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Localized prostate cancer and robot-assisted laparoscopic radical prostatectomy: a retrospective, comparative study between pre- and post-operative Gleason scores

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ABSTRACT
Introduction: To compare the pre- and post-operative Gleason scores (GS) in patients with localized prostate cancer treated with robot-assisted laparoscopic radical prostatectomy.

Materials and methods: A single center, retrospective comparison between pre- and post-operative GS. Age, prostate volume, PSA, number of biopsies, number of positive cores, biopsy GS, cTNM, final pathology GS and pTNM of 286 patients were retrieved. They were divided into risk groups.

Results: A total of 286 patients with a mean age at surgery of 64.64 ± 7.81 y and mean PSA-value of 9.35 ± 8.38 ng/mL. Mean prostate volume was 55.09 ± 24.93 mL, mean number of biopsies was 11.90 ± 4.63. Mean percentage of positive cores was 36.90 ± 22.42%. A GS of <7 was seen in 23.4%, 66.8% had a GS of 7 and 9.7% of >7 in final pathology. Of the total, 38.1% were pre-operative low risk, 58.7% of them had an upgrade in GS on final pathology, 45.1% were in the intermediate risk group, 5.4% showed a downgrade, 64.3% remained stable and 30.2% had an upgrade in GS. Also, 16.8% were high risk patients of which 35.4% had a downgrade, 39.6% remained stable and 25% showed an upgrade of the GS.

Conclusions: We found a substantial underestimation of the GS in the pre-operative setting when compared to the GS in final pathology.

Introduction
Prostate cancer (PCa) is one of the most common forms of cancer in men worldwide and the incidence is still rising [1,2]. Localized or locally advanced non-metastatic disease is found in over 80% of the almost 1 million men diagnosed with PCa worldwide every year [3]. The treatment of PCa has evolved rapidly over the last decade. Despite this progress, PCa still belongs in the top three of most frequent causes of cancer related mortality [1–3]. Choice of treatment is based on risk stratification, derived from the D’Amico classification described in 1999. Since then, it is widely adopted by different international guideline associations [3,4]. All of these risk stratifications are based on presenting PSA-value, Gleason score (GS) after biopsy and the clinical stage of the disease. The risk stratification will enable a classification into three risk groups (low, intermediate and high) [3–5]. For the low and intermediate risk group, there is no simple answer as what is the optimal therapy. In selected cases an expectative attitude can be chosen in the low risk group. However, a radical therapy can be an equally good decision. Over the past years, the correlation between pre- and post-operative GS has been studied abundantly. As results tend to differ, we want to present the data from our peripheral center with a retrospective analysis that assesses how pre-operative GS relates to the post-operative GS. Furthermore, we want to evaluate whether this would have an impact on clinical decision-making and finally, we want to investigate which subcategory of patients would have the most advantages undergoing a radical prostatectomy.

Materials and methods
In this study, we used the database of our peripheral hospital (GZA Sint Augustinus Hospital, Wilrijk, Belgium) for a retrospective comparison between the pre-operative and post-operative GS and
evaluation of the pre-operative risk stratification. Our database contained all the patients that underwent a robot-assisted laparoscopic radical prostatectomy (RARP) for localized PCa between 18 January 2007 and 1 August 2014. Patients that received primary radiotherapy, whether it was brachytherapy or external beam radiation therapy (EBRT), or underwent open or laparoscopic radical prostatectomy, were not included in our study. Patients receiving adjuvant therapy were also not included in the study design. All procedures were performed by two experienced urologic surgeons (V. H. and A. T.) according to the technique as described in literature [6–8]. Both surgeons completed their learning curve for the RARP-procedure prior to this study. A da Vinci S System (Intuitive Surgical\textsuperscript{\textregistered}, Sunnyvale, CA) was used for all procedures. Histopathological study of the prostate biopsies was performed by our pathologist. However, some patients were referred to our center, as we were one of the first centers with a robot in the region. Therefore, in some cases, pathology of the prostate biopsies was done in different hospitals. All final histopathological studies of the whole surgical specimen were performed by the pathologist at our center.

Our database contained a total of 286 patients who underwent RARP and met the inclusion criteria for this study. For every patient in the database we retrieved the age at the time of the operation, the prostate volume, PSA-value, the number of prostate biopsies, the number of positive cores, the GS on needle biopsy and the clinical TNM (pre-operative data), as well as the final pathology GS and pathological TNM-stage of the disease. Using this classification we divided the patients (n = 286) into three subcategories based on the risk of progression.

