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Current Use of Imaging after Primary Treatment of Prostate Cancer

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

BS = radionuclide bone scan

BT = brachytherapy

CAPRA = University of California-San Francisco Cancer of the Prostate Risk Assessment

Cryo = cryosurgery

CT = computerized tomography

EBRT = external beam radiation therapy

MRI = magnetic resonance imaging

PCa = prostate cancer

PSA = prostate specific antigen

RP = radical prostatectomy

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Purpose: Data are limited on imaging after primary treatment of localized prostate cancer.

Materials and Methods: We identified 8,435 men newly diagnosed with nonmetastatic prostate cancer in 1995 to 2012 who were enrolled in CaPSURE™. Patients were followed after primary treatment with radical prostatectomy, cryosurgery, brachytherapy, external beam radiation therapy or androgen deprivation therapy. We assessed the use of bone scan, computerized tomography and magnetic resonance imaging after primary treatment. Factors associated with posttreatment outcomes (number of imaging tests, and time to first imaging and salvage treatment) were evaluated with multivariate Poisson regression and Cox proportional hazards regression.

Results: The incidence of posttreatment bone scan, computerized tomography and magnetic resonance imaging was 20% or less. Last posttreatment log(prostate specific antigen) was associated with multiple posttreatment imaging. Management by radical prostatectomy, cryosurgery, external beam radiation therapy or brachytherapy vs androgen deprivation therapy was associated with a lower likelihood of posttreatment imaging. Of patients who were imaged after treatment 25% with radical prostatectomy and 9% with radiation underwent imaging before prostate specific antigen failure. The 5-year salvage treatment-free survival rate was 81%. Positive findings on posttreatment imaging were associated with a higher risk of salvage treatment.

Conclusions: Patients treated with androgen deprivation therapy for localized disease were most likely to be imaged, primarily by bone scan. Men treated with other therapies were less likely to be imaged and tended to undergo computerized tomography. Imaging may add value to posttreatment prostate specific antigen monitoring to identify disease recurrence and progression. Further studies are needed to establish guidelines for the optimal frequency and imaging type to monitor the treatment response.

Key Words: prostatic neoplasms, diagnostic imaging, prostate-specific antigen, salvage therapy, disease progression

THE role of imaging after PCa diagnosis is primarily to identify metastatic disease and enhance clinical staging with tests such as BS, CT and MRI.[1] Studies show consistent overuse of pretreatment imaging to stage

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low risk, localized PCa.[2–4] In contrast, data are limited on imaging after primary treatment for PCa.

Posttreatment imaging, which is usually triggered by increasing PSA, is typically used to restage cases. Recurrence definitions after radiotherapy or surgery rely mainly on changes in PSA.[5–7] Studies have shown limited value of CT to detect recurrent disease at low PSA[8] and a high false-negative rate for bone metastasis for BS when postoperative PSA is 6 ng/ml or less and the patient lacks skeletal symptoms.[8,9]

In previous studies overall patterns of imaging in this patient cohort were not systematically assessed. We characterized contemporary trends in the use of BS, CT and MRI after primary PCa treatment. We obtained data from a large, national PCa registry to identify factors associated with posttreatment imaging and in turn clarify whether such imaging affects time to salvage therapy.

METHODS

Data Registry

CaPSURE is a longitudinal registry of patients with biopsy proven PCa recruited from 36 community, 4 veteran and 3 academic urological practices nationwide. Participating urologists recruit patients consecutively at diagnosis and report demographic and clinicopathological characteristics, reflecting real-world practice patterns. Followup data are collected at subsequent office visits and by patient reported questionnaires.[10]

Subjects

A total of 14,715 patients have consented to participate in the CaPSURE study under central institutional review board supervision since 1995. The current study included men newly diagnosed with nonmetastatic PCa who underwent active treatment in 1995 to 2012. Patients on watchful waiting or active surveillance and those with clinical stage N1/M1 or with 1 year or less of posttreatment followup were excluded from analysis. The final cohort underwent RP, Cryo, BT, EBRT or ADT as primary treatment. Men who received neoadjuvant or adjuvant treatment were included in study.

