Adverse Pathological Findings in Needle Biopsy Gleason Score 6 Prostate Cancers with Low and Intermediate Preoperative PSA Levels Following Radical Prostatectomy

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Abstract. *Aim: We retrospectively analyzed the risk associated with undergrading Gleason score 6 (GS6) prostate cancer (PCa) at biopsy, in patients with preoperative PSA levels of 2-3,99 and 4-10 ng/ml. Patients and Methods: A total of 674 patients with needle biopsy-diagnosed GS6 PCa, who underwent radical prostatectomy (RP) between 1995 and 2011, were evaluated. Patients were stratified by preoperative PSA levels into low PSA (2-3,99 ng/ml) and an intermediate PSA of 4-10 ng/ml. Subsequently, the percentage of patients with extracapsular disease (pathological stage ≥pT3a) and/or positive surgical margins was determined among those whose RP GS was still 6 and compared to undergraded cases. Results: Out of 674 patients with needle biopsy-diagnosed GS6 PCa, 36.2% had no difference between biopsy and RP GS while 11.4% had been overgraded and 52.4% of patients were undergraded at biopsy. Stratified according to preoperative PSA levels, there was a significantly higher incidence of undergrading in the intermediate PSA group. Among those with ≥pT3a tumors, 74.1 % were undergraded in needle biopsy, out of which 67.7% had intermediate PSA levels and 32.3% low PSA levels. Among patients with R1 resections 75.1 % were underdiagnosed, out of which 75.9% had intermediate PSA levels. Stratifying these data according to preoperative PSA levels, ≥pT3a tumors and R1 resection were found significantly more often in the intermediate-PSA group. Conclusion: The incidence of adverse pathological findings, including extraprostatic extension and positive surgical margins, is significantly higher in patients with undergraded biopsy GS6. Low preoperative PSA levels improved the correlation between primary and final GS and led to the reduction of unfavorable pathological findings.*

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Prostate cancer (PCa) is the leading cancer in occurrence in men and the second most common cause of cancer-related mortality among male patients.

Well-established risk factors for PCa development are race, advanced age and heredity (1, 2). Moreover, a history of prostatitis or sexually transmitted disease is known to increase the risk for developing PCa (1, 2).

Since 1993, screening of men for PCa is a well-established tool in Tyrol in Austria that has significantly reduced the PCa mortality rate in Tyrol (3, 4). The diagnostic workup of patients includes measurement of prostate-specific antigen (PSA) and digital rectal examination, followed by a transrectal ultrasound-guided biopsy in suspicious cases (4). Prostate biopsy consequently results in a determination of histopathological Gleason score (GS), one of the critical predictors of prognostic outcome and therapeutic options in patients (5).

In general, the Gleason grading system is the standard histological classification for grading adenocarcinoma of the prostate on core biopsy and operative specimens (5). The GS is the sum of the two most common patterns of tumor growth found in radical prostatectomy (RP) specimens (5). Concerning needle biopsy specimens since 2005, the worst grade is incorporated in the GS grading, even if comprising less than grade 5 of cancer (5).

Several studies attempted to compare GS of biopsy and RP with conflicting results (6-8). For example, Zam *et al.* demonstrated good pathological correlation between needle biopsies and their RP in a cohort of 100 patients (9). However, Berg *et al.* recently found complete agreement between primary and final GS in 76.9% in a total of 365 patients (10). Data from Oliveira *et al.* showed that 77.9% of cases had the same GS, while 19.5% were undergraded in biopsy (11).

Therapeutically, undergrading of PCa often results in improper assessment of the disease and its treatment, consequently also influencing patient prognosis. It has been

shown in a large study that undergrading in the biopsy is associated with poorer biochemical recurrence-free survival, compared to patients whose GS after RP did not change (6).

In the present study, we investigated whether undergrading of biopsy GS 6 in patients with a low PSA level of 2-3,99 ng/ml and an intermediate PSA level of 4-10 ng/ml following RP, results in adverse pathological findings. To our knowledge, this is the largest study comparing the impact of GS at biopsy and RP, including 788 patients with needle biopsy-verified GS 6 and PSA levels between 2 and 10 ng/ml.

