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The association of a risk group with positive margin in the intraoperative and final pathology examination after robotic radical prostatectomy

Tomasz Kupski, Michał Małek, Igal Mor

Mazovia Hospital Warsaw, Department of Urology, Warsaw, Poland

Introduction The aim of this study was to evaluate the risk of a positive margin in the intraoperative and final pathology depending on the risk group for biochemical recurrence in biopsy specimens after robot-assisted radical prostatectomy (RaRP) with sparing of the neurovascular bundles (NS).
Material and methods The study was prospective and non-randomised. The intraoperative and final pathology examinations were performed in 65 consecutive patients treated with RaRP between 11.2019–08.2020. In the intraoperative examination, the site of the dissected neurovascular bundles and any suspicious places were examined. Patients were divided into 3 risk groups [according to the European Association of Urology (EAU) biochemical recurrence-risk stratification]. Due to the uncertain prognostic value of microscopic positive margins, 3 groups were identified: R0, Rmicro and R1.
Results In the intraoperative examination, the distribution of risk groups in R0, Rmicro and R1 groups is similar (p = 0.132). In the postoperative study, the distribution of risk groups in each margin group is different, and is statistically significant (p <0.001). It has been shown that an increase in the risk group is an indicator of the occurrence of a positive margin in the final histopathological result regardless of the inclusion of Rmicro into R1 or into R0 by 2.68 and 6.52 times, respectively.
Conclusions The preoperative risk group is an important factor for the occurrence of a positive margin, but only in the final examination and not in the intraoperative one. An intraoperative examination of the neurovascular bundles only is pointless and should be extended to the examination of the apex.

Corresponding author
Tomasz Kupski
Mazovia Hospital Warsaw
Department of Urology
41/15 KEN Street
02-797 Warsaw, Poland
phone: +48 698 643 371
t.kupski@wp.pl

INTRODUCTION

Laparoscopic radical prostatectomy using the da Vinci® Surgical System (RaRP) is now an increasingly used method for the treatment of prostate cancer. The advantages of robot-assisted surgery over laparoscopic surgery such as faster recovery of urine continence as well as the return of sexual activity have been demonstrated [1, 2, 3]. In the long-term (24 months), no significant advantage of robotic surgery in relation to functions was demonstrated [4]. Many publications have shown a superiority of RaRP over LRP (laparoscopic radical prostatectomy) surgery in achieving negative margins [3], however, there are also publications according to which there is no statistically significant difference [5]. The first available meta-analysis in 19,064 patients showed that RaRP has a lower risk of intraoperative complications and a reduced risk of a positive surgical margin compared to laparoscopic surgeries (17.6% vs 23.6%) [6].

It is important that achieving a negative surgical margin (R0) in the histopathological examination after surgery is an independent prognostic factor [7]. A negative margin reduces the risk of biochemical recurrence and therefore the need for adjuvant

treatment. It has been proved that a significant factor in achievement of R0 is the experience of the urologist and the number of operations performed in a given centre [8]. On the other hand, patient's body mass index (BMI) and the duration of surgery [9] are factors increasing the risk of a positive margin.

Factors influencing biochemical recurrence after surgery apart from the positive margin are cancer grading according to International Society of Urological Pathology (ISUP) >7, stage pT3b or pT4 and the presence of nodal metastases [10, 11]. A positive surgical margin (PSM) is a risk factor for cancer recurrence but there is insufficient evidence for the relationship between the extent of R1 and the risk of recurrence [12].

It has been shown in numerous publications that preservation of the neurovascular bundles (nerve-sparing surgery – NS) does not increase the risk of prostate cancer recurrence if there is an adequate preoperative qualification for low-grade cancer patients (ISUP 6 and 7) and no suspicious changes the prostate capsule on multiparametric magnetic resonance imaging (mpMRI) [13, 14, 15].

