Comparative analysis of prostate cancer grade at biopsy versus after radical prostatectomy: a retrospective observational study

Keywords
prostate cancer, biopsy, radical prostatectomy, Gleason score, active surveillance, ISUP

Abstract

Introduction

Accurate Gleason grading is essential for optimal treatment selection in prostate cancer, particularly in patients eligible for active surveillance (AS). This study aimed to assess the rate of Gleason score upgrading after radical prostatectomy and its clinical implications in a large Polish cohort of patients with prostate cancer.

Material and methods

The data of 534 men with localized prostate cancer treated with radical prostatectomy at two academic centers (2017–2024) were retrospectively analyzed. Gleason scores of preoperative biopsy specimens were compared with those of whole–mount prostatectomy specimens. Statistical analyses included Wilcoxon signed–rank, chi–square, Kendall's tau, and Cohen's kappa tests.

Results

Overall, Gleason scores were upgraded in 40% of the patients, downgraded in 10%, and concordant in 50%. Among the patients meeting AS criteria at diagnosis (Gleason 6, prostate-specific antigen level <10 ng/mL, clinical stage T1c–T2a), upgrading occurred in 58% and downgrading in 0%. International Society of Urological Pathology grading showed a similar pattern (upgrading in 40%, downgrading in 11%). Agreement between biopsy and prostatectomy grading was low (kappa ≈0.23).

Conclusions

A high Gleason upgrading rate, especially among AS□eligible men, indicates underestimation of biopsy grading in routine practice. Incorporating multiparametric magnetic resonance imaging with targeted biopsy and considering centralized pathology review may improve selection for AS and reduce undertreatment of clinically significant disease.

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Conclusions: A high Gleason upgrading rate, especially among patients who met active surveillance eligibility criteria but ultimately underwent radical prostatectomy, indicates potential underestimation of biopsy grading in routine practice. Incorporating multiparametric magnetic resonance imaging with targeted biopsy and considering centralized pathology review may improve selection for AS and reduce undertreatment of clinically significant disease. These findings underscore the limitations of biopsy-based grading in routine clinical practice and highlight the need for cautious selection of patients for active surveillance.

Keywords: prostate cancer, Gleason score, ISUP, radical prostatectomy, biopsy, active surveillance

Introduction

Prostate cancer is the second most common cancer in men worldwide and the fifth leading cause of cancer-related death [1]. However, screening for this cancer is challenging. While accurate diagnosis impacts treatment decisions and patient prognosis, pathological evaluation of prostate biopsies and radical prostatectomy specimens requires strong expertise and vigilance from uropathologists [2].

Accurate risk stratification at the time of prostate cancer diagnosis is critical for guiding clinical decision making, particularly in patients considered for conservative management. Current treatment algorithms, including those outlined by the National Comprehensive Cancer Network (NCCN), European Association of Urology (EAU), and other international guidelines, designate Gleason score 6 [International Society of Urological Pathology (ISUP) Grade Group 1], together with a prostate-specific antigen (PSA) level of <10 ng/mL and clinical stage T1c–T2a, as essential eligibility criteria for active surveillance (AS) [3,4]. Patients meeting these thresholds are classified as having "low" or "very low" risk disease, and AS is widely recommended as the preferred initial management approach [3].

The rationale for AS in these patients is based on favorable oncologic outcomes, supported by long-term observational data showing low rates of progression and cancer-specific mortality in well-selected individuals with Gleason 6 tumors [5,6]. However, in clinical practice, the Gleason score assigned on biopsy plays a pivotal role in AS decision making. It serves not only as a surrogate marker for tumor aggressiveness but also directly determines patient eligibility for conservative treatment protocols.

Despite its central role, biopsy-assigned Gleason score 6 may not reliably reflect the true pathological grade. Numerous studies have demonstrated that a significant proportion of

patients—often 20–50%—initially diagnosed with Gleason 6 are found to have upgraded disease (Gleason ≥7) upon final pathology after radical prostatectomy [3,5,7]. This discordance is attributed to several factors, including the multifocal nature of prostate cancer, histopathological heterogeneity, and sampling limitations of standard transrectal ultrasound (TRUS)-guided biopsy [8,9]. Interobserver variability among pathologists further complicates diagnostic consistency, particularly in settings lacking centralized review [9].