Patients and Methods

Data of 674 patients with needle biopsy-verified GS 6 and with PSA levels between 2 and 10 ng/ml who underwent RP were evaluated. Due to changes in the biopsy protocol, the number of biopsies obtained increased with time from 10 (1995 to March 2000) to 15 cores (March 2000 to December 2011). According to the European Association of Urology (EAU) guidelines, since 2005 the new GS classification of needle biopsy-verified PCa has been used (5).

Patients were stratified by preoperative PSA levels into two groups: low PSA of 2-3,99 ng/ml and intermediate PSA of 4-10 ng/ml, as described previously by our group (12). The biopsy GS was correlated with the final GS of the corresponding RP specimens and the incidence of adverse pathological findings such as extraprostatic extension (≥pT3a tumors) and positive surgical margins (R1 resections) of GS 6 tumors in RP specimens was compared to the incidence of under- and overgrading. Preoperative assessment of patients consisted of patient history, of physical examination including digital rectal examination, serum PSA levels, transrectal ultrasound and prostate biopsy with the primary and secondary Gleason grade, GS and the number of positive biopsies (4). Preoperative imaging, such as computed tomography and bone scan, was performed depending on the referring physician.

As the data set followed a Gaussian distribution, the Student's *t*-test was applied to calculate the statistical significance of differences between the patient groups. *p*-Values below 0.05 were considered significant.

Results

Out of 674 cases of needle biopsy diagnosed GS 6 PCa after RP, 36.2% (n=245) remained GS 6, however 11.4% (n=77) were overgraded and 52.4% (n=352) were undergraded in the biopsies.

The distribution of final GS after RP is shown in Table I. We stratified the data according to the preoperative PSA level into a low (PSA 2-3,99 mg/ml) and an intermediate PSA group (PSA 4-10 mg/ml) whereof 41.6% (n=281) had low PSA and 58.4% (n=393) of patients presented intermediate PSA levels.

After RP in our department between January 1995 and December 2011, 96 patients (14.2%) had an extraprostatic extension with a pathological stage ≥pT3a. Moreover, positive surgical margins (R1) were found in 141 (20.9%) of all histological specimens. Higher PSA levels are known to correlate with poor prognosis and poor overall survival rates

Table I. *Distribution of final Gleason Score (GS) after radical prostatectomy (n=674; 100%).*

Final GS after RP	n (%)
3	1 (0.2%)
4	2 (0.3%)
5	74 (11%)
6	246 (36.5%)
7	323 (48%)
8	20 (3%)
9	7 (1%)

(1, 2). Consequently we analyzed the GS of our sample set after RP according to PSA levels stratified into low PSA (PSA 2-3,99 ng/ml) and intermediate PSA (PSA 4-10 ng/ml) levels. We found that in the low PSA group 47.9% (n=134) remained GS 6 after RP, however 6.4% (n=18) were overdiagnosed and 45.7% (n=129) were underdiagnosed in needle biopsy. In contrast to this, in the group with intermediate preoperative PSA levels 14.4% (n=57) were overgraded, 28.1% (n=111) remained GS6 and 57.5% (n=225) were undergraded.

In summary, these data suggest that undergrading is statistically significant ($p<0.01$) more often in the intermediate-PSA group than in the low-PSA group. Next, we investigated if there is coherence between extraprostatic extension (≥pT3a) and undergrading in the biopsy.

Among all ≥pT3a tumors, 74.1% (n=78) were undergraded in needle biopsy; however, 5.8% of patients (n=6) were overgraded and 11.5% (n=12) remained GS 6 after RP. Stratified according to PSA levels into intermediate (PSA 4-10 ng/ml) and low (PSA 2-3,99 ng/ml) preoperative PSA levels, 67.7% (n=65), all patients with ≥pT3a tumors had intermediate preoperative PSA; however 32.3% (n=31) showed low PSA levels.

