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ORIGINAL PAPER

Prognostic value of subclassification (pT2 stage) of pathologically organ-confined prostate cancer: Confirmation of the changes introduced in the 8th edition of the American Joint Committee on Cancer (AJCC) staging system

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Summary ***Objective: The last edition of the AJCC staging system eliminated the pT2 subclassification of prostate cancer (PCa). Our objective was to evaluate the association of pT2 subclassification with the oncological results of patients with PCa who underwent radical prostatectomy (RP).***

Material and methods: We evaluated 367 patients who underwent RP between 2009 and 2016, with pT2 disease in the final pathological evaluation. We assessed differences in rates of biochemical recurrence (BCR), metastasis and mortality between T2 substages (pT2a/b vs pT2c).

Results: Fifty-three (14.4%) patients presented pT2a/b disease and 314 (85.6%) pT2c disease. The mean follow-up time was 4.9 ± 2.6 years. Grade group scores (p = 0.1) and prostate specific antigen (PSA) (p = 0.2) did not differed between pT2 substages. The rate of BCR in pT2a/b and pT2c patients was 11.3% and 18.2%, respectively (p = 0.2). Five (9.4%) patients with pT2a/b and 45 (14.3%) with pT2c substage underwent salvage radiotherapy (p = 0.3). The rate of positive surgical margins did not differ between groups (p = 0.2). Seven (2.2%) patients with pT2c had lymph nodes or distant metastases. The overall survival was 92.5% and 93.6% in pT2a/b and pT2c, respectively (p = 0.2).

Conclusion: Our results are in accordance with the changes introduced in the 8th edition of the AJCC staging system in which the pT2 subclassification was eliminated.

KEY WORDS: Prostatic neoplasms; Biochemical recurrence; Prostatectomy; Neoplasm staging.

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INTRODUCTION

The TNM system is an established tool for classification of solid tumors by means of tumor size and extent, the involvement of local lymph nodes, and the presence of distant metastases. The classification was established in order to visualize prognostic implications and to allow establishment of systematic therapeutic algorithms. Successive editions from the most common staging system for prostate cancer, the *American Joint Committee on Cancer* (AJCC) system, have been published reflecting progress in our understanding of prostate cancer biology and prognosis (1).

The 8th edition of AJCC staging system, implemented in January 2018, has set some changes (2, 3). The major anatomic-based change is in the classification of organ-confined disease. All organ-confined disease is now pathologically staged as T2 without further subcategorization by extent of involvement or laterality (3).

This change was assigned a Level of Evidence III, meaning that available evidence was not strong. In fact, there is no consensus whether pT2 subclassification has prognostic value in patients who underwent radical prostatectomy (4). Nonetheless, the collective reasoning and data were deemed sufficient to support this change in pathologic stage.

It is unknown how this updated staging classification will perform in different populations. Given these changes have the potential to influence treatment decisions, and thus patient outcomes, independent validation is necessary to confirm the prognostic accuracy and to ensure generalizability across different settings (5, 6).

The aim of this study was to assess the prognostic association of pT2 subclassification with the probability of *biochemical recurrence* (BCR), metastasis, *cancer specific survival* (CSS) and *overall survival* (OS) in patients who had organ-confined disease in *radical prostatectomy* (RP) specimens.

MATERIALS AND METHODS

We performed a cross-sectional analysis of patients who underwent RP between 2009 and 2016 in a single urology department with pT2 disease. Patients with missing data and/or neoadjuvant treatments were excluded.

The final study population consisted of 367 patients. Surgeries were performed by different surgeons. Patients who received previous treatments or had measurable

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PSA values immediately after surgery were excluded. Patients were followed with serum PSA at 4-6 weeks, every 6 months for 5 years and annually thereafter. Data were collected through the clinical information recorded in the database of our hospital. BCR was defined as the presence of a confirmed PSA value of 0.2 ng/ml or greater. Recurrence was based on clinical, laboratorial and radiological findings.

Data are expressed as mean ± standard deviation, number (%), or median with interquartile range as appropriate. IBM SPSS 24.0 software was used for all statistical analyses. Normality of numerical variables was accessed with Kolmogorov-Smirnov test, and Student t test or Mann-Whitney U test were properly used to assess differences in numerical variables. The chi-square or Fisher exact probability tests were used for categorical data as appropriate. CSS and OS were calculated using Kaplan-Meier analysis and tested for differences with the Mantel-Cox log-rank test. Multivariate analysis was performed with a binary logistic regression. Results were considered statistically significant if the P value was 0.05. For methodological reasons, we decided to focus the comparison between patients with unilateral (pT2a/b) and bilateral (pT2c) disease.

