Indications for intraoperative frozen section in robot assisted radical prostatectomy: a pilot study

Y. AKIN[1], E. AVCI[2], H. GULMEZ[3], M. AKAND[4], M. AKIF CIFTCIOGLU[5], I. BASSORGUN[5], T. ERDOGRU[2]

[1]Department of Urology, Erzincan University School of Medicine, Erzincan, Turkey
[2]Department of Minimally invasive and Robotic Surgery Centre, Memorial Istanbul Atasehir Hospital, Istanbul, Turkey
[3]Department of Family Medicine, Baskent University School of Medicine, Ankara, Turkey
[4]Department of Urology, Selcuklu University School of Medicine, Konya, Turkey
[5]Department of Pathology, Akdeniz University School of Medicine, Antalya, Turkey

Abstract. – INTRODUCTION: To evaluate indications for intraoperative frozen section (IFS) during robot assisted laparoscopic radical prostatectomy (RALRP) in our series.

PATIENTS AND METHODS: Prospectively documented 80 patients with prostate cancer (PCa) who underwent RALRP were evaluated between June 2010 and July 2012. Patients were divided into 2 groups according to whether systematically IFS was performed or not. Group 1 (n=66) consisted of patients on whom systematic IFS was performed, Group 2 (n=14) consisted of patients on whom IFS was not performed. All recorded data evaluated and statistical analyses were performed for determining indications and predictive factors for IFS during RALRP. All patients were operated by single surgeon and IFS, pathological assessments were performed by experienced uro-pathologist. Statistical significant p value was $p < 0.05$.

RESULTS: Mean follow-up was 15±6 (25-4) months. Pre-operative prostate volume in transrectal ultrasonography (TRUS) was statistically higher in Group 1 than Group 2 ($p = 0.037$). The other parameters were statistically similar in both groups. According to outcomes of our study IFS was a dependent factor for positive surgical margin. Additionally, the cut off value of prostate volume in TRUS for IFS was 55.5 cc for IFS.

CONCLUSIONS: Preoperative measured prostate volume in TRUS may be an indicator of IFS. Therefore, more accurate information may be given to patients with prostate cancer (Pca) before RALRP by using preoperative prostate volume in TRUS.

Key Words:
Frozen section, laparoscopy, pathology, prostate cancer, radical prostatectomy.

Introduction

Prostate cancer (PCa) is the most commonly diagnosed cancer among men in the world[1]. Radical prostatectomy is the gold standard surgical treatment option for PCa[2]. Laparoscopic radical prostatectomy (LRP) was introduced as a minimally invasive treatment option for PCa, before[3]. It was reported that LRP can provide successful oncologic and functional outcomes as well as open procedure[3]. However, LRP is a minimally invasive procedure it has a long learning curve (LC)[4]. After the presentation of robot assisted laparoscopic radical prostatectomy (RALRP), minimally invasive surgeries almost jumped an age for PCa[5]. Thus, long LC was exceeded. In addition, there are some advantages such as superior perioperative, functional, and oncologic outcomes with low complication rate can be obtained in RALRP than LRP.

Early recovery and keeping functions such as urinary continence and erection have been debated more frequently as well as removing tumor minimally invasive by RALRP. While removing the tumor and keeping functions in RALRP, it is intended to minimize the positive surgical margin (PSM) rate. These can be provided by intraoperative frozen section (IFS). It is reported that IFS can be used for oncological safety[6]. IFS dependents upon many reasons such as the experience of surgeon, suspicious intraoperative findings and high-risk constellations. There has not been any subjective factor reported for IFS yet. According to our knowledge, this is the first report which indications for IFS were discussed, in the literature.

In light of the data above we investigated the indications for IFS during RALRP by single surgeon and experienced uro-pathologist.