We found that in patients with verified GS 6 in RP specimens the total incidence of ≥pT3a was 4.9% (n=12/245). Stratified for PSA levels the incidence of ≥pT3a tumors was 0.4% (n=1/245) for those with low PSA and 4.5% (n=11/245) for those with intermediate PSA levels. However, in patients underdiagnosed in needle biopsy the total incidence of ≥pT3a was 22.1% (n=78/352). Stratified for PSA levels the incidence of ≥pT3a tumors 6.2% (22/352) for low PSA and 15.9% (n=56/352) for intermediate PSA levels.

In summary, these data give a strong indication that extraprostatic extension occurs prevalently in underdiagnosed PCa with intermediate preoperative PSA levels.

Positive surgical margins (R1 resections) are known to correlate with worse prognosis in most cancer entities, including PCa (13-15). Thus, we investigated if positive surgical margins after RP are influenced by GS and by PSA levels.

Our data show that of all R1 resections, 75.1% (n=106) were underdiagnosed, 1.8% (n=9) were overdiagnosed and

23.1% (n=26) remained GS6 after RP. Stratified according to PSA levels, out of all R1 resections, 75.9% (n=108) had intermediate preoperative PSA levels and only 24.1% (n=33) low preoperative PSA levels.

When investigating the preoperative PSA levels, in the low-PSA group 12.8% (n=4/33) had R1 resections; however in the intermediate-PSA group 30.1% (n=32/108) had R1 after radical prostatectomy.

In patients with verified GS6 in RP specimens, the total incidence of R1 resections was 10.6% (n=26/245). Stratified according to PSA levels, the incidence of R1 tumors was 4.9% (n=11/245) for low PSA and 6.1% (n=15/245) for intermediate PSA levels. In striking contrast, in patients underdiagnosed in RP specimens the total incidence of R1 resections was 30.1% (n=106/352). When stratified for PSA levels the incidence of R1 resections was 9% (n=32/352) for those with low PSA and 21.1% (n=75/352) for those with intermediate PSA levels. Taken together, underdiagnosed PCa is often correlated with R1 resection especially in patients with intermediate preoperative PSA levels.

Discussion

GS is the most powerful predictor of PCa prognosis and in determining therapy (1, 5). The discrepancy between the GS recorded for the needle biopsy and that for surgical specimen often results in improper assessment of the disease and its treatment, consequently influencing prognosis and outcome of patients (8, 16, 17). Thus correct staging and grading of PCa is of importance in making the correct therapeutic decision.

In the present study we investigated the GS after RP in 788 patients diagnosed with GS 6 after needle biopsy. We found that disease in 36.2% of patients remained GS 6 after RP, however 52.4% were undergraded and 11.4% were overgraded in needle biopsy. Studies investigating GS correlation between biopsy and prostatectomy specimens have shown considerable discrepancy. Oliveira *et al*., for example, found agreement with biopsy GS 6 in 77.9% of 408 surgical specimens. They found undergrading and overgrading in the biopsy in only 18.5% and 2.6% of cases, respectively (11). Berg *et al*. also found complete agreement of primary and final GS in 76.9% in a cohort of 350 patients (10).

Another large study including 6,922 patients found coherence between biopsy GS and RP GS in 68.8%. The authors found undergrading in the biopsy to be associated with poorer biochemical recurrence-free survival compared to patients who retained GS after RP (6).

Montironi *et al*. reviewed several studies and found undergrading and overgrading occurring in 42% and 15% of all cases, respectively (18). Another group reported biopsy undergrading and overgrading in 54% and 15% of patients investigated, respectively (19).

To our knowledge, our present study is the largest, comparing the agreement of GS 6 PCa before and after RP. Thus, one reason explaining our increased number of cases of undergraded GS6 PCa in comparison to other studies, might be the high patient number included in our study. Fine *et al*. ascribe the discrepancy between needle biopsy and RP specimen in their own study as differences in pathologists (20). In a large study, they investigated the impact of the pathologist itself on GS. They found that at their own Central Department of Pathology at Memorial Sloan-Kettering Cancer Center, the discrepancy between GS before and after RP was significantly lower than at outside institutions (20). Furthermore, borderline cases, as well as intra-observer and inter-observer variability might be responsible for certain variations. Other factors which have been described as having influenced the discrepancy between needle biopsy and RP GS are age at-diagnosis, biopsy Gleason sum, PSA, prostate weight, biopsy positive-to-total core ratio and maximal percent of tumors in cores (21).