Recently developed risk tools, such as the BADGR nomogram, attempt to predict upgrading using preoperative variables, including PSA density, obesity, and tumor burden on biopsy [7]. Nonetheless, such tools have not been universally implemented in AS decision making, and the biopsy Gleason score remains the cornerstone of risk classification.

In Poland, the increasing adoption of the AS as a management strategy for localized low-risk prostate cancer reflects broader international trends. Polish consensus documents support AS in appropriately selected patients, especially considering the growing concerns regarding overtreatment [6]. However, the absence of second-opinion pathology review in routine clinical practice raises concerns about diagnostic accuracy. Importantly, real-world pathology is inherently mosaic, with multiple pathologists contributing to histological evaluation, which may reduce individual bias but introduces systemic variability [10].

Additional contributors to Gleason upgrading, including histological heterogeneity, delays between biopsy and definitive treatment, and biological disease progression during the AS interval, should also be considered. Moreover, several guidelines now advocate for magnetic resonance imaging (MRI)-targeted fusion biopsy, which has demonstrated superior accuracy compared with conventional TRUS-guided techniques [11]. Given these considerations, the accuracy of biopsy-based Gleason grading has critical implications for treatment selection.

The objective of this study was to assess the concordance between biopsy-based and prostatectomy-based Gleason and ISUP grading in a large, real-world Polish cohort treated with radical prostatectomy. Particular emphasis was placed on patients meeting commonly used eligibility criteria for active surveillance, in order to highlight the potential clinical consequences of diagnostic underestimation at the time of initial biopsy.

Material and Methods

Study design and population

This retrospective observational study included 534 men diagnosed with localized prostate cancer, who underwent radical prostatectomy at two academic urology centers in Poland between 2017 and 2024 (Multidisciplinary Hospital Miedzylesie in Warsaw [MSSW] and Antoni Jurasz University Hospital [AJUH] No. 1 in Bydgoszcz). Histopathological evaluation was performed on all biopsy and prostatectomy specimens.

A subset of 150 patients fulfilled the criteria for AS at the time of diagnosis, based on NCCN and EAU guidelines: clinical stage ≤T2a, PSA level <10 ng/mL, Gleason score 3+3 (ISUP 1), PSA density <0.2 ng/mL/mL, and involvement of ≤2 cores. Patients who had previously undergone prostate cancer treatment and those with incomplete clinical data were excluded.

As a retrospective, pathology-based study, the analysis was limited to patients who ultimately underwent radical prostatectomy, enabling direct comparison between biopsy and whole-mount prostatectomy specimens. Patients managed conservatively without surgery were therefore not represented in this cohort.

This study was conducted in accordance with the principles of the Declaration of Helsinki. The need for informed consent was waived owing to the retrospective nature of the study.

Pathological assessment

Preoperative Gleason scores were determined using TRUS-guided prostate biopsy. Postoperative Gleason grading was based on whole-mount histological analysis of radical prostatectomy specimens according to the Stamey–Bostwick protocol. All evaluations were performed by institutional pathologists without centralized review. Gleason scores were stratified by ISUP grade groups.

The degree of concordance or discrepancy between preoperative and postoperative Gleason scores was classified into three categories: 1) No change; 2) Upgrading, higher Gleason score after surgery compared with that before surgery; 3) Downgrading, higher Gleason score on biopsy compared with that after surgery.

Changes in Gleason score and ISUP Grade Group between biopsy and radical prostatectomy were analyzed separately. Upgrading and downgrading were defined as an increase or decrease in the respective grading system.Prostate biopsies were performed using transrectal ultrasound-guided systematic sampling according to local institutional practice at the time of diagnosis. The biopsy protocols were not fully standardized across centers, and data regarding the exact number of cores or routine use of pre-biopsy multiparametric MRI were not uniformly available for retrospective analysis.

