressing optimal utilization, we decided to consider all cross-sectional imaging together.

While CaPSURE represents a mix of locales and practice types, sites were not chosen at random and, thus, they cannot be assumed to represent a statistically valid sample of United States practice patterns. For example, white patients are relatively over represented in CaPSURE compared with national census data. However, despite these cautionary notes we believe that our data represent the best available sampling of national practice trends. Furthermore, as noted by Kindrick et al,[2] the recommendations with respect to testing at various risk levels were developed through extensive literature review and development of validated nomograms but have not been prospectively tested for clinical and economic outcomes. Therefore, it remains impossible to verify with certainty the extent to which practice patterns represent an appropriate application of available staging modalities.

CONCLUSIONS

We report a sharp decrease in the rates of imaging test utilization for staging clinically localized prostate cancer. However, almost a quarter of patients with low risk disease and more than half with intermediate risk disease continue to undergo tests that are not indicated by extant recommen-

dations and nomograms, while almost 20% at high risk are receiving definitive local therapy without previous imaging. Kindrick et al noted the absence in the urological literature of formal clinical practice guidelines for pretreatment staging for prostate cancer.[2] This void remains unfilled. We hope that updated professional guidelines may address indications for staging test utilization and that such guidelines would mitigate the broad variation in utilization rates. Further studies are needed to assess the eventual impact of guidelines on practice patterns and clinical outcomes.

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