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Does laterality of positive needle biopsy in clinical T2a prostate cancer patients affect biochemical recurrence free survival?

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Abstract

Objectives—To test whether clinical stage T2a prostate cancer patients with biopsy-proven disease only contralateral to the palpable abnormality experience outcomes similar to patients with clinical stage T1c.

Methods—We identified 1,567 patients who underwent radical prostatectomy at our institution from 1995 to 2007 with PSA less than 10 ng/ml and complete information regarding laterality of positive biopsy cores. 1,157 patients were clinical stage T1c and 410 were stage cT2a. Clinical T2a patients were divided into two groups based on the laterality of positive biopsy cores: ipsilateral-only (n=241) and contralateral-only (n=53). Kaplan Meier analyses were used to compare biochemical recurrence-free survival (BRFS) probabilities.

Results—Clinical T2a patients had significantly poorer 5-year BRFS than cT1c patients (83.5% vs. 94.4%, $p<0.001$). The difference in BRFS between the cT2a contralateral and ipsilateral groups was statistically insignificant. There was a significant difference in BRFS between patients with cT1c and cT2a ipsilateral disease. There was a statistically insignificant difference in BRFS between patients with cT1c and cT2a contralateral disease.

Conclusions—The laterality of the needle biopsy in relation to the palpable abnormality in cT2a patients may affect BRFS. Our data demonstrate an insignificant difference between patients with cT2a contralateral and cT1c disease.

Keywords

prostate; prostatic neoplasm; needle biopsy; survival analysis; prostate cancer staging

Introduction

Prostate cancer is the second most common malignancy in American men.¹ Clinicians use the TNM clinical staging system to stratify risk in men with prostate cancer. According to the American Joint Committee on Cancer (AJCC)-TNM 1992/2002 staging criteria for prostate cancer², patients with tumor identified on needle biopsy (NB), but undetectable on digital rectal examination (DRE) or imaging, are staged cT1c. Patients with a palpable, organ confined abnormality on DRE along with a positive NB are staged cT2. Clinical T2 patients are further

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subdivided into those with palpable abnormalities involving less than 50% of one lobe (cT2a), more than 50% of one lobe (cT2b), or both lobes (cT2c). Unilateral NB positive disease (cT2a/b) may be either ipsilateral or contralateral to the palpable abnormality.

There are no formalized guidelines informing clinicians as to the integration of NB results with clinical staging. Therefore, some clinicians restage cT2a patients having NB positive disease only contralateral to the palpable abnormality as cT1c, while other clinicians continue to stage these patients as cT2a. We examined whether men undergoing radical prostatectomy (RP) at a tertiary referral center classified as clinical stage T2a with biopsies only positive contralateral to the palpable abnormality experience outcomes similar to those classified as clinical stage T1c.

Materials and Methods

Study Population and Data Collection

The institutional review board at Johns Hopkins approved this study and, when required, written informed consent was obtained from study participants. Clinical stage was assigned by the attending surgeon at Johns Hopkins prior to surgery. We excluded patients if their clinical stage was reassigned to T1c when NB did not demonstrate cancer ipsilateral to a palpable abnormality, as there was no way to distinguish these patients from those with T1c without palpable abnormalities. We identified 1,157 men staged cT1c and 504 staged cT2a satisfying the following criteria: underwent RP at our institution since 1995, had PSA<10ng/ml, and had available follow-up information. Of the 504 cT2a patients, 410 had complete data regarding laterality of both the palpable abnormality and the positive biopsy. Of the 410 patients, 294 patients with unilateral lesions were further divided into having either ipsilateral-only (n=241) or contralateral-only (n=53) prostate cancer on NB. All diagnostic NB slides provided by referring urologists were reviewed preoperatively by dedicated genitourinary pathologists at our institution.

Statistical Analysis

Age and preoperative PSA were evaluated as continuous variables. Two-sample rank-sum test was used for continuous variables to evaluate similarities between comparison groups. Other clinical characteristics were evaluated as categorical variables. NB and pathologic Gleason score were divided into 4 categories (3+3 or less, 3+4, 4+3, and 8-10), with 3+3 or less as the reference category. Pathologic stage parameters were binary (categorical variables) and included positive surgical margins (SM), extraprostatic extension (EPE), positive seminal vesicle (SV) involvement, and lymph node (LN) involvement. Chi-square analysis was used for all categorical variables to determine similarities between groups.