Statistical analysis

Statistical analysis was conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio version 2023.06.1 (RStudio, PBC, Boston, MA). Descriptive statistics are reported as the mean with standard deviation, or median with interquartile range (IQR), as appropriate. Normality of data distributions was assessed using Q-Q plots. For

comparison of paired ordinal variables (e.g., Gleason or ISUP grade before and after surgery), the Wilcoxon signed-rank test was used. Correlations between ordinal scores were evaluated with Kendall's tau coefficient. Agreement analysis was performed using Cohen's kappa statistic. Categorical variables were compared using chi-square tests. A p-value <0.05 was considered statistically significant.

Results

Patient characteristics

The cohort consisted of 534 male patients with a median age of 67 (IQR: 62–71) years. The mean PSA level was 11.8 ± 15.3 ng/mL. The distribution by center was 334 patients from AJUH and 200 from MSSW. Baseline characteristics, including clinical T stage and preoperative Gleason scores, were comparable between the centers.

Gleason scores before and after prostatectomy

A significant increase in the median Gleason score was observed after radical prostatectomy, increasing from 7 (IQR: 6–7) preoperatively to 7 (IQR: 7–7) postoperatively (p<0.001, Wilcoxon test) (Figure 1). Upgrading was observed in 40% of the overall cohort, whereas downgrading was noted in 10% and no change in 50%. Sub-analysis by center revealed upgrading in 37% of the patients at AJUH and in 46% of those at MSSW. This difference did not reach significance (p=0.086, chi-square test) (Table 1).

Patients meeting active surveillance eligibility criteria who underwent radical prostatectomy

This subgroup represents patients who met commonly accepted active surveillance eligibility criteria at diagnosis but subsequently underwent radical prostatectomy, and does not reflect outcomes of patients remaining on active surveillance.

Among the 150 patients meeting the AS criteria, Gleason upgrading was observed in 58% overall, in 55% at AJUH, and in 62% at MSSW; the difference between centers was not significant (p=0.37) (Table 2). No cases of Gleason score downgrading were reported in this subgroup.

ISUP score changes

A similar pattern was observed in ISUP grading. Upgrading occurred in 40% of the patients, while downgrading occurred in 11% (Figure 2). Cohen's kappa for the ISUP score was 0.23 (agreement: 42.9%). The difference between the pre- and postoperative ISUP grades was significant ($p<0.001$, Wilcoxon test). By center, ISUP upgrading was found in 33.2% of the patients at AJUH and in 45.9% of those at MSSW. Downgrading occurred in 15.8% and 18.4% of the patients at AJUH and MSSW, respectively. In 51.0% and 35.7% of the patients at AJUH and MSSW, respectively, no ISUP score change was observed (Table 3).

Although the difference in upgrading rates between centers did not reach statistical significance, the observed trend suggests potential institutional variability, which may reflect differences in case mix, biopsy practices, or pathological interpretation.

Discussion

Our findings revealed a markedly high rate of Gleason score upgrading after radical prostatectomy in Polish patients with prostate cancer, especially those initially diagnosed with Gleason 6 disease. In the total cohort of 534 patients, 40% experienced an increased Gleason score postoperatively;

this proportion rose to 58% in the subcohort of patients considered eligible for AS. These results significantly exceed the rates reported in international cohorts, where upgrading rates for Gleason 6 disease typically range between 20 and 30% [12-18]. Several factors may have contributed to this discrepancy. First, the inherent limitation of needle biopsy in capturing tumor heterogeneity is well recognized. Prostate cancer is often multifocal and may present with histologic variability within different regions of the gland. Consequently, standard TRUS-guided biopsies may fail to identify clinically significant lesions, particularly those located in the anterior prostate or transition zone [16,17,19,20]. This sampling limitation is a known contributor to undergrading.