Patients and Methods

In this prospective study 83 male patients who underwent RALRP were included between June 2010 and July 2012. Signed informed consents were obtained from all patients. The study proto-

Corresponding Author: Yigit Akin, MD; e-mail: yigitakin@yahoo.com

col was approved by the Institutional Review Board. Eighty patients who were followed-up regularly and were without missing data were enrolled. All patients were divided into 2 Groups according to IFS which was performed for analysing the perioperative pathological PSM or not. Group 1 consisted of patients on whom IFS had been performed, and Group 2 consisted of patients on whom IFS had not been performed. There were no criteria for performing IFS. Patients who were performed or not performed IFS were selected by randomization.

Recorded data for statistical analyses included age, body mass index (BMI) in kg/m^2, operation history, PSA (ng/ml) levels, prostate volume in trans-rectal ultrasonography (TRUS), preoperative Gleason scores, rate of positive cores in preoperative prostate biopsy and preoperative and operation outcomes, which included complications in operation, hemoglobin levels, operation time, bleeding volume in operation, pathologic stage, IFS, positive surgical margin (PSM), and the estimated blood loss (EBL) rate were recorded from patients' files. Functional outcomes such as urinary continence and potency were evaluated at baseline, 6 weeks, and then every 3 months for the first year after surgery. Follow-up PSA measurements were obtained at the same intervals. Continence was defined as the use of either no pads or one security pad daily. Potency was defined as erections hard enough for vaginal penetration with or without the use of PDE-5 (phosphodiesterase type 5) inhibitors.

The preoperative measurements of prostate in TRUS and prostate biopsies as 12 to 20 cores were obtained in Urology Outpatient Clinic[7,8].

IFSs were obtained during RALRP by our surgeon (T.E.) from apex, bladder neck and suspicious locations in the neurovascular bundles systematically as Dillenburg et al described[9]. IFSs and prostate materials were evaluated by single experienced pathologist (M.A.C.). Prostate materials were evaluated by using the Modified Gleason scoring system[10]. TNM classification was used for diagnosing and follow-up periods[11].

All patients were diagnosed as organ defined prostatic neoplasm as clinical T1 and T2 tumors in prostate biopsy. Exclusion criteria were clinical T3 or greater and, missing data.

The 4-armed daVinci Robot (Intuitive Surgical, Inc., Sunnyvale, CA, USA) was used for all cases. Transperitoenal RALRP was performed as Feicke et al described[12] and extraperitoneal LALRP was performed as Gettamn et al described[13].

All complications were graded according to the modified Clavien classifications[14]. Clavien grade I and II accounted for minor complications and grade III, IV and V accounted for major complications.

Statsticall Analysis

In statistical analysis, descriptive results were reported for all studied parameters. Non-parametric results were analysed by the Kruskall-Wallis test. The independent samples T test and paired samples *t* test were used for statistical analysis. Linear regression analysis was performed to identify factors predicting outcomes. The Pearson correlation test was used for identifying correlation among parameters. The Receiver Operating Characteristic (ROC) curve was used to identify cut-off points. Statistical significance was considered $p < 0.05$ and all p values were 2-sided. All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) for Windows 16.0 (SPSS Inc., Chicago, IL, USA) and graphics were plotted using the same software.

Results

Mean follow-up was 15.4±6 (4-25) months and mean age was 60.18±7.8 years. Mean BMI was 27.9±3.2 kg/m^2. Mean PSA (Prostate Specific Antigen) was 8.1±6.2 ng/dl and mean Gleason score in prostate biopsy by TRUS was 6.2±0.7. The mean rate of tumor was 21.6±19.1% in biopsy chips. The mean measured volume of prostate was 43.25±16.9 cc in TRUS.

There were 66 (82.5%) patients in Group 1. Thirty-eight (57.7%) patients had no tumor in IFS as well as in pathological examinations of surgical margins. Despite no malign cell were found by IFS in 23 patients, they had PSM in pathological assessments. One of 23 patient had biochemical recurrence and external beam radiotherapy (EB-RT) was performed in follow-up. The patient has not experienced biochemical recurrence again. However surgical limits were forced in 3 patients for gathering tumor negative IFS, the IFSs were with tumor in apex of prostate. Pathology revealed PSM in 2 patients and negative surgical margin in 1 patient in prostate specimens. In follow-up there was no biochemical recurrence for these 3 patients.