Table 1.
Demographics and disease characteristics by pT2 subclassification.

	pT2a/b	pT2c	p Value[1]
Patients (%)	53 (14.4%)	314 (85.6%)	-
PSA pre-RP, ng/ml (mean ± SD)	7.4 ± 4.9	8.3 ± 8.3	n.s.
Age at RP, years (mean ± SD)	62.9 ± 6.9	63.0 ± 6.8	n.s.
RP specimen Grade group (%)			
Grade Group 1	17 (32.1%)	104 (33.1%)	n.s.
Grade Group 2	32 (60.4%)	190 (60.5%)	
Grade Group 3	2 (3.8%)	17 (5.4%)	
Grade Group 4	1 (1.9%)	3 (1.0%)	
Grade Group 5	1 (1.9%)	0 (0%)	
Prostate size, cc (median)	45 (16-105)	45 (20-163)	n.s.
Perineural invasion, n (%)	31 (58.5%)	245 (78.0%)	0.01
Positive surgical margins (%)	5 (9.4%)	50 (15.9%)	n.s.
BCR rate (%)	6 (11.3%)	57 (18.2%)	n.s.
Time to BCR, years (mean ± SD)	2.6 ± 1.8	2.3 ± 2.0	n.s.
Salvage radiotherapy (%)	5 (9.4%)	45 (14.3%)	n.s.
Lymph node metastases (%)	0 (0%)	5 (1.6%)	n.s.
Distant metastases (%)	0 (0%)	2 (0.6%)	n.s.

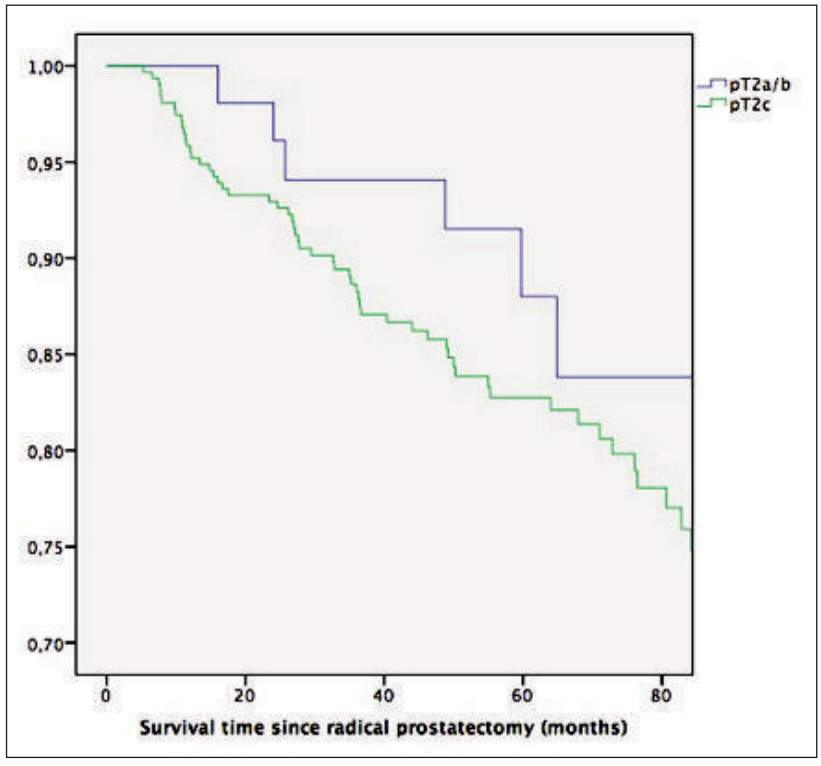
[1]*Statistical significances: p < 0.05; Abbreviations: BCR, biochemical recurrence; n.s., not significant; PSA, prostate specific antigen; SD, standard deviation.*

Results

Fifty-three (14.4%) patients presented pT2a/b disease and 314 (85.6%) pT2c disease. The mean age of our study population was 63.0 ± 6.8 years.

