

Upgrading and upstaging in prostate cancer: From prostate biopsy to radical prostatectomy

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Abstract. Prostate cancer (CaP) is the most common malignancy in men and the second cause of cancer-related mortality after lung cancer. Several studies have evaluated the correlation between bioptic and pathological Gleason score (GS), documenting a correlation ranging between 30 and 60%. The aim of this study was the evaluation of the association between bioptic and pathological GS in a series of patients undergoing prostate needle biopsy and subsequent radical prostatectomy. We also aimed to evaluate the possible prognostic factors of upgrading and upstaging. We prospectively collected and retrospectively reviewed data from 300 consecutive patients who underwent radical retropubic or robot-assisted prostatectomy at our Institution. Patients who underwent prostate needle biopsy, transrectal or transperineal, with a minimum of 5 samples, were included in this study. Upgrading and downgrading were defined as increase or decrease, respectively, from one prognostic grade group to another, similar to up- or downstaging. The mean age of the patients was 62.97 years and the mean prostate-specific antigen (PSA) level was 7.83 ng/ml. A total of 51.3% of the population underwent a transperineal prostate biopsy. The most frequently represented bioptic GS was 3+3 (64.0%) followed by 3+4=7 (15.6%); the most frequent pathological Gleason score was 3+4 (44.3%), followed by 3+3 (31.0%). With regard to the bioptic GS 4-5-6 group, approximately half of the specimens (46.7%) were subsequently upgraded to GS 3+4, and 5.3% to 4+3. With regards to the bioptic GS 3+4 group, 57.4% was confirmed in the surgical specimen. In the 4+3 group, 23.5% of the cases was downgraded to 3+4 and 35.3% was confirmed. With regards to stage, ~39.7% of the patients received an upstaging on the pathological specimen. We evaluated the correlations between preoperative serum PSA level, prostate

volume, digital rectal examination and biopsy type and none of the variables considered exhibited a correlation with any upgrading ($P>0.05$). Moreover, we evaluated the correlations between the aforementioned variables and upstaging and, at the multivariate analysis, only a serum PSA <4 ng/ml was found to be an independent variable predictive of upstaging ($P=0.017$). Therefore, new tools are required to predict upgrading and upstaging of our patients, in order to ensure better counseling for optimal treatment planning.

Introduction

Prostate cancer (CaP) is the most common malignancy in men and the second cause of cancer-related mortality after lung cancer (1). The diagnosis of CaP is mainly performed by digital rectal examination (DRE), serum prostate-specific antigen (PSA) measurement and transperineal or transrectal ultrasound-guided biopsies. Prostate needle biopsy is one of the most common procedures performed in the common urological clinical practice; it is estimated that, in the U.S. alone, at least 800,000 prostate biopsies are performed annually (2).

Prostate biopsy has evolved over the years, starting from the technique described by Astraldi in 1937 (3) until the sextant prostate biopsy, described by Hodge *et al* in 1989 (4). Prostatic needle biopsy is currently considered the gold standard for the diagnosis of CaP and may be performed transrectally or transperineally, guided by ultrasound. The detection rates of these two techniques are comparable (5,6) and there is no final consensus regarding the optimal number of samples, although the British Prostate Testing for Cancer and Treatment Study has recommended 10 core biopsies (7), with antibiotic therapy, commonly quinolone, under local anesthesia.

The International Society of Urological Pathology (ISUP) Conference was held in March, 2005 in San Antonio, Texas (8), during which a panel of international expert uropathologists updated the Gleason grading, in order to increase the reproducibility and reliability of the evaluation of the biopsy specimens. A correct assignment of the Gleason score (GS) may be crucial in terms of prognostic and therapeutic management of CaP. Several studies have assessed the effect of the ISUP Conference on the concordance of Gleason pattern and the possible change of prognostic group.

Billis *et al* (9) evaluated 172 patients who underwent prostate needle biopsy and subsequent radical prostatectomy and

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described a significant effect of the ISUP Conference modifications on the evaluation of the Gleason patterns and the resulting change in prognostic group. Following re-evaluation of the specimens, an increase by 1 or even 2 score points was observed in 16.8 and 0.6% of the cases, respectively.

Furthermore, 26.7% of the 'reassigned' patients had a higher preoperative PSA level, a larger tumor, more frequent positive surgical margins and higher-stage pathological disease. After the re-evaluation, a higher number of patients was assigned to the prognostic group of GS 8-10, exhibiting, at follow-up, a shorter time to biochemical disease recurrence (log-rank $P=0.011$) (9).

