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Should Centralized Histopathological Review in Prostate Cancer be the Gold Standard?

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Abstract

Background: To assess the potential impact of centralized histopathological review on prostate cancer management.

Methods: 1) Biopsy slides of 277 men with newly diagnosed prostate cancer between January 2010 and March 2014 from 22 centers were referred to our tertiary referral center for centralized histopathological review. 2) The biopsy Gleason score and D'Amico prognostic risk group were compared between those of the referring pathologists and those after assessment by a centralized histopathological review committee consisting of two specialized uro-pathologists. 3) Alterations in biopsy Gleason score and D'Amico prognostic risk group between referring pathologists and centralized histopathological committee were subdivided into treatment changes (i.e., lymph-node dissection, nerve sparing surgery, or active surveillance) and diagnostic changes (bone scintigraphy).

Results: 1) Consensus was reached in all cases between the two uro-pathologists of the centralized histological committee. 2) Overall concordance between referring pathologists and the centralized histopathological committee for Gleason score was 69.0%, with upgrading in 24.5% and downgrading in 6.5% of cases (κ 0.55). 3) Overall concordance for D'Amico risk group was 81.6% with a shift to a higher risk group in 15.5%. A shift to a lower risk group occurred in 2.9% of cases. 4) Treatment changes due to histopathological review would have occurred in 22.7% of patients. Diagnostic procedures would have changed in 8.0% of patients.

Conclusion: After centralized review, a substantial proportion of histology reports was revised, for biopsy Gleason score and D'Amico prognostic risk group. In almost one third of patients, a centralized histopathological review would have led to altered diagnostic work-up and/or treatment decisions.

Keywords: Gleason score; Pathology; Centralization; Biopsy; Prostate cancer

Abbreviations: AS: Active Surveillance; CE: Continuing Education; EAU: European Association of Urology; EPE: Extra-Prostatic Extension; ePLND: Extended Pelvic Lymph Node Dissection; iPSA: Initial Prostate-Specific Antigen level; ISUP: International Society of Urological Pathology; MSKCC: Memorial Sloan Kettering Cancer Center; PRIAS: Prostate Cancer Research International Active Surveillance; SPSS: Statistical Package for the Social Sciences

Introduction

Centralization of cancer services in urological cancers such as prostate cancer is slowly becoming standard of care in most Western European countries. It is proved that centralization of cancer services consolidates the service infrastructure, providing specialized multidisciplinary teams, which deliver improved cancer management [1]. This integrated approach may result in improved oncological outcome and improved patient reported quality of life [2].

In the Netherlands, most patients with prostate cancer are diagnosed in smaller general hospitals and are referred to larger specialized centers for curative treatment such as (robot assisted) radical prostatectomy, external beam radiation therapy, or brachytherapy. All of these treatments may have serious side effects that could affect patient reported quality of life. An accurate assessment of the aggressiveness of prostate cancer is essential to prevent unnecessary aggressive treatment in earlier stage disease and to ensure that more advanced disease receives adequate treatment. One of the key determinants of the aggressiveness of prostate cancer is the Gleason score. The importance of prostate biopsy is demonstrated by the fact that decisions on diagnostic work-up and treatment are largely based on the assessment of diagnostic prostate biopsy specimens.

Potentially, an increased exposure of pathologists to prostate cancer biopsies may help improve histological grading and staging. This could also improve patient outcome; however, this is not proven yet [3].

In the present study, we investigated the interobserver variability of histological grading of diagnostic prostate biopsies between a centralized histological board consisting of two uro-pathologists and that of local pathologists. It was assessed whether centralized histological review would have affected diagnostic work-up and treatment related decisions in a series of 277 patients referred for treatment to our tertiary referral center.

Patients and Methods

Patient population and pathology review

We aimed to explore the effects of centralized histopathological

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review of diagnostic prostate biopsy specimens on diagnostic work-up and treatment related decisions.