Demographics and disease characteristics by pT2 subclassification are shown in Table 1. The mean follow-up time was 4.9 ± 2.6 years. We found no significant difference between the preoperative PSA values of the two groups (p = 0.2, Table 1). Approximately two-thirds of patients with pT2a/b and pT2c stage had a grade group 2 PCa or higher (p = 0.1, Table 1). The prostate volume did not show significant differences between the groups (p = 0.5, Table 1). The rate of perineural invasion in RP specimens was higher in pT2c patients (p = 0.01, Table 1). Patients with pT2c substage showed no higher rates of positive surgical margins (p = 0.2, Table 1). Sixty-three (17.2%) patients had BCR in the entire cohort during follow-up. The rate of BCR in pT2a/b and pT2c patients was 11.3% and 18.2%, respectively (p = 0.2, Table 1). There was no significant difference in time from RP to BCR between pT2a/b and pT2c patients (p = 0.7). Five (9.4%) patients with pT2a/b and 45 (14.3%) with pT2c substage underwent salvage radiotherapy (p = 0.3, Table 1). No patient with pT2a/b disease developed lymph node or distant metastases (Table 1). In contrast, in the pT2c group 5 patients developed lymph node metastases and 2 pre-

Figure 1.
Overall survival of patients with pT2a/b and pT2c prostate cancer in radical prostatectomy specimens.



sented bone metastases during follow-up. The overall survival was 92.5% and 93.6% in pT2a/b and pT2c, respectively (p = 0.2, Figure 1).
No cancer related deaths were identified in both groups. One (1.9%) patient in the pT2a/b group did androgen-deprivation therapy. In the pT2c group, 7 (2.2%) patients were treated with androgen-deprivation.
No patient was treated with docetaxel, abiraterone, enzalutamide or another new drug.
In addition, we performed a binary logistic regression to access a multivariate analysis between ISUP grade, pT2 sub staging and surgical margins status from one side and survival or BCR on the other side. There was no association between these pathological variants and survival (p = 0.564; p = 0.748; p = 0.345) or BCR (p = 0.180; p = 0.246; p = 0.288), respectively.

Discussion

PCa grading has undergone significant evolution in the past half century (7, 8) and the AJCC staging system has been repeatedly revised with the current 2017 system eliminating the 3-tiered pT2 subclassification (4, 9). Since the adoption of the 1992 AJCC/UICC TNM prostate cancer staging system, the pT2 subclassification has remained controversial due to the lack of robust evidence that it adds meaningful prognostic value (10).
Our results confirm the 8th edition AJCC staging system for PCa. We confirmed that pT2 subclassification offers limited prognostic value, which supports its elimination. We found that the pT2 subclassification did not add prognostic information to the outcomes of BCR, distant metastases and overall survival. The subclassification of pT2 disease has been previously evaluated (4, 11-14). Multifocal cancer has been noted in up to 80% of prostatectomy specimens and thus subclassification into pT2a/b/c may depend more on detection than underlying biology (5, 15).
Freeland et al. evaluated the rate of BCR in patients with unilateral and bilateral organ confined PCa. They found no significant difference between both groups (16).
Other studies have observed results similar to those of our study (12, 13, 17, 18).
Nguyen et al. in a long follow-up study with 15.305 patients showed that the rates of metastases and cancer specific death at 10 years were relatively low in the pT2 population (4). The authors validate in their work the elimination of the pT2 subclassification and argue that the preoperative serum PSA level and pathological grade remain the strongest prognostic factors in patients with pT2 disease.
Our results are similar to these previous studies.
We observed higher rates of perineural invasion and positive surgical margins in patients with pT2c disease. However, these results had no significant impact on the development of BCR, metastases or survival. In agreement with the study of Nguyen, we found a very low overall metastases rate (0.5%) (4).
Our study showed no cancer-specific deaths. This finding may be justified by a relatively short follow-up for a disease with a long natural history. However, other studies with longer follow-up time also show rates of cancer-specific death below 0.5% (4, 19). Our work presents some limitations. First, it is a retrospective study which may introduce mis-classification or information bias. Some data regarding patients were missing. Another limitation is related to the sample size and duration of follow-up. A larger sample and length of follow-up would allow a further understanding of the prognostic value of the pT2 subclassification.

Conclusions

The pT2 subclassification showed no prognostic value in patients with PCa who underwent RP. Our results are in accordance with the changes introduced in the 8th edition of the AJCC staging system in which the pT2 subclassification was eliminated.

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