However, the magnitude of upgrading observed in our cohort suggests additional contributing factors. The consistently high undergrading rates in both centers included in this analysis support the hypothesis that methodological or interpretive differences may be present. Variability in biopsy protocols (e.g., number of cores, targeted versus systematic sampling) or differences in pathological grading practices could influence the accuracy of preoperative Gleason assessment. Similar concerns have been raised in the literature regarding interobserver variability among pathologists, particularly in borderline or moderately differentiated tumors [10,14,21].

The clinical significance of this finding is substantial. Gleason 6 (ISUP Grade Group 1) is the primary histological criterion for recommending AS. Misclassification of higher-grade tumors as low risk can lead to inappropriate inclusion of patients into surveillance protocols, delaying curative treatment and potentially compromising oncologic outcomes. Notably, in our cohort, 58% of the patients with initial Gleason 6 disease were upgraded after prostatectomy, highlighting the vulnerability of this group to diagnostic underestimation. This phenomenon is consistent with prior studies emphasizing the diagnostic uncertainty surrounding Gleason 6 cancers and risk of underdetection of pattern 4 components [22-24].

Our findings call for a critical reassessment of diagnostic protocols in clinical settings in Poland. Incorporation of multiparametric MRI (mpMRI) in the initial diagnostic workup, along with MRI-targeted biopsy, may enhance detection of clinically significant disease and reduce reliance on limited sampling alone [7,10,19]. MpMRI is considered a sensitive imaging method for the detection of prostate cancer. Of note, Choudhary et al. [25] revealed that lesion volume can be used as a non-invasive indicator of clinically significant prostate cancer. It also seems that the experience of the operator performing the biopsy is important in prostate cancer diagnosis. The abilities and precision of the operator are enhanced with the increase in the number of biopsies performed; the shortened biopsy time reflects the urologist's skill improvement. Most importantly, as experience is gained, the accuracy of prostate cancer detection during the procedure improves [26]. Furthermore, centralized or second-opinion pathology review, particularly in AS candidates, could mitigate the risks associated with interobserver variability [14,19,22].

The results of the trial by Hamdy et al. demonstrated no significant differences in prostate cancer-specific mortality at 10 years between patients receiving active monitoring, radical prostatectomy, and radiotherapy, although rates of progression and metastasis were higher in those receiving active monitoring [27]. These findings triggered substantial debate in the field. Subsequently, De Reijke and van Moorselaar highlighted that nearly 60% of the trial participants involved in Hamdy et al.'s study had Gleason 6 disease, which likely contributed to the very low prostate cancer-related mortality (~1%) and limited the statistical power to detect survival differences [28]. Cooperberg emphasized that the monitoring protocol utilized by Hamdy et al. was suboptimal, relying largely on PSA level evaluation without scheduled repeat biopsies, and cautioned against misinterpreting the results as evidence that all prostate cancers can be safely monitored [29]. In contrast, Albertsen highlighted that the trial confirmed the generally indolent course of screen-

detected Gleason 6 tumors and supported the safety of AS in carefully selected low-risk patients, while stressing that longer-term follow-up is essential [30]. Our finding of frequent Gleason score upgrading among biopsy-assigned Gleason 6 cases adds to this discussion, suggesting that misclassification at diagnosis may have led to underestimated risk and could similarly expose contemporary patients to inappropriate inclusion in surveillance protocols.

The observed differences between centers, particularly with respect to ISUP grade changes, further underscore the impact of real-world variability in diagnostic pathways. Differences in biopsy technique, pathological workload, and absence of centralized pathology review may all contribute to grading discordance.

In addition to mpMRI-targeted biopsy, potential strategies to improve diagnostic accuracy include standardized biopsy protocols, quality assurance in pathological grading, and second-opinion pathology review in patients considered for conservative management.