Our surgeon (T.E.) did not perform IFS in 14 (17.5%) patients (Group 2). One of 14 had PSM at the far lateral side of prostate. This patient had biochemical recurrence. The patient did not experience further biochemical recurrence after EB-RT was performed.

Table I. Comparison of two groups for pre-operative data.

Parameter	Group 1	Group 2	*p* value
Mean age (year)	59.62 ± 8	62.79 ± 6.6	0.172
Mean BMI (kg/m2)	27.73 ± 3.2	28.73 ± 3	0.291
Mean PSA (ng/ml)	8.07 ± 6.3	8.47 ± 5.4	0.837
Gleason score in prostate biopsy	6.32 ± 0.6	6.07 ± 1.3	0.324
Rate of tumor in prostate biopsy (%)	22.61 ± 19.7	17.14 ± 15.2	0.334
Prostate volume in Trans-rectal ultrasonography (cc)	51.26 ± 16.2	40.86 ± 18.4	0.037*

Abbreviations: BMI: Body mass index, PSA; Prostate specific antigen. *Statistical significant *p* value

A total of 66 patients (Group 1) underwent IFS and nearly 34.8% of them had PSM in IFS. On the other hand, of the patients who did not receive IFS examination (Group 2) 7% had PSM. There was statistical significant difference in PSM between groups ($p = 0.041$)

Prostate volume in TRUS was statistical significant higher in Group 1 than Group 2 ($p = 0.037$) (Table I). There was no statistical difference in operative and post-operative parameters for groups (Table II).

Pelvic lymphadenectomy was performed in 21 (26.25%) patients to investigate metastasis. There was no metastasis in pelvic lymphadenectomy.

Although measured mean prostate volume in TRUS was significant higher in Group 1 than Group 2, there was no statistical difference between groups for mean specimen volume after pathological evaluations. However, the mean specimen volume was bigger in Group 1 than Group 2 without statistical significance.

PSM was positive correlated with mean prostate volume in TRUS and mean PSA in correlation analyses (Table III).

Prostate volume in TRUS and pathologic stage were a dependent factor for PSM in linear regression analyses (Table IV). Thus, we may determine the PSM according to prostate volume in TRUS before operation. In ROC curve, the cut-off value of prostate volume for IFS was determined 55.5cc. The area under the ROC curve was 0.854 ($p < 0.001$) (Figure 1).

Our surgeon (T.E.) began the RALRP series with the transperitoneal technique. After 63 transperitoneal cases he began to perform the extraperitoenal technique by developing his technique. There was no statistical difference between transperitoneal and extraperitoneal cases for outcomes such as complications, erection and continence after surgery in mid-term ($p > 0.05$).

Bilateral nerve sparing (NS) technique was performed in 70 (87.5%) patients. Unilateral NS technique was performed in 8 (10%) patients. NS technique was not performed in 2 (2.5%) patients due to erectile dysfunction before operation. Furthermore, when dependent variables calculated, NS surgical technique was not effective on IFS in statistical analyses ($p = 0.093$). Mean EBL was 215.7±133.3cc. Delta hemoglobin (preoperative hemoglobin – post-operative hemoglobin) was determined as 1.5±0.8. There was no need blood transfusion during operation, 5 patients needed blood transfusion after operation (Clavien 2).