Data Analysis

Demographics (age at diagnosis, race and insurance type), clinical factors at diagnosis (PSA, Gleason grade, cT stage and CAPRA score[11]) and primary treatment modality are shown as the frequency and mean. The CAPRA score ranges from 0 to 10 with validated risk groups defined as low—0 to 2, intermediate—3 to 5 and high—6 to 10.[12] We calculated the imaging rates of BS, CT and MRI within 5 years after primary treatment and before salvage treatment. Biochemical recurrence was defined as 2 consecutive PSA values 0.2 ng/ml or greater after RP, or as a 2 ng/ml increase in PSA after nadir following radiotherapy (the Phoenix definition).[7]

Outcomes

Primary outcomes were the number of posttreatment imaging tests and time to first posttreatment imaging. The initial multivariate Poisson regression model identified factors associated with multiple posttreatment imaging to evaluate the volume of imaging. The second multivariate model assessed time to first posttreatment imaging with Cox proportional hazards regression to determine the risk of any imaging after treatment. Independent variables in the 2 models were primary treatment type, receipt of pretreatment imaging and last posttreatment PSA before the outcome event or last followup. We also evaluated a third outcome, time to salvage treatment, to determine the impact of posttreatment imaging findings on the likelihood of salvage treatment. This Cox model was restricted to men who underwent imaging after treatment. All models were adjusted for age, race, insurance coverage, CAPRA clinical risk, type of clinical site and diagnosis year. Covariates were selected a priori and assessed for interitem correlations with none excluded due to collinearity. We used the Pearson chi-square test, Mantel-Haenszel test for trend and ANOVA for statistical analysis with 2-sided $p < 0.05$ considered significant. All analysis was done with SAS® 9.2.

RESULTS

Of the 14,715 men ever enrolled in CaPSURE 10,977 were diagnosed with localized disease in or after 1995. We selected 8,435 patients treated with RP, Cryo, BT, EBRT or ADT who had any imaging data available and 1 year or greater of followup data as the final study cohort. At diagnosis mean ± SD age was 65 ± 8.6 years, median PSA was 6.3 ng/ml (IQR 4.6–9.7) and 78% of the men were at low or intermediate CAPRA risk (5 or less). Of the patients 48% had private health insurance, 44% had Medicare with or without supplement, 3% had veteran coverage and 5% had other or unreported insurance. The primary treatment type was RP in 4,629 patients (55%, including 104 with adjuvant EBRT), Cryo in 341 (4%), BT in 1,321 (16%), EBRT in 962 (11%) and primary ADT in 1,182 (14%). Median followup was 61 months (IQR 35–97) (supplementary table, http://jurology.com/).

Of the 8,435 patients 1,458 underwent posttreatment imaging with BS, CT and/or MRI. The posttreatment imaging rate by BS, MRI and CT was less than 20%, which decreased with time in patients diagnosed in 1995 to 1999 (20%), 2000 to 2004 (17%) and 2005 to 2012 (13%) ($p < 0.01$). In men with posttreatment imaging BS decreased from 54% to 35% and MRI decreased from 9% to 7% between 1995 and 2012. CT increased from 37% to 58% during the same periods ($p < 0.01$, fig. 1, *A* and *B*).

The rate of posttreatment imaging was the highest in patients who received ADT (37%) and similar in the other treatment groups (range 13% to 15%). BS was the predominant modality after primary