This study has certain limitations, including its retrospective design and potential selection bias. Another important limitation of this study is the potential for verification bias, as only patients who proceeded to radical prostatectomy were included. Patients who remained on active surveillance were not represented, and the true upgrading rate among all biopsy-diagnosed patients may therefore be lower. Consequently, the results should be interpreted as reflecting diagnostic discordance in surgically treated patients rather than as an estimate of upgrading risk in the entire active surveillance population. Nevertheless, the inclusion of two independent centers and a large sample size strengthen the validity of our findings. Future prospective, multicenter studies with standardized biopsy and grading protocols are needed to better quantify and address regional differences in Gleason assessment accuracy.

Conclusions

In this real-world Polish cohort, concordance between biopsy and prostatectomy Gleason grading was limited, with a high rate of upgrading, particularly among patients meeting active surveillance eligibility criteria who ultimately underwent surgery. These findings emphasize the need for cautious reliance on biopsy-based grading in treatment decision-making and highlight the importance of optimizing diagnostic pathways to avoid underestimation of clinically significant disease.

Acknowledgements

Conflict of interest: The authors declare no conflicts of interest.

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Figure legends

Figure 1. Gleason score before and after surgery

95% confidence intervals are shown

Figure 2. ISUP score before and after surgery

95% confidence intervals are shown. ISUP, International Society of Urological Pathology

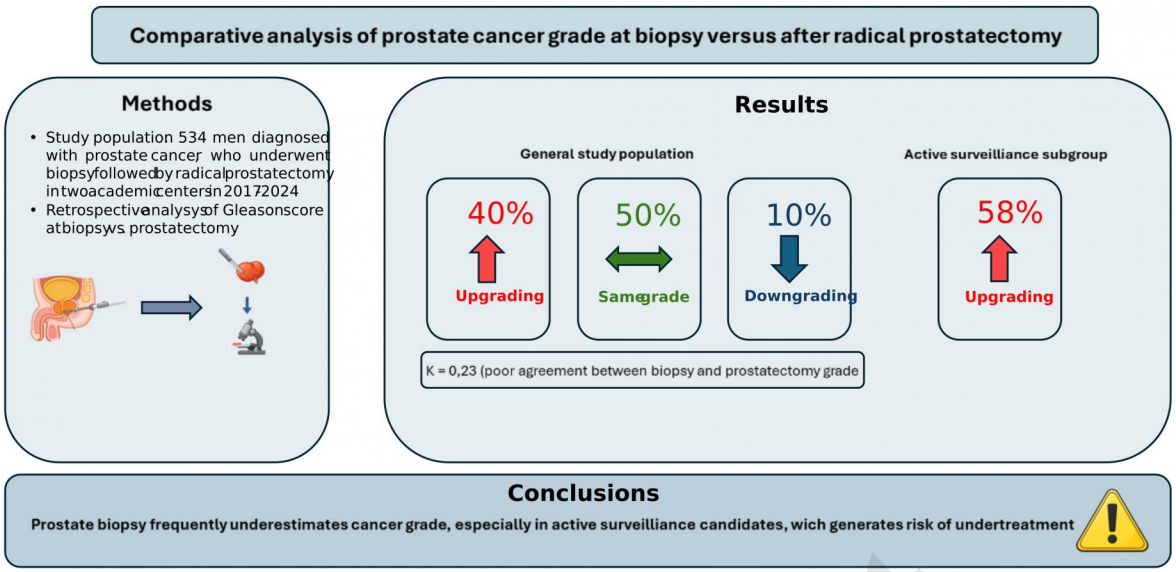

Comparative analysis of prostate cancer grade at biopsy versus after radical prostatectomy
Methods
Study population 534 men diagnosed with prostate cancer who underwent biopsy followed by radical prostatectomy in two academic centers in 2017-2024
Retrospective analysis of Gleason score at biopsy vs prostatectomy
Results
General study population
Active surveilliance subgroup
40%
Upgrading
50%
Same grade
10%
Downgrading
58%
Upgrading
K = 0,23 (poor agreement between biopsy and prostatectomy grade
Conclusions
Prostate biopsy frequently underestimates cancer grade, especially in active surveilliance candidates, wich generates risk of undertreatment