A chart analysis was performed on 277 consecutive patients who underwent (robot-assisted) radical prostatectomy at our tertiary referral center. Patients were diagnosed with prostate cancer on prostate needle biopsy in 22 general and university medical centers between January 2010 and May 2014. We retrieved the original pathology reports issued by a total of 46 pathologists. We collected data on e.g. Gleason score, tumor volume, number of positive biopsies.

All study data were retrospectively collected and analyzed according to our institutional review board protocol.

Pathological assessment

All prostate biopsy slides were initially reviewed at our tertiary referral center by a single uro-pathologist (LR). Then, an external specialized uro-pathologist (ThvdK) re-examined all biopsy slides blinded of previous findings. The local uro-pathologist and external uro-pathologist closely followed the ISUP 2005 recommendations when reviewing the prostate biopsies [4]. In cases of discrepancy, expert consensus was reached between the two uro-pathologists viewing the slides in a combined session (centralized histopathological review). To assure the quality between the uro-pathologists, we chose this as gold standard. With only one expert pathologist, there is no evidence presented to show that one's interpretation was correct and the other one is not.

The concordance rate for Gleason score of the referring pathologist and the centralized histopathological review was recorded, as were the number of cores positive for prostate cancer. Gleason score assigned was based on the 2005 ISUP recommendations, and further stratified ≤ 6, 3+4, 4+3 and 8-10.

Prognostic risk group classification

The biopsy Gleason score, the initial prostate-specific antigen (iPSA) level, and the clinical tumor (cT) stage were used to categorize patients into the following risk groups:

1. **Low risk:** Gleason score 3+3=6, cT1c/T2a, and iPSA less than 10 ng/ml;
2. **Intermediate risk:** Total Gleason score of 7 (3+4 or 4+3), and/or maximal cT2c, and/or iPSA 10-20 ng/mL, and no high-risk features;
3. **High risk:** Gleason score 8 or higher, cT3 or higher, or iPSA of 20 ng/mL or higher [5].

If an alteration of biopsy Gleason score or prognostic risk group occurred after centralized histopathological review, this was documented. As the iPSA level and cT-score were constant parameters, a shift in prognostic risk group is then a result of a change in biopsy Gleason score.

Treatment decisions and diagnostic work-up: To examine the impact of centralized histopathological review on diagnostic work-up and therapeutic decisions, data from the referring pathologists and the centralized histopathological review committee, next to iPSA and clinical T-stage were entered in our predefined algorithms shown in Table 1. We determined if a centralized review of the prostate biopsy resulted in a change in 1) the indication to perform a bone scintigraphy, 2) the indication for an extended pelvic lymph node dissection (ePLND), 3) the decision to perform nerve-sparing radical prostatectomy, and 4) the eligibility of patients to participate into an active surveillance (AS) protocol for prostate cancer.

According to Dutch guidelines (www.oncoline.nl), patients with a Gleason score 8 or higher and/or an iPSA ≥ 20 ng/mL routinely undergo bone scintigraphy as part of diagnostic and staging work-up [6]. After centralized histopathological review, it was determined whether patients had a change in indication for bone scintigraphy.

We calculated the risk of lymph node involvement using the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram to estimate the outcome of primary treatment such as radical prostatectomy or brachytherapy [7]. In the MSKCC nomogram the iPSA level, age, the primary and secondary Gleason grade, the biopsy Gleason sum, the clinical tumor stage, and the number of positive and negative biopsy cores for prostate cancer needed to be filled in an internet web-based form to predict the risk of lymph node involvement (https://www.mskcc.org/nomograms/prostate/pre-op). The European Association of Urology (EAU) guidelines does not provide a cut-off point. We therefore chose to use multiple cut-off points of 5%, 8% and 10% to determine whether an ePLND should be performed [6].