Statistical analysis was performed using IBM SPSS Statistic software version 23 (SPSS Inc., Chicago, IL). Patient data were expressed in median. We performed a one-way ANOVA test to analyze continuous variables. For categorical variables chi-square test was performed. For agreement testing the Cohen’s kappa coefficient was used. In this study we considered a 2-sided p value <.05 as statistically significant.

**Results**

**Population**

A total of 286 patients were included for analysis in this study. Mean age at surgery was 64.64 ± 7.81 years old (median 65, range 43–80 years old), mean PSA-value was 9.35 ± 8.38 ng/mL. Transrectal prostatic ultrasound showed a mean prostate volume of 55.09 ± 24.93 mL. In our population the number of biopsies taken showed a mean of 11.90 ± 4.63 with median of 11 and a range of 3–30. The mean percentage of positive cores was 36.90 ± 22.42% with a median of 36.36% and a range of 4.55–100%.

For further analysis, our population was divided into three risk groups according to the EAU classification based on the D’Amico system. Table 2 shows similar population characteristics between

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**Table 1. European association of urology risk group classification.**

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>&lt;10 ng/mL</td>
<td>10–20 ng/mL</td>
<td>&gt;20 ng/mL</td>
</tr>
<tr>
<td>AND</td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>Gleason score</td>
<td>&lt;7</td>
<td>=7</td>
<td>&gt;7</td>
</tr>
<tr>
<td>AND</td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>cTNM</td>
<td>cT1-2a</td>
<td>cT2b</td>
<td>cT2c</td>
</tr>
<tr>
<td></td>
<td>Localized PCa</td>
<td></td>
<td>cT3-4 OR cN+</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Locally advanced PCa</td>
</tr>
</tbody>
</table>

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For further analysis, our population was divided into three risk groups according to the EAU classification based on the D’Amico system. Table 2 shows similar population characteristics between...
these risk groups. There was no statistical difference in mean age at surgery ($p = .579$) and number of biopsies ($p = .503$). A statistical difference was found between the groups for PSA-value ($p < .001$), with a mean PSA of 5.91 ng/mL ±2.23 for the low risk group, 8.96 ng/mL ±4.51 for the intermediate risk group and 18.63 ng/mL ±16.03 for the high risk group. The prostate volume was significantly different ($p < .001$) between the low, intermediate and high risk group (61.72 mL ± 30.25, 48.95 mL ±17.21 and 56.87 mL ±25.81, respectively). Finally, the percentage of positive cores (low risk group = 24.47% ± 20.03; intermediate risk group = 38.62% ± 22.62; and high risk group = 51.59% ± 19.25) was significantly different ($p < .001$).

Table 2. Population characteristics based on risk groups.

<table>
<thead>
<tr>
<th></th>
<th>Low risk (mean ± SD)</th>
<th>Intermediate risk (mean ± SD)</th>
<th>High risk (mean ± SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery (years)</td>
<td>64 ± 7.88</td>
<td>65 ± 7.55</td>
<td>64.85 ± 8.41</td>
<td>.579</td>
</tr>
<tr>
<td>PSA (ng/mL)</td>
<td>5.91 ± 2.23</td>
<td>8.96 ± 4.51</td>
<td>18.63 ± 16.03</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prostate Volume (mL)</td>
<td>61.72 ± 30.25</td>
<td>48.95 ± 17.21</td>
<td>56.87 ± 25.81</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number of biopsies</td>
<td>11.63 ± 4.69</td>
<td>11.88 ± 4.29</td>
<td>12.59 ± 5.38</td>
<td>.503</td>
</tr>
<tr>
<td>Percentage of cores positive (%)</td>
<td>24.47 ± 20.03</td>
<td>38.62 ± 22.62</td>
<td>51.59 ± 19.25</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Figure 1. Frequency of discordance between pre- and post-operative GS.

On final pathology of the whole surgical specimen, a GS < 7 was seen in 23.4% of patients, and 66.8% had a GS of 7 in their resection specimen. A GS > 7 was found in 9.7% of cases.

**Frequency of discordance between pre- and post-operative GS (Figure 1)**

Of the total population ($n = 286$), 38.1% ($n = 109$) were pre-operatively seen as low risk patients, thus having a GS < 7. In this group 58.7% of the patients ($n = 64$) had an upgrade in GS on the final pathology specimen. Remarkably, all of these patients had an upgrade to a GS of 7. No upgrades to GS 8, 9 or 10 were observed.