Kaplan-Meier analyses were used to compare differences in BRFS amongst the clinical stage subgroups—cT2a patients as a whole (n=410), ipsilateral-only (n=241), and contralateral-only (n=53). Log rank tests for equality of BRFS were performed for cT1c compared to cT2a as a whole, cT1c to each cT2a subgroup, and cT2a subgroups to one another. Cox proportional hazards modeling was used to determine both univariate and multivariable BRFS hazard ratios of cT1c compared to each cT2a subgroup and cT2a as a whole, as well as the BRFS hazard ratios of cT2a ipsilateral compared to cT2a contralateral. The covariates included in the multivariable Cox proportional hazards model were age (continuous), preoperative PSA (continuous), and biopsy Gleason score (categorical). A 2-tailed p-value <0.05 was considered significant in all analyses. All statistical analyses were performed using STATA® 9.0 (College Station, TX).

Results

The clinical characteristics of the study cohort are depicted in Table 1. Compared to cT1c patients, cT2a patients as a whole had lower PSA, higher biopsy and prostatectomy Gleason scores, and a greater proportion of EPE, positive SM, SV, and LN (all $p < 0.02$). Of the 410 cT2a patients with laterality data, 241 had ipsilateral-only disease (58.8%) and 53 had contralateral-only disease (12.9%). Between these two cT2a groups, there were no significant differences in any of the clinicopathologic characteristics (all $p > 0.1$).

Figure 1 depicts Kaplan Meier BRFS curves and 5 year BRFS rates of the various patient groups. Overall, cT2a patients had significantly poorer 5-year BRFS than cT1c (83.5% vs. 94.4%, $p < 0.001$). As depicted in Table 2, there were significant differences in BRFS between cT1c patients compared to cT2a patients with ipsilateral-only disease ($p = 0.0021$). Conversely, the BRFS difference between cT1c and cT2a patients with contralateral-only disease was statistically insignificant ($p = 0.077$). Univariate Cox regression demonstrated significant differences in BRFS hazard ratios of cT1c compared to cT2a as a whole and to the ipsilateral group (all $p < 0.01$), but the difference between cT1c patients and patients with cT2a contralateral disease was statistically insignificant ($p = 0.087$). The BRFS difference between the cT2a subgroups was also statistically insignificant ($p = 0.94$). Upon multivariable analysis, controlling for age, preoperative PSA and Gleason score, the BRFS hazard ratios remained statistically significant for cT1c patients compared to cT2a patients with ipsilateral disease ($p = 0.035$). BRFS differences between cT1c patients and cT2a patients with contralateral-only disease remained insignificant ($p = 0.19$).

Discussion

In the modern era, the indications to pursue a diagnostic evaluation for prostate cancer include abnormalities in physical findings on the DRE, abnormalities in serum marker (PSA), or both. These differences in biopsy indication are reflected in the current TNM system. Regardless of the indication for biopsy, the standard of care is to perform systematic sampling of the prostate gland. Given the typically multifocal nature of prostate cancer,³ a patient with a palpable abnormality on DRE may have cancer diagnosed on the same side, the opposite side, or bilaterally. Vis et al reported that patients with PSA level less than 4.0 ng/ml who only had an abnormal DRE, 37% had positive NB only on the contralateral side, a finding they determined to be “serendipitous”.⁴ Despite this common finding, there is no widely held consensus on the prognostic implications of biopsy laterality in conjunction with TNM staging. Some clinicians restage cT2a patients with contralateral-only positive NB to cT1c, whereas others do not. We undertook the present study to evaluate the prognostic significance of biopsy laterality in cT2a patients compared to cT1c patients in regard to BRFS.