MATERIAL AND METHODS

The intraoperative histopathological examination of the prostate gland for positive margins was performed between November 2019 and August 2020 on a consecutive series of 65 patients who underwent RaRP with NS. After removal of the prostate gland, the specimen was viewed by the operator who marked with ink the place where neurovascular bundles were prepared and any suspicious areas on the prostate capsule. The area of inked material was not to exceed 4 cm² (the mean was 1.8 cm² on each side of the prostate gland). The whole prostate prepared in this way was transferred to the pathomorphology department. The result of the intraoperative examination was communicated by telephone to the operator, who, in the case of a positive margin, made the decision to radicalise the surgical procedure, taking into account the risk of loss of sexual function or oncological incompetence. The preparation was also subjected to a routine histopathological examination. For both histopathological examinations (intra- and final examination) a 3-grade scale was adopted to assess the size of a positive margin: R0 – no tumour cells in contact with the ink line, Rmicro – single glandular tubules (up to 1 mm) in contact with the ink and R1 – tumour cells in contact with the ink over a length exceeding 1 mm.

In the statistical analysis, patients were divided into 3 biochemical recurrence risk groups according to the European Association of Urology (EAU): low, intermediate and high-risk.

In the first part, intraoperative and postoperative results were analysed independently in the same manner. The data was archived in a worksheet due to the size of a positive margin in each risk group, and the results were then graphically visualised. The level of statistical significance was set at p = 0.05. Basing on publications showing the clinical insignificance of a microscopic positive margin, it was included in both the R1 group and then in the R0 group.

To estimate whether the risk group was indicative of a positive margin in the intraoperative findings, the data was subjected to the univariate logistic regression (for both Rmicro in R1 and Rmicro in R0). The consistency of intraoperative and postoperative results was compared, with consideration given to the limitations of the method.

The impact of taking additional biopsy specimens on the final histopathological result was evaluated.

RESULTS

The analysis involved sixty-five consecutive patients aged between 45 and 76 years. The median age of the patients was 65 years (IQR: 61–69). Prostate-specific antigen (PSA) before surgery: median = 6.6 (IQR: 4.7–9.3), range: 1.6–35.0. The low-risk group included 55.4% (n–36), intermediate 35.4% (n = 23), high 9.2% (n–6).

The analysis of intra-operative results

The results of intraoperative tests were analyzed. Negative surgical margin in the whole intraoperative material was obtained in 72.3%, a microscopic margin in 20%, a positive margin in 7.7% (n = 47, n = 13, n = 5 respectively). After taking into account different risk groups, the results have been shown in Table 1 and Figure 1.

The distribution of risk groups in each of the R groups is similar, not statistically significantly different (p = 0.132). Subsequently, Rmicro was included in both R1 and R0 groups obtaining p = 0.244 and 0.035 respectively. Using p <0.05 as a cut-off point, it can be concluded that the distribution of risk groups is the same irrespective of which group Rmicro is included in.

The obtained results were also subjected to the univariate logistic regression. Rmicro was first included in R1 and then in R0 (Table 2).

With Rmicro included into R1, the risk group is not a predictor of the occurrence of a positive margin in the intra-operative examination. The odds ratio is 1.76 but the confidence interval of this result contains the value 1, i.e. this result is not statistically significant (p = 0.170).

Table 1. *Intraoperative histopatological examination*

Risk group	R0 n = 47	Rmicro n = 13	R1 n = 5	p
Low-risk	29 (6%)	7 (54%)	0 (0%)	
Intermediate-risk	14 (30%)	5 (38%)	4 (80%)	0.132
High-risk	4 (8%)	1 (8 %)	1 (20%)	

n – number

Table 2. *The univariate logistic regression for intraoperative results (Rmicro id R1 and Rmicro in R0)*

Parameter	Rmicro	OR (95% CI)	p
Risk group	In R1	1.76 (0.79–3.94)	0.170
	In R0	4.26 (1.11–16.43)	0.035

OR – odds ratio; CI – confidence interval

Table 3. *Final histopatological examination*

Risk group	R0 n = 38	Rmicro n = 12	R1 n = 15	p
Low-risk	24 (63%)	9 (75%)	3 (20%)	
Intermediate-risk	14 (37%)	2 (17%)	7 (47%)	<0.001
High-risk	0 (0%)	1 (8%)	5 (33%)	

n – number

Table 4. *The univariate logistic regression for final results (Rmicro id R1 and Rmicro in R0)*

Parameter	Rmicro	OR (95% CI)	p
Risk group	In R1	2.68 (1.19–6.04)	0.018
	In R0	6.52 (2.21–19.25)	0.001

OR – odds ratio; CI – confidence interval

With Rmicro included into R0, the confidence interval of this result contains the value 1, i.e. the result is not statistically significant. In this case, the problem is the too small number of patients in the R0 group (n = 5).