In a more recent study that evaluated 590 biopsy specimens according to the classic and modified GS, the number of cores with 75-100% pattern 4 cancer was increased by 95% (10). Over the last few years, the bioptic GS has become increasingly important, since several patients may be offered therapeutic alternatives to radical prostatectomy, such as active surveillance, and prostate biopsy results represent a crucial point in the management of the disease.

Several studies have evaluated the correlation between bioptic and pathological GS, documenting a correlation ranging between 30 and 60%, particularly regarding low GS. The aim of this study was, therefore, to evaluate the association between bioptic and pathological GS in a series of patients undergoing prostate needle biopsy and subsequent radical prostatectomy and the possible prognostic factors of upgrading and upstaging.

Materials and methods

Patients. We prospectively collected and retrospectively reviewed data from 300 consecutive patients who underwent radical retropubic prostatectomy or laparoscopic robot-assisted prostatectomy at our Institution between January, 2010 and May, 2012. Patients who underwent prostate needle biopsy, transrectal or transperineal, at our Institution or at other centers, with a minimum of 5 samples, were included in this study.

Data collection. We collected clinical data regarding age, serum PSA level, free to total ratio, prostate volume calculated by transrectal ultrasound and clinical stage. Cases with neoadjuvant therapy were excluded from this analysis.

Surgical treatment. All the patients were subjected to radical prostatectomy within 6 months following prostate biopsy. The radical prostatectomy was performed by five operators. Retropubic prostatectomies were performed according to the technique described by Walsh and Donker (11) and robot-assisted laparoscopic prostatectomies were performed as previously described in the literature (12). Pelvic lymphadenectomy was performed in accordance with the indications of the Guidelines of the European Association of Urology (13).

Specimen grading. All the specimens were processed by two experienced uropathologists according to the TNM of 2009. The biopsies not performed at our center were not subjected to central review. Upgrading and downgrading were defined as an increase or decrease, respectively, from one prognostic

grade group to another, similar to up- or downstaging. The grading prognostic groups were established according to the GS and grouped as follows: 5-6, 3+4, 4+3, 8 and 9-10.

Statistical analysis. Continuous variables were evaluated using mean and standard deviation or median and interquartile range, according to their distribution. The association between upgrading or upstaging and age, preoperative PSA level, PSA density, free to total ratio, number of positive samples and weight of the surgical specimen were evaluated using the Student's t-test or the Mann Whitney U test, depending on their distribution. The association between upgrading or upstaging and rectal findings, type and site of biopsy were evaluated using the Chi-square test, Student's t-test and multivariate logistic regression, as appropriate. Statistical analyses were performed using SPSS software, version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinicopathological characteristics. The clinical and pathological characteristics of the study population are summarized in Table I. The mean age of the patients was 62.97 years and 64.7% of patients were aged <65 years. The mean PSA level was 7.83 ng/ml, with a free/total mean ratio of 12.66%. Approximately 67% of the patients had a PSA level in the grey zone between 4 and 10 ng/ml. The majority of the patients (79.7%) presented with a negative DRE; 51.3% of the population underwent a transperineal prostate biopsy. Approximately half of the patients (48.0%) underwent prostate biopsy at our Institution.

Upgrading and downgrading. The prostate volume was <50 cm³ in 70.0% of the cases. The most frequently represented bioptic GS was 3+3 (64.0%) followed by 3+4=7 (15.6%), whereas the most frequent pathologic GS was 3+4 (44.3%), followed by 3+3 (31.0%). The surgical margins were negative in 227 patients. Table II shows the correspondence between bioptic and pathological GS. With regard to the bioptic GS 4-5-6 group, approximately half of the specimens (46.7%) was subsequently upgraded to GS 3+4, and 5.3% to 4+3.

With regards to the bioptic GS 3+4 group, 57.4% was confirmed in the surgical specimen. In the 4+3 group, 23.5% of the cases were downgraded to 3+4 and 35.3% were confirmed. With regards to the stage, ~39.7% of the patients received an upstaging on the pathological specimen.

Correlation analysis. We evaluated the correlations between preoperative serum PSA level, prostate volume, DRE and biopsy type and none of the variables considered exhibited a correlation with any upgrading ($P>0.05$). We also evaluated the correlations between the aforementioned variables and upstaging and, at the multivariate analysis, only a serum PSA level <4 ng/ml was found to be an independent variable predictive of upstaging ($P 0.017$) (Table III).

Discussion

The determination of the GS remains crucial in the evaluation of patients affected by CaP and in the management of this disease,

Table I. Clinicopathological characteristics of the patients.