We applied the EAU guidelines to determine whether patients are eligible for nerve-sparing surgery [6]. Nerve-sparing radical prostatectomy is generally not recommended when a high risk of extra-prostatic extension (EPE) exists, i.e. in cT2c stage disease, or when iPSA>10 ng/mL, if Gleason score 4+3=7 or higher and/or when 4 or more cores positive for cancer are present. In this respect, a change in the decision to perform nerve-sparing radical prostatectomy is due to a shift in biopsy Gleason score or the number of biopsy cores with cancer after pathology review. According to the pre-defined algorithm, we estimated the frequency with which the decision to perform nerve-sparing surgery changed due to centralized pathological review (Table 1) [8,9].

We used the eligibility criteria for AS according to the Prostate Cancer Research International Active Surveillance (PRIAS) protocol: biopsy Gleason score of 3+3=6 or lower, a maximum of 2 cores positive for cancer, and serum iPSA level lower than 10 ng/mL with a clinical T-stage T1c or T2a/b/c [10]. A change to a higher Gleason score or when more than two biopsies positive for cancer were found by the centralized pathological review, the treatment recommendation would have altered to an active treatment management. Otherwise, if the prostate biopsy was downgraded to a Gleason score of 3+3=6, or when less than 3 cores positive for cancer were assessed, a patient might have been suitable for an AS protocol (Table 1). As this is a retrospective study and patients were referred for surgery from surrounding hospitals and were alleged to undergo surgery, all of these patients underwent radical prostatectomy.

Statistical analysis

All statistical analyses described above were performed using the statistical package for the social sciences (SPSS version 22.0; SPSS; Chicago). The Gleason score concordance between referring pathologists and the centralized histopathological review committee was calculated using kappa (κ) statistics. It corrects for the percent agreement expected by chance [11].

Results

Gleason score and prognostic risk group agreement between referring pathologists and the centralized histopathological review committee.

	More aggressive strategy if…	Less aggressive strategy if…
Bone scintigraphy	Gleason score 8 or higher, iPSA ≥ 20 ng⁄mL	Gleason score 4+3=7 or lower, iPSA <20 ng⁄mL
Extended lymph node dissection	MSKCC ≥ 5, 8 or 10% chance of lymph node involvement	MSKCC <5, 8 or 10% chance of lymph node involvement
Nerve-sparing surgery (uni- or bilateral surgery)	High risk of EPE: ≥ cT2c stage and/or iPSA >10 and/or Gleason score 4+3=7 or higher, and/or ≥ 4 cores positive	Low risk of EPE: <cT2c stage and/or iPSA <10 and/or Gleason score 3+4=7 or lower, and/ or <4 cores positive
Recommendation shift from AS to active treatment and vice versa	iPSA-level ≥ 10 ng/mL, clinical stage >T2c, Gleason score >3+3=6, >2 biopsy cores invaded with prostate cancer	iPSA-level ≤ 10 ng/mL, clinical stage T1c or T2a/b/c, Gleason score 3+3=6, one or 2 biopsy cores invaded with prostate cancer

Table 1: Algorithm for diagnostic work-up and treatment decisions in prostate cancer patients.

After centralized pathological review, the biopsy Gleason score was upgraded in 24.5% and downgraded in 6.5% of cases (Table 2). Consensus between referring hospital pathologists and the histopathological review committee was 69.0% (κ 0.55). The most common change was from a biopsy Gleason score of ≤ 3+3=6 to a biopsy Gleason score of 3+4=7, which occurred in 33 cases (48.5% of the upgraded cases) (Figure 1). This was a case in which the referring pathologist gave a Gleason score 3+3=6, whereas the histological board assigned it a Gleason score 4+3=7.

The percentage of patients with D'Amico risk group low-, moderate-, or high risk prostate cancer according to the referring pathologists and after centralized histopathological review is depicted in Table 3. Overall agreement between referring pathologists and the histopathological review committee was 81.6%. In 43 patients (15.5%), the risk group shifted to a higher prognostic risk group, and 8 patients (2.9%) shifted to a lower prognostic risk group.