According to pathology specimens, mean Gleason score was 6.6 ± 0.5. Besides this, mean prostate specimen volume was 45.2±15.7 cc, the mean tumor volume was 4.3cc (10-30). Mean

Table II. Comparison parameters of two groups for operative and post-operative data

Parameter	Group 1	Group 2	*p* value
Post-operative Gleason score	6.67 ± 0.5	6.64 ± 0.6	0.879
Specimen volume (cc)	45.11 ± 12.6	40.86 ± 12.2	0.256
Tumor volume (cc %)	4.68 ± 5.5	3.03 ± 2.6	0.279
Estimated blood loss (ml)	216.21 ± 136.2	213.57 ± 123.2	0.947
Delta hemoglobin	1.62 ± 0.7	1.28 ± 0.6	0.124
Operation time (minute)	252.02	237.50	0.329

Table III. Correlation table of parameters.

Parameters		Prostate volume in TRUS (cc)	BMI (kg/m²)	Age (Year)	PSA (nd/dl)	Gleason score in prostate biopsy	Specimen volume (cc)	PSM
Prostate volume in TRUS (cc)	r	1	.076	.214	.205	-.195	.172	.525**
	p value		0.502	0.056	0.074	0.096	0.126	< 0.001*
BMI (kg/m²)	r		1	.069	.135	.146	.111	-.053
	p value			0.545	0.242	0.213	0.325	0.639
Age (year)	r			1	.218	.066	-.062	.189
	p value				0.057	0.574	0.586	0.093
PSA (ng/dl)	r				1	.092	.038	.253*
	p value					0.446	0.744	0.026*
Gleason score in prostate biopsy	r					1	.220	.106
	p value						0.059	0.368
Specimen volume	r						1	.040
	p value							0.722

Abbreviations: BMI: Body Mass index; PSA: Prostate specific antigen; PSM: Positive surgical margin; r: Pearson correlation; TRUS: Trans-rectal ultrasonography; *Statistical significant *p* value.

hospital stay was 3.4 (2-14) days. Mean catheterization was 7.1 (3-21) days.

Postoperative fever was determined in 7 patients (8.75%) and this was accepted as minor complications which was the most common occurred (Clavien 1). It disappeared after medical treatment. Ileus was determined in a patient; gastric decompression and medical treatments were performed, it was not regressed. The patient was referred to the Department of General Surgery. They performed laparotomy and bridectomy (Clavien 3b). After laparotomy, ileus was disappeared. This patient's urethral catheter was taken off on the 13th day of RALRP and patient discharged on the 14th day of surgery. There was no mortality in this series.

In the short-term follow-up (the first 3 months), 21 patients (26.25%) had erections. In mid-term, potency was defined as "erections hard enough for

Table IV. Linear regression analysis, prostate volume in trans-rectal ultrasonography and pathologic stage was dependent factors for positive surgical margin.

Parameter	*t*	*p* value
(Constant)	-2.241	0.029
Age	-.166	0.869
BMI	-.812	0.420
PSA	.597	0.553
Clinic stage	-.354	0.725
Gleason score in prostate biopsy	1.496	0.140
Pathological stage	4.730	<0.001*
Gleason score in prostate specimen	.293	0.770
Tumor volume	-1.057	0.295
Specimen volume	-.357	0.722
Prostate volume in TRUS	4.241	<0.001*
IFS	-1.108	0.272

Statistical significant p value. Abbreviations: BMI: Body mass index, PSA: Prostate specific antigen TRUS: Trans-rectal ultrasonography IFS: Intraoperative frozen section.