Characteristics	Values
Age, years	
Mean	62.97
Median	63
Range	41-77
PSA, ng/ml	
Mean	7.83
Median	6.1
Range	0.6-57.4
Free/total ratio, %	
Mean	12.66
Median	11
Range	2-48
Volume, cm ³	
Mean	42.69
Median	40
Range	13-120
PSA density, ng/ml/cm ³	
Mean	0.20
Median	0.15
Range	0.02-1.4
Clinical stage, no. (%)	
cT1c	239 (79.7)
T2a - b	36 (12.0)
cT2c	25 (8.3)
Biopsy, no. (%)	
Transperineal	154 (51.3)
Transrectal	146 (48.7)
Biopsy site, no. (%)	
Our institution	144 (48.0)
Other institution	156 (52.0)
Cores, no.	
Mean	13.57
Median	14
Range	5-28
Positive cores, no.	
Mean	4.15
Median	3
Range	1-15
Bioptic Gleason score, no. (%)	
NA	5 (1.7)
4	2 (0.7)
5	14 (4.7)
3+3	192 (64.0)
3+4	47 (15.6)
4+3	17 (5.7)
8	20 (6.6)
9-10	3 (1.0)
Specimen weight, g	
Mean	56.91
Median	52
Range	20-140

Table I. Continued.

Characteristics	Values
Pathological Gleason score, no. (%)	
NA	5 (1.7)
5	3 (1.0)
3+3	93 (31.0)
3+4	133 (44.3)
4+3	23 (7.6)
8	26 (8.7)
9-10	17 (5.7)
Surgical margins, no. (%)	
Negative	227 (76.0)
Positive	73 (24.0)
PSA, prostate-specific antigen; NA, not available.	

which may range from an active surveillance protocol to radical prostatectomy and multimodal therapies. Several previous studies have analyzed the correlation between the biopsy evaluation and the results obtained from surgical specimens.

The comparisons between the results of the histological biopsy compared to the surgical specimen exhibited a correlation equal to ~50% (14-17). The results of the prostate biopsy and the surgical specimen may differ for several reasons, such as incorrect evaluation by the pathologist, sampling errors and the presence of borderline grading. Several studies demonstrated that a higher number of cores, compared to the sextant biopsy, may lead to a lower percentage of upgrading.

Capitanio *et al* (18) evaluated a series of 301 patients with low-risk CaP according to the D'Amico criteria (19) (clinical stage T1c - T2a, PSA<10 ng/ml and biopsy GS 6) that underwent extended prostate biopsy (median number of cores, 18) and subsequent radical prostatectomy. The GS agreement between biopsies and surgical specimens was 47.5% (143 patients), while upgrading was recorded in 38.5% cases (116 patients), 31.9% of which (96 patients) presented with a significant upgrade to GS ≥7. In patients evaluated with 10-12 core biopsies, the upgrading was 47.9%, compared to 31.6 and 23.5% with 13-18 or >18 cores, respectively, with a statistically significant P-value, demonstrating that a larger sampling of the gland may avoid subsequent upgrading and may help in planning an appropriate treatment approach.

In our series, however, variables predictive of upgrading were not detected and the type of biopsy or the number of samples taken were not identified as predictors of upgrading. In 2012, Epstein *et al* (20) evaluated the largest series in the literature, with 7,643 patients, analysing the correlation between bioptic and definitive GS. Of the patients with GS 5-6, 36.3% underwent an upgrading and ~20% of the patients exhibited a tertiary Gleason pattern. In half of the remaining cases, there was an equal proportion of up- and downgrading. Half of the cases had matching GS 3+4=7 at biopsy and RP, with an approximately equal number of cases down- and upgraded at RP.

A bioptic GS 8 led to an almost equal distribution between RP GS 4+3=7, 8 and 9-10. A total of 58% of the cases had

Table II. Upgrading and downgrading.

Bioptic GS	4-5-6		3+4=7		4+3=7		8		9-10		NA		Total	
	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%	no.	%
RP GS														
0-NA	3	1.4	1	2.1	0	0.0	0		0		1	20.0	5	1.7
5-6	92	44.2	2	4.3	0	0.0	0		0		2	40.0	96	32.0
3+4=7	97	46.7	27	57.4	4	23.5	3	15.0	0		2	40.0	133	44.3
4+3=7	11	5.3	5	10.7	6	35.3	1	5.0	0		0	0.0	23	7.6
8	3	1.4	9	19.1	5	29.4	8	40.0	1	33.3	0	0.0	26	8.7
9-10	2	1.0	3	6.4	2	11.8	8	40.0	2	66.7	0	0.0	17	5.7
Total	208	100.0	47	100.0	17	100.0	20	100.0	3	100.0	5	100.0	300	100.0

GS, Gleason score; RP, radical prostatectomy; NA, not available.

Table III. Upstaging multivariable analysis.