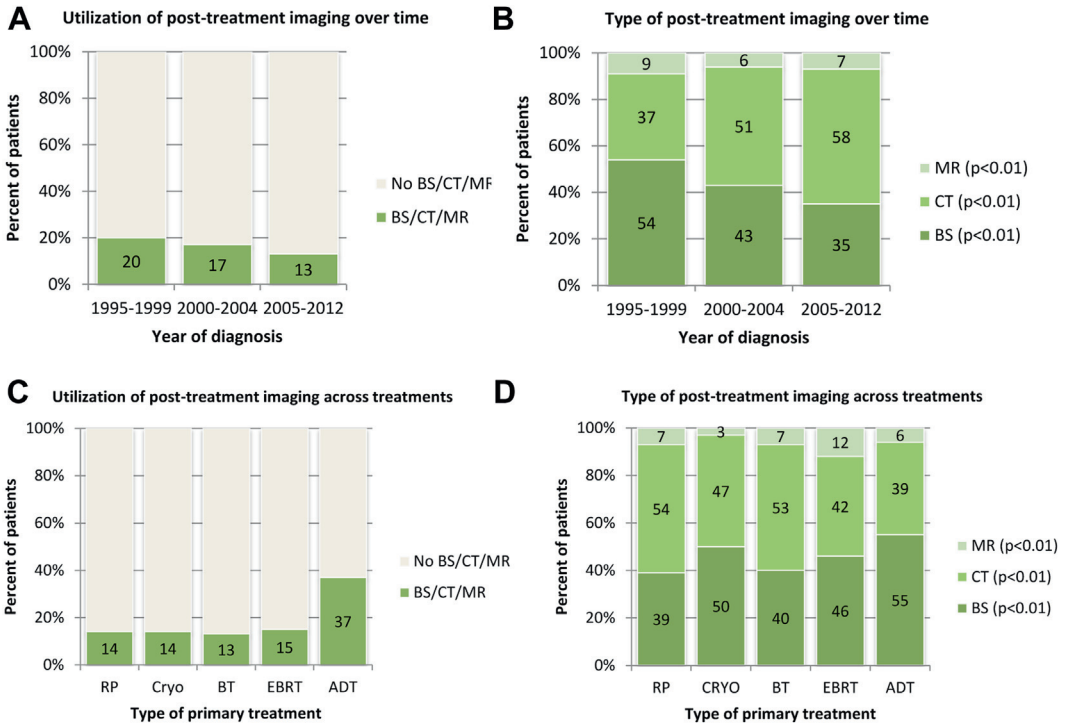

Figure 1. Use (*A*) and type (*B*) of posttreatment imaging with time by diagnosis year, and use (*C*) and type (*D*) across treatments by primary treatment modality in 8,435 men treated for PCa between 1995 and 2012, of whom 6% overall and 36% of those imaged underwent multiple posttreatment imaging modalities.

ADT (55% of cases) while CT was done most frequently after surgery and BT (54%). Patients treated with EBRT showed the highest MRI rate (12%) (fig. 1, *C* and *D*).

Median time from treatment to first posttreatment imaging varied among treatment types. Radiotherapy (EBRT and BT) had the longest and ADT had the shortest time (24 and 2.6 months, respectively, log rank p <0.01, fig. 2). The median number of posttreatment images in patients who underwent any imaging was 1 regardless of treatment modality. Of men who underwent RP or RT and then experienced recurrence imaging was done in 48% before biochemical recurrence developed. Of patients treated with RP 25% and 75% underwent imaging before and after PSA failure, respectively. Of patients treated with radiation who experienced recurrence imaging was done before and after PSA failure in 9% and 91%, respectively.

On initial Poisson regression analysis assessing imaging volume, primary treatment type (BT vs ADT, RR 0.76, 95% CI 0.58–0.99 and EBRT vs ADT, RR 0.73, 95% CI 0.55–0.98, p <0.05) and last posttreatment PSA (logarithm) (RR 1.49, 95% CI 1.39–1.59, p <0.01) were associated with multiple posttreatment imaging. Medicare plus supplement coverage, CAPRA clinical risk, white race/ethnicity and earlier diagnosis year were also associated with multiple imaging. There was a borderline but nonsignificant association between academic centers and multiple images compared to community urologists (HR 1.63, 95% CI 1.11–2.39, p = 0.06). Age and pretreatment imaging were not significant (table 1).