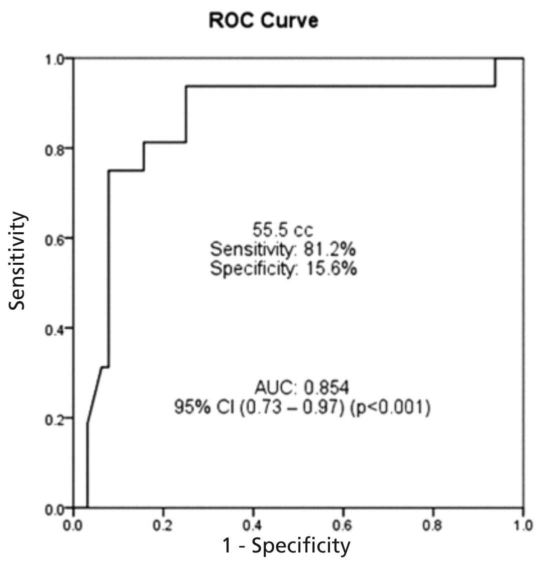

Figure 1. Receiver Operating Characteristic of cut-off value of prostate volume in trans-rectal ultrasonography for perioperative frozen section is shown in the figure. It is 55.5 cc with 81.2% sensitivity and 15.6% specificity ($p < 0.001$). The area under the curve is 0.854.

vaginal penetration with or without the use of PDE-5 inhibitors" in 67 patients (83.75%) (62 from the bilateral NS group and 5 from the unilateral NS group).

All patients were continent before surgery; in the short-term, 63 (78.75%) of them were continent. In the mid-term 78 (97.5%) of them were continent.

8 inguinal hernias were repaired simultaneously with RALRP.

Discussion

IFS was first used by Welch in 1891[15]. Afterwards IFS was used for the first time for intraoperative diagnosis by Wilson and MacCarty in 1905[15]. IFS is usually used for determining the surgical margin, distinction of malign or benign and, in order to obtain information about lesions. As a result, IFS may give us directions for surgical treatment. The method of processing is usually performed with the bread loafing technique for investigating malign cells in the surgical margin. Additionally, margin controlled surgery can be performed using a variety of tissue cutting and mounting methods, including mohs surgery for circumferential peripheral and deep margin assessment[16]. According to the descriptions above, we used IFS to investigate malign cells in surgical margins during RALRP. IFSs were also used for intraoperative consultations to pathologist in this series. PSM was able to be minimalized by IFS. In our series performing PSM due to IFS was statistical significant different between groups. To our best knowledge, objective criteria for IFS during RALRP was not published before in literature. Therefore, our study is unique. All patients were divided into 2 groups according to whether to perform IFS or not during RALRP in a prospective study pilot study. Thus, we investigated our RALRP database for indications of IFS. Although the numbers of participants were limited, this is the first report in literature that objective criteria were put forth for IFS.

Numbers of patients were different in groups there was no statistical difference in demographic data such as age, BMI, PSA. Additionally, there was no statistical difference between groups in mean Gleason scores, and rate of tumor in prostate biopsies. There was no statistical significant difference between groups for perioperative and postoperative data. These may provide us to perform statistical analysis with more accurate comparison. In addition, these results were similar to Lavery et al[17]. They performed IFS to 20% of patients who were 4% of all participants had either malignant or benign prostate tissue removed from their prostatic fossa[17]. Additionally, they reported that a reduction of biochemical recurrence had not been demonstrated in short-term follow-up[17]. They concluded that *in situ* IFSs were an effective way of reducing PSM during RALRP[17]. Additionally, Schlomm et al[18] reported that IFS from the neurovascular bundle (NVB) enabled real-time histologic monitoring of the oncologic safety of an NS procedure. Moreover, they reported systematic IFS significantly increased outcomes of NS surgery and reduced PSMs[18]. Outcomes of our series were similar like report of Schlomm et al[18]. Heinrich et al[19] did not recommend routine IFS during NS radical prostatectomy. However, we did not get IFS from all patients. IFS procedures were performed systematically as Dillenburg et al[9] described. Gillitzer et al[20] did not recommend routine IFS during RALRP. We also agree with them. The decision of IFS may vary on surgeons' decisions. Despite these conflicting data on performing IFS, these did not affect surgical technique such as NS, transpertioneal or extraperitoneal during RALRP (p = 0.093). IFSs were performed in 82.5% of our patients, these were determined by randomization. Our surgeon (T.E.) is an experienced in surgeon on laparoscopic surgery and had a long fellow-ship program. We also included patients in his LC for RALRP. However, we performed systematic IFSs additional IFSs may be related to patients in LC[9]. Wolanski et al[21] reported no additional effects of fellowship training in LRP on RALRP we did not agree with them. Although the numbers of participants were low in groups, outcomes of our series were similar like reports of RALRP series in literature[22,23]. There is no doubt that LC of RALRP is shorter than LRP, there are some contradictions on LC of RALRP in literature[22-24]. Patel et al[22] reported that LRP had a long LC including 100 and/or over 100 cases, when compared with RALRP which includes 12-18 cases. Ploussard et al[23] reported LC was completed with the first 100 cases in RALRP. Atug et al[24] reported that experience could be gained with time led to a decrease in the incidence of PSMs in RALRP. They concluded that the selection bias did not affect their results[24]. Because of clinical and pathologic staging were evenly distributed within the study groups[24]. In our clinical aspects our surgeon completed his LC with 40 cases but we believe that LC of him has been still continuing. We also agree with Atug et al[24]. The selection for IFS was determined by randomization these did not affect outcomes of the study. Although there was statistical significant difference in PSM the demographic, preoperative, postoperative, and functional outcomes were statistical similar between groups.