Table 1. Gleason score changes from before to after radical prostatectomy

Gleason score change	Overall (n=534)	AJUH (n=334)	MSSW (n=200)	p-value
Higher after surgery	214 (40%)	123 (37%)	91 (46%)	0.086
Higher before surgery	55 (10%)	33 (10%)	22 (11%)	NS
No difference	265 (50%)	178 (53%)	87 (44%)	—

Data are reported as frequency (%) and are shown for the overall cohort and each center. AJUH, Antoni Jurasz University Hospital; MSSW, Multidisciplinary Hospital Miedzylesie

Table 2. Gleason score changes in the active surveillance subgroup

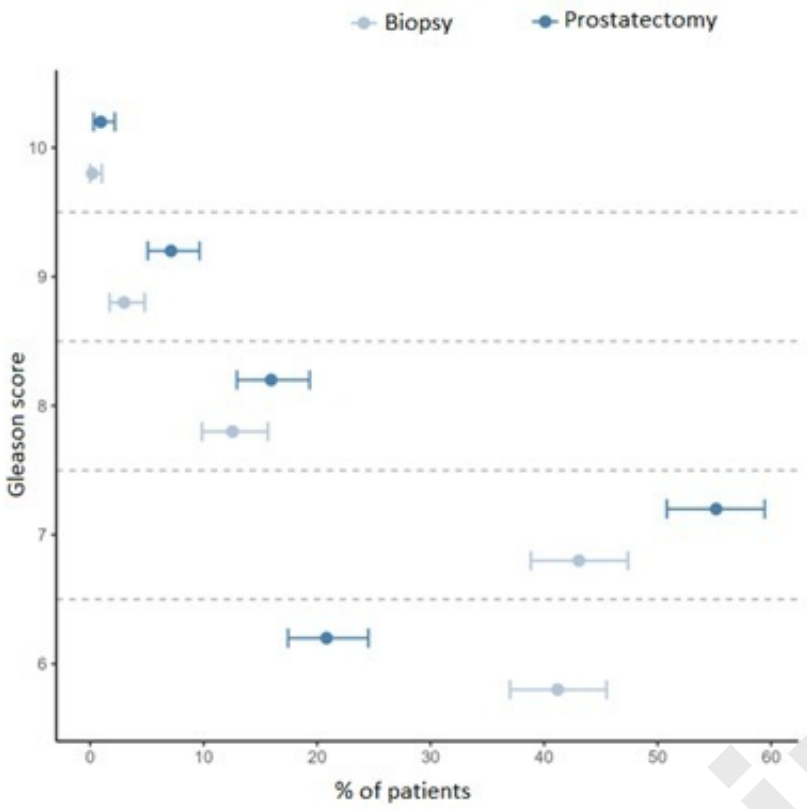
Gleason score change	Overall (n=150)	AJUH (n=85)	MSSW (n=65)	p-value
Higher after surgery	87 (58%)	47 (55%)	40 (62%)	0.37
Higher before surgery	0 (0%)	0 (0%)	0 (0%)	—
No difference	63 (42%)	38 (45%)	25 (38%)	