In the intermediate risk group ($n = 129$, 45.1% of the total population), a downgrade of the GS was seen in 5.4% ($n = 7$). Stable GS was observed in 64.3% ($n = 83$) and 30.2% ($n = 39$) of individuals had an upgrade in their GS on final pathology.

Analyzing the high risk group ($n = 48$, 16.8% of the total population), we found a downgrade of the GS in 35.4% ($n = 17$), 39.6% ($n = 19$) had a
stable GS result and in 25% ($n = 12$) an upgrade was found.

Finally, we calculated the accuracy and agreement of biopsy GS in regard of final pathology. To do this we divided the pre- and post-operative GS into three groups according to the EAU classification based on the D’Amico system: GS $\leq 6$, GS equal to 7 and GS $\geq 8$ [4, 5].

Calculating the Cohen’s kappa coefficient shows a value of 0.256 with a standard error of 0.042 ($p < .001$), thus showing a minimal to fair level of agreement based on the various definitions of interpretation of this test found in literature [12, 13]. Analysis of the accuracy of the pre-operative GS in our population are listed in Table 3.

**Table 3. Accuracy of the pre-operative Gleason score.**

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>Sensitivity</th>
<th>Positive predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS $\leq 6$</td>
<td>86.57%</td>
<td>37.91%</td>
</tr>
<tr>
<td>GS = 7</td>
<td>44.50%</td>
<td>79.44%</td>
</tr>
<tr>
<td>GS $\geq 8$</td>
<td>42.86%</td>
<td>46.15%</td>
</tr>
</tbody>
</table>

Frequency of discordance between pre- and post-operative tumor localization

When pre-operative prostate biopsies showed tumor limitation to only a single prostatic lobe, 39.3% ($n = 43$) of the low risk patients, 36.9% ($n = 48$) of intermediate risk individuals and 30.4% ($n = 15$) of high risk patients were post-operatively reclassified as bilateral disease in final pathology. There was no significant difference found between the risk groups for this upgrade in tumor localization ($p = .583$).

Discussion

Early detection of PCa is possible through screening with PSA as a part of the prostate investigation. The role of screening in the entire population is until now still controversial. A Cochrane review by Ilic et al. demonstrated that screening leads to an increase in diagnosis of PCa [14]. However, screening also led to an increase in diagnosis of localized PCa and less advanced PCa. These findings did not have a decrease of PCA associated mortality as a result, or a decrease in overall mortality. The fact that screening failed to show any effect on mortality combined with the observation that overdiagnosis often leads to overtreatment had as a result, that screening of the population is frowned upon by several authors [14–17].

Although the ERSPC-trial showed a reduction of 21% in PCA in intention to screen analyses and a reduction of 27% in actually screened men between 55 and 69 year old, they found no effect on the overall survival [15]. They conclude that in this group, 781 men have to be screened and 27 men have to be diagnosed with PCa to avoid one prostate related death over a period of 13 years. Despite the fact that a general population screening is not recommended, it has to be said that screening is not entirely useless. PSA-testing should be accessible for well-informed men suitable for screening.

The treatment options in localized PCa are divers and depend on the stage of the disease, life-expectancy and co-morbidities. Important is that not the absolute age of the patient, but the life-expectancy based on the co-morbidities is taken into account. In addition, it is important to look at possible PCa related complications or local problems, obstructive and/or irritative miction and the wishes of the patient. The widely used therapies for localized PCa consist of watchful waiting (WW), AS, radical surgery (open radical prostatectomy, laparoscopic radical prostatectomy and RARP), radiotherapy (EBRT and brachytherapy) and hormonal therapy (ADT) [5]. There is no evidence that shows that one therapy is superior to another. Meta-analyses show no explicit advantage for a certain technique [5]. Each therapy has its inherent advantages and disadvantages. These should be discussed with the patient before selecting a therapy [5].