The rate of “serendipitous” NB in our study (PSA < 10 ng/ml) was 12.9%. However, this lower rate may reflect the exclusion of patients restaged to cT1c or the effect of higher PSA levels. There is disagreement in the literature as to whether there is a BRFS difference between cT1c and cT2a staged patients. Several previously published studies have demonstrated no difference in BRFS between patients of clinical stage T1c versus cT2a,^{5,6} but others have found significant differences.⁷ In our study, we found a statistically significant difference in BRFS between cT1c and cT2a patients. There was a significant difference in BRFS between cT1c patients and cT2a patients with ipsilateral disease, but the difference in BRFS between cT1c patients and cT2a patients with contralateral-only disease was insignificant. The difference in BRFS between the cT1c and cT2a groups may be due to different demographic characteristics such as PSA, NB and RRP Gleason scores, positive SM, LN involvement, SV involvement, and EPE. With the exception of PSA and NB Gleason score, the other characteristics are only determined after RRP and therefore are not available for prognostic

and treatment decisions. Multivariable analysis including only those covariates available preoperatively (PSA, NB Gleason, and age) demonstrated the BRFS remains significantly different between cT1c and cT2a. This indicates that even when other commonly available preoperative covariates are accounted for, clinical stage is an important and significant predictor of BRFS.

Between the cT2a groups, the differences in either demographic characteristics or BRFS were statistically insignificant. However, when the groups were each compared to cT1c patients, an interesting pattern appeared. BRFS rates were significantly worse in cT2a patients with ipsilateral disease than cT1c patients. However, cT2a patients who had positive biopsy only on the contralateral side to the palpable lesion had BRFS rates similar to patients staged cT1c. Although the differences in BRFS between cT1c patients and cT2a contralateral patients, and between cT2a contralateral patients and cT2a patients with ipsilateral disease were statistically insignificant, the difference in BRFS between cT1c and cT2a patients with ipsilateral disease was significant. This non-significant trend towards a difference in these groups suggests there may be a balance of competing influences determining prognosis among these groups. While larger, more likely palpable, tumors are hypothesized to have worse outcomes, this phenomenon maybe countered by the superficial location of these lesions, able to be detected earlier (these lesions have lower PSA than those in the cT1c cohort) in their course.

Several previous studies have addressed the use of laterality data in conjunction with TNM staging criteria. Daniels et al examined the implications of bilaterally positive biopsy in comparison to negative contralateral biopsy in cT2a patients and determined that patients with bilaterally positive biopsies had larger tumor volume and a non significant decrease in BRFS.⁸ We further substratified this analysis by comparing ipsilateral only, any ipsilateral (including bilateral), and contralateral-only disease. Freedland et al determined that biopsy laterality (unilateral versus bilateral) improved the predictive value clinical staging in patients with low risk cancer (cT1c and cT2a patients) compared to high risk cancer (cT2b and cT2c).⁹ Our study examines cT1c and cT2a patients separately and further subdivides unilateral disease into ipsilateral-only and contralateral-only. Our study complements the work of Freedland et al by demonstrating that NB laterality in relation to the palpable abnormality may inform clinical staging decisions even within low risk cancer groups.

There are several limitations to our study. TNM staging is subjective and suffers from poor interobserver reliability.^{10,11} In our retrospective study, the screening DRE would be the most informative method by which to determine contralateral-only or ipsilateral-only designation because of the possible difference in sensitivity of screening versus pre-treatment DRE, but the laterality of the initial abnormal DRE was often not available to the researchers. There may have also been inconsistencies with the timing of the DRE. Palpable lesions may be less likely to be significant tumors as some patients may have developed them as a result of benign pathology such as fibrosis or hematoma in the time period after NB. However, as all patients were reexamined by our clinicians prior to treatment, there is the potential of added reliability and further confirmation of clinical staging. Rapidly growing, aggressive tumors may have developed into palpable lesions in the time between biopsy and referral consultation. Additionally, greater numbers of biopsy cores would provide more sensitive preoperative information regarding tumor location. However, the NB technique varies amongst operators from referring institutions, with potential differences in number of core biopsies taken. This data is not consistently available in our institution's database. Our institution's role as a tertiary referral center may have led to a selection bias of patients with more severe disease as measured by Gleason score or PSA levels. Also contributing to selection bias is the fact that all patients in the study underwent RP. Patients with the most aggressive cT2a cancers may have been referred for radiation therapy.

Conclusion

There is a significant difference between patients with cT2a ipsilateral disease and patients with cT1c disease; however, there is an insignificant difference between the BRFS probabilities of patients with cT2a contralateral and cT1c disease. Therefore cT2a patients who present with disease contralateral to their palpable lesion may have a prognosis better than previously believed. The TNM staging system may be refined with the addition of laterality data. However, further studies should be conducted to explore better the relationship between biopsy laterality and outcomes.