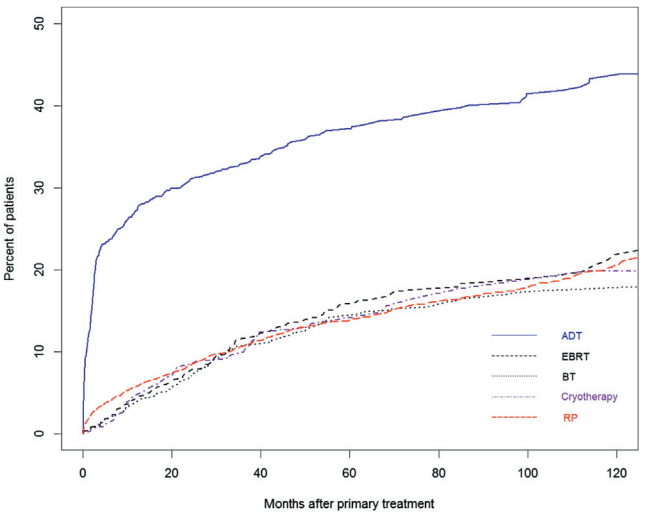

Figure 2. Time to first posttreatment imaging by primary treatment modality in 8,435 men treated for PCa between 1995 and 2012 (log rank test p <0.01).

Table 1. *Poisson regression of factors associated with multiple posttreatment imaging in 8,435 men treated for PCa between 1995 and 2012*

	RR (95% CI)	Parameter p Value	Global p Value
Age at diagnosis	0.99 (0.98–1.00)	0.22	0.22
Primary treatment:			
ADT	Referent		<0.05
RP	0.94 (0.73–1.20)	0.61	
Cryo	0.72 (0.51–1.03)	0.08	
BT	0.76 (0.58–0.99)	<0.05	
EBRT	0.73 (0.55–0.98)	<0.05	
Race/ethnicity:			
White	Referent		<0.01
Black	0.57 (0.44–0.75)	<0.01	
Other	0.68 (0.39–1.17)	0.17	
Insurance:			
Medicare + supplement	Referent		<0.01
Medicare	0.74 (0.58–0.94)	<0.05	
Private	0.70 (0.57–0.86)	<0.01	
Veteran	0.55 (0.27–1.12)	0.10	
Unknown	0.65 (0.43–0.99)	<0.05	
CAPRA clinical risk (0–10)	1.09 (1.05–1.13)	<0.01	<0.01
Clinical site:			
Community	Referent		0.06
Veteran	1.57 (0.87–2.83)	0.13	
Academic	1.63 (1.11–2.39)	<0.05	
Diagnosis yr	0.96 (0.94–0.98)	<0.01	<0.01
Pretreatment imaging:			
No	Referent		0.16
1 or Greater	1.12 (0.96–1.32)	0.16	
Posttreatment PSA (log[ng/ml])	1.49 (1.39–1.59)	<0.01	<0.01

On Cox analysis of time to first imaging RP (HR 0.64, 95% CI 0.53–0.78), Cryo (HR 0.46, 95% CI 0.33–0.64), BT (HR 0.48, 95% CI 0.39–0.60) or EBRT (HR 0.43, 95% CI 0.30–0.53, p <0.01) was associated with a lower likelihood of posttreatment imaging compared to ADT (table 2). Higher posttreatment PSA (logarithm) (HR 1.56, 95% CI 1.50–1.63, p <0.01) as well as white race/ethnicity, Medicare plus supplement coverage and higher CAPRA were associated with a higher likelihood (table 2).

The salvage treatment-free survival rate was 81% 5 years after primary therapy. In a subset of men who underwent posttreatment imaging positive findings on imaging were associated with a higher likelihood of salvage treatment (HR 2.13, 95% CI 1.71–2.66, p <0.01). RP (HR 0.65, 95% CI 0.50–0.83), BT (HR 0.74, 95% CI 0.56–0.99) or EBRT (HR 0.70, 95% CI 0.52–0.94, p <0.01) was associated with a lower likelihood of salvage treatment compared to ADT. A higher CAPRA score was also significant (table 2).

DISCUSSION

PCa can be difficult to evaluate with imaging and there is no consensus on the type, timing or frequency of imaging to monitor treatment response. NCCN Guidelines® recommend that clinical risk, patient age, stage, grade, PSA kinetics and general health should inform decisions about the use and frequency of posttreatment imaging.[13] In this context we assessed a large, national PCa registry to characterize BS, CT and MRI patterns after primary treatment and found that use generally decreased with time. BS and MRI use decreased while CT increased.