The undergrading rate of more than 50% in our patient collective underscores the risk and consequence of incorrect grade evaluation at needle biopsy. Watchful waiting, active surveillance or low-dose brachytherapy, for example, are typically reserved for patients with GS 6 PCa (1). Especially for those patients, a proper recognition of histological grade of PCa is imperative. Thus, all patients undergoing these therapeutic options should be informed about the risk of underdiagnosis.

Additionally, we investigated the risk associated with undergrading GS 6 PCa at biopsy, stratified according to preoperative PSA levels. We found that undergrading of GS 6 in needle biopsy occurs more often in the intermediate-PSA group with an incidence of 57.5% *vs*. 45.7% in the low-PSA group. In accordance with our results, other groups also found preoperative PSA to be predictive for PCa undergrading (22, 23).

The tumor, lymph node and metastasis (TNM) staging system for PCa defines pT3a as extension of tumor into periprostatic soft tissue (1). In general, extraprostatic extension and positive surgical margins (R1 resection) of PCa are known to correlate with a worse prognosis and thus, with shortened survival time (15).

In the present study, we show that undergrading resulted in a significantly higher incidence of ≥pT3a tumors than of organ-confined PCa. Additionally, we found that 67.7% of all ≥pT3a tumors were associated with intermediate perioperative PSA levels (PSA 4-10 ng/ml).

Investigating the impact of R1 resections our data clearly show that 75.1% of all R1 resections were underdiagnosed in needle biopsy. Stratifying all R1 resections according to PSA levels, 75.9% of patients had intermediate preoperative PSA levels (PSA 4-10 ng/ml).

In accordance with the extra-prostatic extension, R1 resections were observed more often in underdiagnosed PCa (22.1%) than in the group which remained GS6 in the RP

specimen (10.6%). Stratifying the underdiagnosed cases according to PSA levels, R1 resections occured significantly more often in the intermediate PSA group. In contrast to our findings, Bulbul *et al*. compared the incidence of laterality of PCa or surgical margins in patients and found that increased PSA levels were not associated with a higher incidence of positive surgical margins (24).

There are several limitations in our study. The retrospective nature of our study and the lack of a multicenter character are inherent limitations. Randomized controlled multicenter studies need to confirm the present findings, moreover, not all specimens were assessed by the same pathologist, resulting in an inter-observer variability. As previously described by our group, the estimates of underdiagnosis and overdiagnosis are highly dependent on the definition used, and are subject to debate (12). Another possible limitation is that there were two different biopsy techniques, in the periods 1996-2000 and 2000-2012. In a study by our group, investigating on different prostate biopsy techniques, no differences in the biological behavior of the PCa were detected, nor for the pathological stage; there was only a difference in core detection rates (12).

As the GS represents the most important tool for therapeutic decisions in PCa, the goal should be to find a way to eliminate errors in grading needle biopsy specimens. Recently, additional tools for predicting high-grade PCa have been described. Diffusion-weighted magnetic resonance imaging, for example, is known to predict the presence of high-grade tumors in patients with GS 6 PCa (25). Moreover, measurement of pro-PSA isoforms results, were a significant independent predictor of the GS and non-organ-confined PCa in RP specimens [reviewed in (26)].

In summary, our study provides evidence that more than 50% of GS6 PCa diagnosed with needle biopsy exhibit an intermediate tumor grade in the RP specimen, especially in patients with intermediate preoperative PSA levels (4-10 ng/ml). Moreover we show that the incidence of adverse pathological findings, including extraprostatic extension and positive surgical margins is significantly higher in patients with undergraded biopsy GS6. Low preoperative PSA levels improved the correlation between primary and final GS and led to reduction of unfavorable pathological findings.

Conflicts of Interest

None.

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