Therefore, it can be assumed that the risk group is not an indicator of a positive margin in the intraoperative outcome.

The analysis of postoperative results

The analysis was also performed of the final histopathological result. A negative surgical margin in the whole postoperative material was obtained in 58.5%, microscopic margin in 18.5%, positive margin 23% (n = 38, n = 12, n = 15 respectively). Re-

sults by the risk group are presented in Table 3 and Figure 2.

The summary above shows that the distribution of risk groups by the margin varies, being statistically significant (p <0.001). As in the analysis of intraoperative outcomes, Rmicro was then included in R1 as well as in R0 obtaining p = 0.009 and p <0.001 respectively, confirming that regardless of the R0/R1 criterion the distribution of groups is different i.e. statistically significant.

The data obtained was then subjected to univariate logistic regression. Rmicro was first included in R1 and then in R0 (Table 4).

With Rmicro included in R1, the risk group is a predictor of the occurrence of a positive margin in the postoperative examination. The odds ratio is 2.68, i.e. an increase in risk group by 1, results in a 2.68-fold increase in the likelihood of a positive margin. The confidence interval of this result does not contain the value 1, i.e. this result is statistically significant (which is also confirmed by the value: p = 0.018)

With Rmicro included in R0, risk group is a predictor of the occurrence of a positive margin at postoperative examination. An increase in risk group by 1, results in 6.52-fold increase in the likelihood of a positive margin. Although the confidence inter-
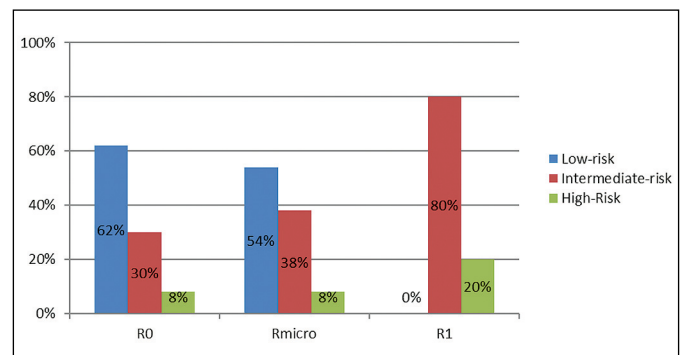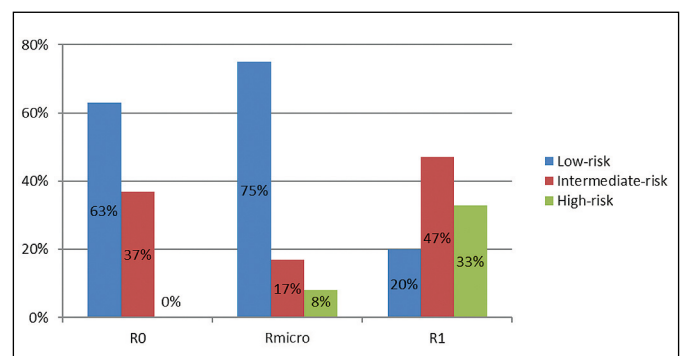

Figure 1. *Intraopertive histopatological examination.*

Figure 2. *Final histopatological examination.*

Table 5. *The comparison of intra- and postoperative results*

		Postoperative evaluation:			Total
		R0	Rmicro	R1	
Intra-operative evaluation	R0	33	6	8	47
	Rmicro	4	5	4	13
	R1	1	1	3	5
Total		38	12	15	65

val of this result is quite wide, it does not include the value 1, i.e. this result is statistically significant. An increase in risk group has been proven to be a predictor of the occurrence of a positive margin in the final histopathological result regardless of the inclusion of Rmicro in R1 or in R0 by 2.68 and 6.52 times respectively.