Alteration of diagnostic and treatment recommendations

Table 4 summarizes the number of diagnostic and treatment changes that would have occurred after review of the biopsies. Overall, diagnostic work-up (e.g. bone scintigraphy) would have changed in 22 cases (7.9%). Considering ePLND, we divided this in the cut-off groups of 5, 8 and 10% risk on lymph node invasion. Changes in ePLKD would have occurred in 32 patients (11.5%) when using a cut-off point of 5% on lymph node invasion, 33 patients (11.9%) when using a cut-off of 8% on lymph node invasion, and 35 patients (12.7%) using a cut-off of 10% on lymph node invasion. Changes in nerve-sparing surgery and recommendation shift from AS to an active treatment or vice versa, occurred in 76 patients (27.4%). Combined (since 1 patient could have more than 1 change; we corrected for this), the total recommendations would have changed in 88 patients (31.8% using a 5% cut-off point for lymph node invasion), 85 patients (30.7% using 8% as cut-off point) or 82 patients (29.6% using 10% as cut-off point).

Discussion

In the present study, we provided evidence that pathological grading by a centralized histopathological review committee may help to select patients with prostate cancer to suit their need for diagnostic work-up or to advice an appropriate treatment. We showed that pathological review by a centralized histopathological board changed diagnostic work-up in almost 8% of cases and changed treatment planning in almost one third of cases as compared to the original histopathological assessment performed by referring pathologists. The limitation in our study was that it reports on retrospective data of already treated patients. However, it supports a positive volume-outcome relationship in the quality of pathology reporting with possibly subsequent improvement of clinical outcomes. Previous studies indeed showed that pathology review of prostate biopsies resulted in a significant change in the original diagnosis. In 1.2% to 10% of cases, a diagnosis of prostate cancer was either refuted, changed or adapted and consequently might have led to a change in treatment [12-14].

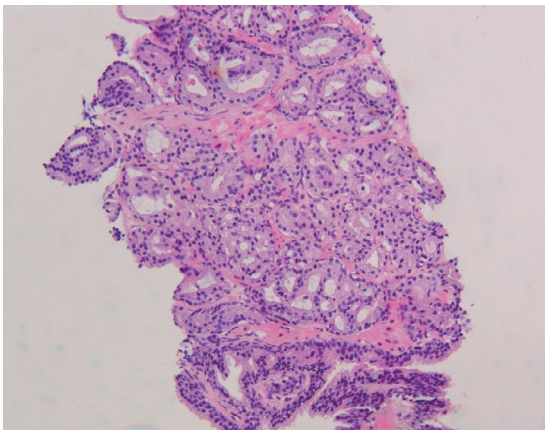

Figure 1: Gleason score.

Indeed, one of the main aims of centralization of prostate cancer grading in a histopathological review committee was to allow pathologists to develop expertise in this common disease and discuss the differences. In the case of histopathology, it is evident that increased exposure has helped to improve the accuracy of histological staging [3,15-19].

Given the significant number of pathology reports from referring hospitals that were reclassified on subsequent histopathological review in our report, the questions raise as to whether all suspicious prostate biopsies should be discussed directly in a histopathological review committee of uro-pathologists before reporting. This would streamline the service by reducing duplication of work and cost-effectiveness [20]. Further research is needed, involving larger multicenter collaboration, to address this question fully and make recommendations regarding acceptable reporting differences from referring hospitals.

We believe that the gain of accurate pathological grading could be in the consultation and discussion in a histopathological review committee, and consensus could be reached by a histopathological committee consisting of at least one uro-pathologist. Centralization of prostate biopsies could reduce the differences between pathologists, as was demonstrated between the two specialized uro-pathologists.

Another potential limitation of this study is that it remains unclear which particular patients are to be selected for ePLND or nerve-sparing radical prostatectomy, and if the used treatment algorithm is plausible and reproducible. It is evident that when other risk parameters or other cut-off points (e.g. number of cores with cancer or biopsy Gleason score) would have been selected within the algorithms, the frequency of treatment alterations will change.