The treatment of PCa and the idea of a gold standard in its therapy have evolved a great deal the past decade. Between 2005 and 2014 a radical technique through RARP was the first choice of treatment. However, AS is seen as a more than valid treatment alternative in the low risk group. This approach is getting more and more approval. EAU guidelines state that in the low risk group WW, AS, radical surgery, EBRT and brachytherapy are possible forms of treatment [5]. Whereas, AS and brachytherapy are not recommended in the intermediate risk group [5]. WW is reserved for patients with a life-expectancy $< 10$ y or who are not eligible for local curative treatment. The decision to choose for this treatment should be based on symptoms and disease progression [5]. When patients have a life-expectancy of $> 10$ years, there will be a risk-stratification to select a therapy for that specific patient. AS is only feasible in patients with the lowest risk of cancer progression [5]. Brachytherapy is possible in selected cases in the low risk group. Important is that there was no previous transurethral resection of the prostate, the patient has a good International Prostate Symptom
Score and a prostate volume of < 50 mL [5]. In high risk patients, who are about 15–25% of the total group of PCa, it is recommended to choose a radical technique (surgery or radiotherapy combined with ADT) [5]. In the low risk and intermediate risk group there is no easy answer as what is the optimal treatment. An expectative attitude, such as AS, can be chosen in selected cases in the low risk group. However, a radical therapy can be an equally alternative [5].

Our data show a substantial underestimation of the GS in the pre-operative risk estimation based on prostate biopsies. Especially in de pre-operative low risk group, where we find a GS upgrade in 58.7% of the cases. These findings are comparable with the study of Tavangar et al., who described a high chance of underestimation of the real GS of the radical prostatectomy specimen in low-grade tumors [18]. This was also described by Shen et al., they state that the chance for grading errors is highest in patients with a pre-operative GS < 7 [19].

Further analysis of the GS showed that 98.4% of the patients, who upgrade from a GS 6 to a GS 7, have a primary GS of 3. Remarkably we found no upgrades to GS > 7. This GS upgrade would post-operatively assess these individuals as intermediate risk patients. Therefore, this upgrade might provide an extra reason for radical curative techniques as a valid treatment option in the low risk group. A recent study by Pessoa et al. evaluated the role of MRI in patients with the diagnosis low-risk Pca [20]. They found that PIRADS score 1–3 had a low risk of reclassifying to a higher risk. However, PIRADS scores 4–5 had a change of 70–100% being reclassified. There was a 93% sensitivity for MRI to predict presence of a clinically significant PCa [20,21]. Other studies present similar data, advocating the use of MRI in low-risk Pca [21–23]. Furthermore, MRI in combination with targeted biopsies would lead to a better indication [21–23]. Further study is however required, as there is still controversy on the role of systematic biopsies compared to targeted biopsies [21,22].

There is a minimal level of agreement between the pre- and post-operative GS based on Kappa analysis for the population in this study. A low positive predictive value is seen for biopsies resulting in a GS of ≤ 6. This trend corresponds with the findings described by Tavangar et al. [18]. When analyzing the intermediate risk group, an upgrade in GS in 30.2% of the individuals was found. Comparable with the low risk group, there is a substantial pre-operative underestimation of the GS for patients in the intermediate risk group. Therefore, it is of great importance to identify these patients, because these are the patients who will benefit from a radical technique. These findings correspond with the EAU guidelines that suggest radical treatment in the intermediate risk group [5].

This study did not look further into the high risk group, because the role of radical treatment, alone or in a multidisciplinary approach is generally accepted in this subgroup.

A literature search showed a lot of discrepancy concerning possible upgrading of GS in final pathology. The data in this study differ from the findings of Khoddami et al. [24]. They describe a study population of 45 patients with downgrading of the GS in 9.1% and upgrading of the GS score in only 22.7% of the cases. Köksal et al. then again described an accuracy of 97% in pre-operative graded GS 5–7 and 100% in GS 8–10 [25]. Shen et al. have similar findings concerning the accuracy in pre-operative GS 5–7 (78%) and GS 8–10 (100%) [19].

An important reflection concerning this study is that pre- and post-operative pathology was revised by different pathologists. There can be a difference in interpretation of the tissue samples between different pathologists, because there is still no standardized procedure for the entire cycle of investigation (taking biopsies, preservation of the samples, treatment of the samples and analysis). This could lead to a different interpretation of the tissue samples. Furthermore, the fact that the prostate biopsies were taken by different urologists can have an influence (amount, technique, etc.).

**Conclusion**

In our study, we found a substantial underestimation of the GS in the pre-operative setting when compared to the GS in final pathology. This is especially true for patients in the low risk group. In general, there also was an arguable agreement between pre- and post-operative GS. Therefore, we could conclude that caution is necessary when interpreting pre-operative GS and to keep in account that upgrading of the GS is possible when a choice of treatment is made according to the pre-operative risk stratification. According to recent studies, MRI in combination with targeted biopsies can lead to a better risk stratification. Further study is still required.

**Disclosure statement**

No potential conflict of interest was reported by the authors.
References