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	No. at risk at 5 years	5 yr survival	95% CI
cT1c	19	0.94	0.91 to 0.96
cT2a (overall)	96	0.83	0.78 to 0.88
Ipsilateral only	38	0.85	0.75 to 0.91
Contralateral only	10	0.79	0.51 to 0.92

Figure 1.

TABLE 1
Demographic and clinical characteristics of study population

	All	cT1c	cT2a		
			All with complete data	Ipsilateral only	Contralateral only
No patients	1661	1157	410	241	53
Age (yr)					
Mean ± SD	58.18±6.10	58.12±6.06	58.44±6.15	57.99±6.17	59.60±6.28
Median (range)	58 (38-71)	58 (40-73)	59 (38-71)	58 (40-70)	61 (47-71)
Preoperative PSA					
Mean ± SD	5.42±2.12	5.59±1.99	4.88±2.31	4.80±2.36	4.38±2.36
Median (range)	5.4 (1-9.89)	5.5 (1-9.89)	4.9 (1-9.89)	4.8 (1-9.89)	4.69 (56-9.0)
Biopsy Gleason (%) *					
≤3+3	1377 (83)	1006 (87)	305 (75)	188 (78)	46 (87)
3+4	187 (11)	106 (9)	64 (16)	29 (12)	3 (6)
4+3	61 (4)	32 (3)	21 (5)	13 (5)	2 (4)
≥4+4	34 (2)	13 (1)	19 (5)	11 (5)	2 (4)
Pathological Gleason (%) **					
≤3+3	1148 (69)	834 (72)	256 (63)	160 (67)	40 (75)
3+4	348 (21)	226 (20)	99 (24)	52 (22)	11 (22)
4+3	103 (6)	62 (5)	31 (8)	18 (8)	1 (2)
≥4+4	59 (4)	34 (3)	22 (5)	9 (4)	1 (2)
Positive surgical margins (%) ***	9.77	8.48	12.25	10	11.32
Lymph node involvement (%)	0.72	0.26	1.46	0.83	0
Seminal vesicle involvement (%)	2.11	1.56	3.14	1.66	0
Extraprostatic extension (%) ****	26.24	22.12	34.89	32.64	26.42

* Data missing for 2 cT2a patients (1 bilateral positive biopsy)
** Data missing for 1 cT1c patient and 2 cT2a patients (2 ipsilateral positive patients)
*** Data missing for 1 cT1c patient and 2 cT2a patients (1 ipsilateral only, 1 bilateral)
**** Data missing for 18 cT1c patients and 4 cT2a patients (2 ipsilateral only, 1 bilateral, 1 with no data)

P-values† between comparison groups for each characteristic: 1) age‡; 2) preoperative PSA‡; 3) biopsy Gleason; 4) pathological Gleason; 5) positive surgical margins; 6) lymph node involvement; 7) seminal vesicle involvement; 8) extraprostatic extension

cT1c vs cT2a: 1) .5; 2) <0.001; 3) <0.001; 4) <0.001; 5) 0.007; 6) <0.001; 7) 0.02; 8) <0.001

cT1c vs ipsilateral only: 1) .9; 2) <0.001; 3) <0.001; 4) 0.4; 5) 0.5; 6) 0.2; 7) 0.9; 8) 0.001

cT1c vs contralateral only: 1) 0.09; 2) <0.001; 3) 0.3; 4) 0.7; 5) 0.5; 6) 0.7; 7) 0.4; 8) 0.5

Ipsilateral vs contralateral: 1) 0.1; 2) 0.3; 3) 0.5; 4) 0.3; 5) 0.8; 6) 0.5; 7) 0.4; 8) 0.4

† p value by Chi-squared except where noted

‡ p value by rank-sum

TABLE 2
Log rank test for equality of biochemical recurrence free survival functions and hazard ratios

Log rank	Univariate Cox Regression			Multivariable Cox Regression		
	HR	95% CI	p-value	HR	95% CI	p-value
cT1c vs cT2a	2.76	1.79 to 4.26	<0.001	2.25	1.44 to 3.51	<0.001
cT1c vs ipsilateral only	2.30	1.33 to 3.98	0.0021	1.85	1.04 to 3.28	0.035
cT1c vs contralateral only	2.32	0.88 to 6.08	0.077	1.95	0.71 to 5.36	0.19
Contralateral only vs ipsilateral only	0.96	0.36 to 2.55	0.94	1.91	0.36 to 2.82	0.98