Lastly, we only selected patients who had undergone a radical prostatectomy. Our study could therefore be subject to selection bias. In the future, a study should be conducted to check if the results also

		Gleason scores review				Total
		Gleason score 3+3 N (% of total)	Gleason score 3+4 N (% of total)	Gleason score 4+3 N (% of total)	Gleason score 8-10 N (% of total)	
Gleason scores referring pathologists	Gleason score ≤ 3+3	91 (32.9%)	33 (11.9%)	6 (2.2%)	2 (0.7%)	132 (47.7%)
	Gleason score 3+4	1 (0.4%)	59 (21.3%)	18 (6.5%)	5 (1.8%)	83 (30.0%)
	Gleason score 4+3	0 (0%)	6 (2.2%)	15 (5.4%)	4 (1.4%)	25 (9.0%)
	Gleason score 8-10	1 (0.4%)	5 (1.8%)	5 (1.8%)	26 (9.4%)	37 (13.4%)
Total		93 (33.6%)	103 (37.2%)	44 (15.9%)	37 (13.4%)	277 (100%)

Table 2: The concordance in the reporting of Gleason score between referring pathologists and a centralized histopathological review committee.

		Risk group centralized histopathological review committee			Total
		Low risk N (% of total)	Intermediate risk N (% of total)	High risk N (% of total)	
Risk group referring pathologists	Low risk	62 (22.4%)	21 (7.6%)	2 (0.7%)	85 (30.7%)
	Intermediate risk	2 (0.7%)	123 (44.4%)	20 (7.2%)	145 (52.3%)
	High risk	0 (0.0%)	6 (2.2%)	41 (14.8%)	47 (17.0%)
Total		64 (23.1%)	150 (54.2%)	63 (22.7%)	277 (100%)

Low Risk: Gleason score 3+3=6, cT1c/T2a, and iPSA less than 10 ng/ml; Intermediate Risk: Total Gleason score of 7 (3+4 or 4+3), and/or maximal cT2b, and/or iPSA 10-20 ng/mL, and no high-risk features; High Risk: Gleason score 8 or higher, cT2c or higher, or iPSA of 20 ng/mL or higher.

Table 3: The concordance in prognostic risk group stratification according to D'Amico et al. [5], when the prostate biopsies of patients were assessed by referring pathologists and a centralized histopathological review committee.

	More aggressive strategy if…	Less aggressive strategy if…	Total change in treatment/ diagnostic decision
Bone scintigraphy	11 (4.0%)	11 (4.0%)	22 (8.0%)
Extended lymph node dissection - Cut-off 5% - Cut-off 8% - Cut-off 10%	 28 (10.1%) 27 (9.7%) 29 (10.5%)	 4 (1.4%) 6 (2.2%) 6 (2.2%)	 32 (11.5%) 33 (11.9%) 35 (12.7%)
Nerve-sparing surgery (uni- or bilateral surgery)	31 (11.2%)	12 (4.3%)	43 (15.5%)
Recommendation shift from AS to active treatment and vice versa	31 (11.2%)	3 (1.1%)	33 (11.9%)
Number (%) of cases in whom diagnostic and/or treatment decisions changed due to pathological review			5% cut-off: 88 (31.8%) 8% cut-off: 85 (30.7%) 10% cut-off: 82 (29.6%)

Table 4: Alteration of treatment or diagnostic strategy after review by the centralized histopathological review committee.

apply on patients who e.g. chose for brachytherapy/ active surveillance or external beam radiotherapy.

In conclusion, our study showed that after centralized histopathological review of a series of diagnostic prostate biopsy specimens, a substantial proportion of histology reports was revised, mostly resulting in a change in biopsy Gleason score and subsequently D'Amico prognostic risk group. Treatment advice and diagnostic work-up would have changed in almost a third of surgically treated cases due to centralized histopathological review, and therefore we strongly suggest that prostate cancer care should be centralized.

Conflict of Interest

The authors declare that they have no conflict of interest.

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