The measured mean prostate volume in TRUS was significant bigger in Group 1 than Group 2 ($p = 0.037$). This may be predictive objective data for IFS before surgery, according to outcomes of this study. There was no statistical difference between groups for operation time and EBL. These results were similar to Lavery et al[17]. However, they reported the utilities of IFS during RALRP, they did not mention the predictive value of prostate volume for IFS[17]. Gillitzer et al[20] reported a postoperative Gleason score and prostate volume did not correlate with IFS and PSM. Outcomes of this series were not parallel to Gillitzer et al[20]. According to our results, preoperative prostate volume in TRUS may be an indication of IFS (Figure 1). IFSs were performed during RALRP when the prostate volume was determined at least 55.5 cc in TRUS. Furthermore, outcomes of the study revealed that prostate volume was positively correlated with PSM. Prostate volume in TRUS was a dependent factor for PSM. Our results are unique that either measurements of prostate volume in TRUS and RALRP were performed by single surgeon, and IFSs, pathological assessments were performed by single experienced uro-pathologist. All of outcomes may provide us to give better and accurate knowledge to patients before RALRP. However, there was no statistical difference between groups in oncological follow-up in mid-term. We may give more accurate information to patients about the course of surgery, according to their preoperative assessments. When the prostate volume was higher than 55.5 cc in TRUS, surgery time may be extended according to perform IFS.

The complication rate in the groups was similar in statistical analysis ($p > 0.05$). The rate of all complications, short-term and mid-term functional and oncologic results were similar to the literature[25-28]. This may be related to our surgeon having laparoscopic experience, and also the RALRP has a short LC. These were mentioned above. Given the improved lighting and magnification of the robotic console, this enabled better detection of macroscopic deposits of prostate tissue and in particular NVB. These may also provide surgeons with a shortened LC for RALRP.

In this study, we evaluated IFS and its indications during RALRP in the guidance of PSM status. It was not possible to conduct statistical analysis accurately for LC and the effects of LC on IFS in this series. Moreover, NS surgical technique was not statistically significantly effective on IFS or vice versa. Although we performed randomization for performing IFS or not, numbers of participants might affect outcomes. Results of our study may not be translatable to other surgeons, our results may be pathfinder on performing IFS during RALRP. Therefore, surgeons should keep in their mind to perform IFS during RALRP when prostate volume was bigger than 55.5 cc in TRUS. Randomized controlled double-blind studies are needed in this field[29].