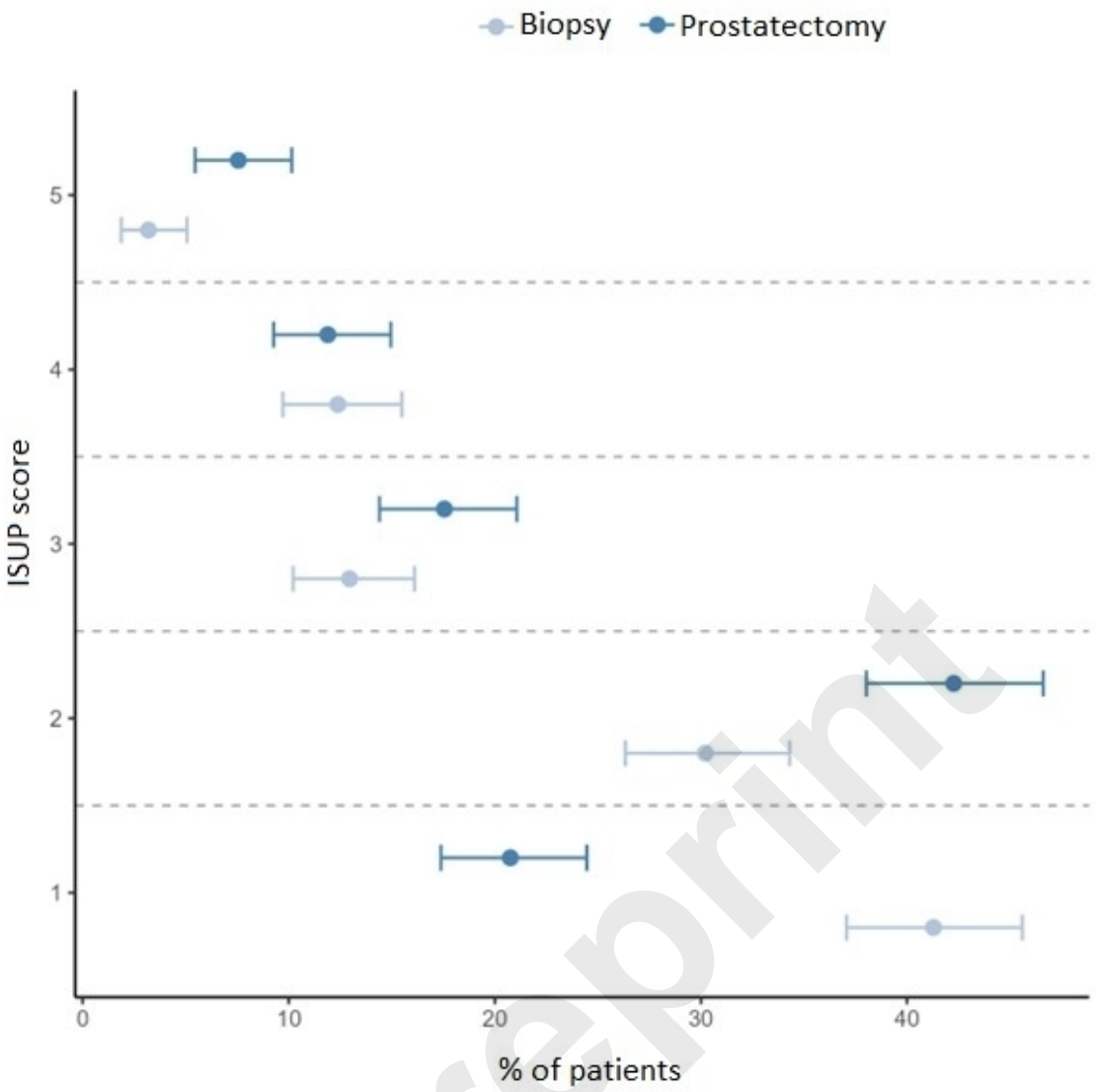
Data are reported as frequency (%) and are shown for the overall cohort and each center. AJUH, Antoni Jurasz University Hospital; MSSW, Multidisciplinary Hospital Miedzylesie

Table 3. ISUP score change before and after radical prostatectomy

ISUP score change	Overall (n=533)	AJUH (n=334)	MSSW (n=200)	p-value
Higher after surgery	213 (40%)	111 (33.2%)	91 (45.9%)	<0.001
Lower after surgery	84 (15.8%)	53 (15.8%)	31 (18.4%)	—
No change	228 (42.9%)	170 (51.0%)	71 (35.7%)	—

Data are reported as frequency (%) and are shown for the overall cohort and each center. AJUH, Antoni Jurasz University Hospital; MSSW, Multidisciplinary Hospital Miedzylesie; ISUP, International Society of Urological Pathology


Biopsy
Prostatectomy
Gleason score
10
9
8
7
6
0
10
20
30
40
50
60
% of patients


Biopsy
Prostatectomy
ISUP score
5
4
3
2
1
0
10
20
30
40
% of patients