The comparison of intra- and postoperative results

The consistency of intraoperative and postoperative results was also assessed, the results are presented (Table 5).
The evaluations are consistent in 41 cases, or 63%. In contrast, the Cohen's kappa coefficient of agreement (κ) is: 0.294 (95% CI: 0.069–0.518).
For the interpretation of the coefficient (κ) in the range 0-1 scale proposed by JR Landis and GG Koch is used. The coefficient (κ) between 0.2 and 0.4 indicates moderate agreement [16].

The significance of taking additional surgical excisions

In our material, additional specimens (due to Rmicro or R1 in the intraoperative examination) were taken in only 8 cases making the statistical analysis impossible. Only in one of them was tumour cell infiltration found. In this case, positive surgical margin was also in the final result. In 4 cases, in which no cancer was found in additional biopsy specimens, the final histopathological result was R1/Rmicro.

DISCUSSION

Surgical robot-assisted radical prostatectomy has become one of the main procedures in the treatment of prostate cancer [17]. The advantages of the robotic system over the laparoscopic system are mainly the stable image even at 30 times magnification and the easiness in tissue preparation and a better early postoperative functional outcome. Despite the use of this modern technology, it is not always possible to achieve a negative surgical margin.

As found in our study, the preoperative risk group (estimated by 3 criteria: cT stage, ISUP, PSA) is a significant risk factor for a positive margin in the final histopathological result, but not in the intraoperative result.
However, it is important to note that in the intraoperative examination, only the area of inking was assessed (the areas of dissection of the neurovascular (n-v) bundles or suspicious areas according to the operator), not the whole prostate surface so these results cannot be directly compared. The mean volume of the prostate gland in our study was 50 ml, so its surface area is approximately 66 cm^2. During the intraoperative examination only about 6% of the prostate surface was assessed. In our material, the final result showed a positive margin in 23% (n = 15) and Rmicro in 18.5% (n = 12), which is slightly worse than other literature results. The material showed an incidence of R1 in the top of 45%, in the base of 10% and in the periphery of 45%. By performing the intraoperative examination of the site of the n-v bundle dissection, we can estimate the risk of R1 with an accuracy of <50%. It was found in the analysis that the presence of a positive margin in the area of the n-v bundles does not coexist with the prognostic group, which, in the situation of a clear correlation of a positive postoperative margin with an increase in the risk group, allows us to question the importance of the intraoperative examination of only the area of the bundles.
The intraoperative examination in all patients in the low-risk group seems pointless, since the final outcome in this group is the lowest risk of R1. However, the intraoperative examination of the dissection sites of n-v bundles should be reserved for intermediate and high-risk patients who are particularly concerned about preserving sexual function. In these two groups, the intraoperative examination could be extended to include the evaluation of the top and base of the prostate gland, even at the expense of prolonging the surgical operation. In preliminary studies, it has been shown that prolonging the surgery by the time of waiting for the intraoperative result is safe for the patient [18].
In addition, it has been reported that there is a lower risk of biochemical recurrence if R1 was found near the posterolateral surface of the prostate gland, as compared to the top of the prostate gland [19].
The use of laser confocal microscopy, which offers the possibility of a faster and more extensive intraoperative diagnosis, seems to be encouraging [20].
Taking additional specimens due to a positive result of the intraoperative examination during RaRP often requires resection of the n-v bundles which negatively affects sexual function in a later period. In the analysis, it was shown that deepening the resection

was often not justified because the material obtained did not contain tumour cells and did not affect the final histopathological result. Due to the frequent location of R1 at the top and the potentially higher risk of biochemical recurrence resulting from a positive margin at this location [19], additional peri-urethral specimens are to be considered.

CONCLUSIONS

A risk group is a predictor of a positive margin only in the final outcome after RaRP but not in the intra-operative outcome.

An increase in risk group by 1 has been proven to be a predictor of the occurrence of a positive margin in the final histopathological result by 2.68–6.52 times (depending on the criteria of R1/Rmicro). The intraoperative examination should be reserved only for intermediate and high-risk patients who are particularly concerned about preserving sexual functions. The intraoperative examination of only the sites of neurovascular bundle dissection is pointless; an extension of the examination to the evaluation of the top of the prostate gland is advisable. The re-section of neurovascular bundles in the case of R1 intra-operatively seems to be inadvisable as it does not affect the final histopathological result and worsens sexual function – due to the small amount of material, a further analysis is advisable.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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