Typically practice guidelines define disease progression in terms of posttreatment biochemical failure, which in turn might trigger imaging. With the downward stage migration of PCa in the PSA screening era many patients are diagnosed and treated at early stages with a high cure rate.[14] Consequently lower biochemical recurrence rates indicate lower rates of posttreatment imaging and may explain why posttreatment imaging was performed more in earlier years. Previous studies also show decreased pretreatment imaging in practice,[3] which may have influenced decisions to forego posttreatment imaging. On the other hand, imaging was done before PSA failure in 25% and 9% of patients with recurrence after RP and RT, respectively, raising further questions about appropriate use.

Patients treated with primary ADT showed the highest rate of posttreatment imaging, primarily with BS, regardless of disease risk. Primary ADT was independently associated with an increased likelihood of multiple imaging and with the risk of any imaging after treatment. These findings may be explained by differences in the risk status of patients who received ADT beyond what was captured by the CAPRA score or by more rapid progression. Men treated with ADT are also usually at higher risk for disease progression, metastasis and mortality than those treated with more definitive local therapy.[15,16] Given the suppressive effect of ADT on serum PSA and the increased risk of metastatic disease in these patients, many physicians believe that combining posttreatment imaging (BS in particular) with testing for increasing PSA could improve monitoring for metastasis.[17]

In our study patient age was not significantly associated with multiple posttreatment imaging. However, previous reports show that degenerative changes associated with aging may lead to increased uptake and false-positive findings on BS and in turn to additional confirmatory imaging.[18] We found a trend toward multiple imaging being ordered at academic centers (nonsignificant p = 0.06) compared to community urologists. This finding could have been due to a higher volume of advanced cases enrolled in clinical trials at academic centers. In our study patients treated with more definitive local therapy were less likely to undergo posttreatment imaging but those who did

Table 2. *Cox proportional hazards regression of factors associated with time to posttreatment imaging in 8,435 men treated for PCa and time to salvage treatment in subset of 1,458 with posttreatment imaging after primary treatment for PCa between 1995 and 2012*

	Overall Time to Posttreatment Imaging			Subset Time to Salvage Treatment		
	HR (95% CI)	Parameter p Value	Global p Value	HR (95% CI)	Parameter p Value	Global p Value
Age at diagnosis	1.00 (0.99–1.01)	0.68	0.68	1.00 (0.99–1.01)	0.97	0.97
Primary treatment:						
ADT	Referent		<0.01	Referent		<0.01
RP	0.64 (0.53–0.78)	<0.01		0.65 (0.50–0.83)	<0.01	
Cryo	0.46 (0.33–0.64)	<0.01		1.14 (0.75–1.71)	0.54	
BT	0.48 (0.39–0.60)	<0.01		0.74 (0.56–0.99)	<0.05	
EBRT	0.43 (0.34–0.53)	<0.01		0.70 (0.52–0.94)	<0.05	
Race/ethnicity:						
White	Referent		<0.01	Referent		0.69
Black	0.69 (0.55–0.87)	<0.01		0.90 (0.64–1.26)	0.53	
Other	0.65 (0.46–0.91)	<0.05		0.84 (0.49–1.44)	0.52	
Insurance:						
Medicare + supplement	Referent		<0.01	Referent		0.53
Medicare	0.86 (0.73–1.02)	0.09		0.89 (0.69–1.14)	0.35	
Private	0.73 (0.62–0.86)	<0.01		0.89 (0.70–1.12)	0.33	
Veteran	0.53 (0.22–1.24)	0.14		0.66 (0.10–4.22)	0.66	
Unknown	0.64 (0.47–0.88)	<0.01		0.68 (0.42–1.11)	0.12	
CAPRA clinical risk (0–10)	1.05 (1.02–1.09)	<0.01	<0.01	1.12 (1.08–1.17)	<0.01	<0.01
Clinical site:						
Community	Referent		0.37	Referent		0.99
Veteran	1.65 (0.73–3.77)	0.23		1.07 (0.18–6.50)	0.94	
Academic	1.10 (0.87–1.40)	0.44		1.03 (0.71–1.48)	0.89	
Diagnosis yr	1.02 (1.00–1.03)	0.07	0.07	1.00 (0.97–1.03)	0.99	0.99
Pretreatment imaging:				–	–	–
No	Referent					
1 or Greater	0.98 (0.87–1.10)	0.725	0.73			
Posttreatment PSA (ng/ml)	1.56 (1.50–1.63)	<0.0001	<0.01	–	–	–
Posttreatment imaging finding:	–	–	–			
Neg				Referent	–	<0.01
Pos				2.13 (1.71–2.66)	<0.01	–

tended to undergo CT. The latter modality was performed most frequently after surgery and after BT (54% and 53% of cases, respectively, $p < 0.01$).