Variables	SE	P-value	95% CI
Age, years ≤65	0.259	0.280	0.455-1.256
DRE	0.302	0.655	0.633-2.071
PSA, ng/ml <4	0.372	0.017 ^a	1.171-5.027
>4	0.333	0.877	0.495-1.824
Volume <50 cc	0.270	0.625	0.673-1.936
Biopsy TP	0.378	0.997	0.477-2.100
TR	0.273	0.795	0.545-1.591
Bio = trans	-	-	-

^aStatistically significant. SE, standard error; CI, confidence interval; DRE, digital rectal exploration; PSA, prostate-specific antigen; TP, transperineal; TR, transrectal.

matching GS 9-10 at biopsy and RP. In addition, at the multivariate analysis, the authors reported that increasing age ($P<0.0001$), increasing serum prostate-specific antigen level ($P<0.0001$), decreasing RP weight ($P<0.0001$) and increasing maximum percentage cancer/core ($P<0.0001$) predicted the upgrading from a bioptic GS 5-6 to a higher one at RP (20). In our series, the presence of tertiary pattern was not assessed; therefore, we could not perform an evaluation regarding the presence and possibility of up- or downgrading.

In our study, with regards to GS 4-5-6, 44.2% of cases matched, while there was an upgrading in 54.4% of the cases. With pattern 3+4, there was a correlation between bioptic and definitive GS in 57.4% of the cases, downgrading in 6.4% of the cases and upgrading in 36.2%, a higher percentage when compared to the data presented by our colleagues. With GS 4+3, concordance was obtained in 35.3% of cases and a preponderance of upgrading (41.2%) compared to the downgrading (23.5%), an even higher percentage if compared to the

data presented by Epstein *et al* (20). GS 8 was matched in 40% and GS 9-10 in 66.7% of the cases, almost overlapping with the data presented by our colleagues.

Epstein *et al* (20) also conducted a wide literature review, selecting only studies that evaluated series of patients with numerosity >100, documenting the presence of GS upgrading from 6 to 7 in 3,975 out of 11,472 cases (35%), with a mean percentage of 36.0% and a median of 35.5%, with results ranging from 14 to 51% (21-23). In our series, none of the analyzed variables was identified as an independent predictor of up- or downgrading, whereas a PSA level <4 ng/ml was found to be predictive of upstaging. In the literature, as in our study, age was not found to be a variable correlated with upgrading or upstaging, whereas age was found to be predictive in the study of Epstein *et al* (20), with a difference between the 2 groups of only 1.6 years.

PSA values, in contrast to our data, are often found to be predictive of upgrading, albeit with weak associations. According to our data, a preoperative PSA <4 ng/ml was found to be an independent predictor of upstaging; this highlights the questions regarding cancer as an incidental finding, which, even with low PSA levels, is found to be significant, as already suggested by Thompson *et al* (24). Moreover, in the literature, an increase in prostate volume was found to be less predictive of upgrading, while in the study of Epstein *et al* a decrease was documented in the upgrading ratio in prostate glands weighing >75 g.

Approximately half of the studies available in the literature documented an association between the percentage of cores invaded by cancer and upgrading; however, in this study, we did not consider this variable. The significance of the ability to predict a possible upgrading or upstaging of prostate biopsy lies with the risk of 'falsely' estimating a low GS, which may lead to the selection of a treatment not adequately aggressive, potentially putting the patient at risk of poor oncologic outcomes. For this reason, Serkin *et al* (25) retrospectively evaluated 2,884 patients who underwent radical prostatectomy, documenting an upgrading in 36.8% of patients with a bioptic GS 6. The authors of that study also demonstrated that the status of the surgical margins, capsule, seminal vesicles and lymph node involvement were more favorable in patients

with a GS correlation between bioptic and surgical specimens ($P<0.0001$).

Moreover, patients with lower prostate volume had a higher PSA density and an increased risk of upgrading. The Kaplan-Meier curves suggested that patients with upgrading were at an increased risk of biochemical disease recurrence compared to patients with a correlation between the specimens ($P<0.0001$) and a higher risk to undergo salvage hormone therapy ($P<0.0001$).

Our study had several limitations, as follows: the design of the study was retrospective and over half of the biopsies were not performed in our Institution; we did not perform a centralized review of the specimens, with a variable number of biopsies and with the inability to evaluate, in some cases, the percentage of cores involved; we do not have an oncological follow-up of the patients and, therefore, we cannot correlate the biopsy results with the follow-up of the patients.

The upgrading and upstaging from prostate biopsy to radical prostatectomy is an important topic of discussion and may be of significant value at the clinical level, for treatment planning, as well as for the prediction of cancer outcomes. Therefore, new tools are required to predict upgrading and upstaging of our patients, in order to ensure better counseling for optimal treatment planning.

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