Studies show that PCa recurrence, which is often preceded by biochemical failure, develops in 20% to 50% of men by 10 years after surgery[19] and in 30% by 5 years after radiation therapy.[20] Up to a third of patients with biochemical relapse receive a second line treatment, usually without clinical or radiological evidence of disease.[19,21] The ability to distinguish local recurrence from systemic disease with posttreatment imaging may be critical because local recurrence is often amenable to local salvage treatment.[22] Some criteria, such as time to biochemical failure, PSA doubling time and positive surgical margins, were proposed to differentiate local recurrence from systemic disease.[23] However, imaging may still be needed to detect disease relapse in the absence of increased PSA[24] or in cases in which increased PSA after RP is suspected to be due to retained benign tissue. Some groups reported that the rate of surgical margins with benign prostatic tissue was as high as 60% after RP.[25,26]

Many patients receive salvage therapy, mainly ADT, in response to biochemical failure after RP or radiation therapy without posttreatment imaging.[27] In the current study positive findings on posttreatment imaging were associated with salvage treatment, suggesting that posttreatment imaging may influence subsequent management. Primary therapy with surgery or radiation and a higher CAPRA risk were also associated with the risk of salvage treatment. The association between high CAPRA risk, and pretreatment and multiple posttreatment imaging likely reflects risk adapted practice patterns in imaging use. For example, as newer drugs come to market that are approved only to treat metastatic disease, a diagnosis of systemic disease is mandatory for patients to be eligible for clinical trials. In a recent study of men considered for a large, phase 3 clinical trial comparing zibotentan vs placebo for nonmetastatic PCa Yu et al found that almost a third of patients presumed to have nonmetastatic disease were found to have metastasis on MRI, CT or BS.[28] This suggests that a high proportion of patients thought to have nonmetastatic, castrate resistant PCa may harbor asymptomatic metastasis. With the emergence of newer drugs for metastatic disease, such as sipuleucel-T[29] and denosumab,[30] it is critical to identify good candidates early. This may necessitate earlier and more intensive imaging with more novel technologies, which may lead to downward stage migration in the nature of early M1 PCa.

This study has several limitations. In addition to the retrospective and descriptive nature of the study design, there may be other compelling clinical motivations that drive CT that were unaccounted for in our analysis, including comorbid stones, hematuria, renal mass and others. However, we believe that nonPCa cross-sectional imaging is of little consequence, given the clearly PCa driven focus of clinical information captured in the database. Although the CaPSURE database does not differentiate between positron emission tomography/CT and CT, we estimated that few CTs in the data registry were positron emission tomography/CT based on the raw data submitted from individual sites. Because CaPSURE reflects real-world practice patterns, imaging was performed at treating physician discretion and not standardized in any way. Therefore, we did not address the adequacy or appropriateness of the imaging that was reported.

Despite these considerations our study has several strengths that merit recognition. The most significant strength is the novel use of a large, nationwide, largely community based PCa registry with longitudinal followup to address a common clinical question. Lastly, the independent associations between definitive treatment modality and followup imaging warrant further investigation, given the lack of data on the use of imaging after primary treatment.

CONCLUSIONS

Currently there are no established guidelines for posttreatment imaging for PCa. This study shows that although the rate of imaging after primary management decreased with time, BS use decreased while CT use increased. Patients treated with ADT were most likely to be imaged, primarily with BS, while those who underwent more definitive local therapy were less likely to be imaged and those who were imaged tended to undergo CT. Imaging may add value to PSA monitoring after definitive treatment to identify disease recurrence and progression because PSA fluctuations are common. Posttreatment imaging may be particularly valuable to differentiate metastasis from local recurrence and identify patients who are candidates for local salvage therapy. Further studies are needed to establish guidelines for the optimal frequency and type of imaging to monitor treatment response.

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