Conclusions

RALRP provides successful outcomes with short LC. However IFS may not be performed routinely in NS RALRP. When it is needed to be performed IFS, it should be performed systematically. Preoperative measured prostate volume in TRUS may be an indication for IFS. Thus, more accurate information may be given to patients with PCa about course of RALRP by using preoperative parameters such as prostate volume in TRUS. More comprehensive studies which have long follow-up periods on this issue may provide better indications and predictive parameter for IFS by holding the light of findings in this study.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Akin Y, Koksoy S, Yucel S, Erdogru T, Baykara M. Increased peripheral CD4+CD25high Treg in prostate cancer patients is correlated with PSA. Saudi Med J 2011; 32: 1003-1008.
2) Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ. Cancer statistics 2005. CA Cancer J Clin 2005; 55: 10-30.
3) 3-Guillonneau B, el-Fettouh H, Baumert H, Cathelineau X, Doublet JD, Fromont G, Vallancien G. Laparoscopic radical prostatectomy: oncological evaluation after 1,000 cases a Montsouris Institute. J Urol 2003; 169: 1261-1266.
4) Erdogru T, Yucel S, Frede T, Baykara M, Rassweiler J, Teber D. Laparoscopic radical prostatectomy: transfer validity. Int J Urol 2010; 17: 476-482

5) Novara G, Ficarra V, Mocellin S, Ahlering TE, Carroll PR, Graefen M, Guazzoni G, Menon M, Patel VR, Shariat SF, Tewari AK, Van Poppel H, Zattoni F, Montorsi F, Mottrie A, Rosen RC, Wilson TG. Systematic review and metaanalysis of studies reporting oncologic outcome after robot-assisted radical prostatectomy. Eur Urol 2012; 62: 382-404.

6) Fromont G, Baumert H, Cathelineau X, Rozet F, Validire P, Vallancien G. Intraoperative frozen section analysis during nerve sparing laparoscopic radical prostatectomy: feasibility study. J Urol 2003; 170: 1843-1846.

7) Eskicorapci SY, Guliyev F, Islamoglu E, Ergen A, Ozen H. The effect of prior biopsy scheme on prostate cancer detection for repeat biopsy population: results of the 14-core prostate biopsy technique. Int Urol Nephrol 2007; 39: 189-195.

8) Akin Y, Yuksel K, Bassorgun I, Ciftcioglu MA, Yucel S, Baykara M, Nuhoglu B, Bozkurt A, Erdogru T. The consistency of Gleason scores may effect the operation outcomes for laparoscopic radical prostatectomy: a single surgeon and a single pathologist data. Eur Rev Med Pharmacol Sci 2013; 17: 123-129.

9) Dillenburg W, Poulakis V, Witzsch U, de Vries R, Skriapas K, Altmansberger HM, Becht E. Laparoscopic radical prostatectomy: the value of intraoperative frozen sections. Eur Urol 2005; 48: 614-621.

10) Harden P, Shelley MD, Coles B, Staffurth J, Mason MD. Should the Gleason grading system for prostate cancer be modified to account for highgrade tertiary components? A systematic review and meta-analysis. Lancet Oncol 2007; 8: 411-419.

11) van der Kwast TH, Amin MB, Billis A, Epstein JI, Griffiths D, Humphrey PA, Montironi R, Wheeler TM, Srigley JR, Egevad L, Delahunt B. ISUP Prostate Cancer Group: International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 2: T2 substaging and prostate cancer volume. Mod Pathol 2011; 24: 16-25.

12) Feicke A, Baumgartner M, Talimi S, Schmid DM, Seifert HH, Müntener M, Fatzer M, Sulser T, Strebel RT. Robotic-assisted laparoscopic extended pelvic lymph node dissection for prostate cancer: surgical technique and experience with the first 99 cases. Eur Urol 2009; 55: 876-883.

13) Gettman MT, Hoznek A, Salomon L, Katz R, Borkowski T, Antiphon P, Lobontiu A, Abbou CC. Laparoscopic radical prostatectomy: description of the extraperitoneal approach using the da Vinci robotic system. J Urol 2003; 170: 416-419.

14) Hruza MO, Wei. H, Pini G, Gozen SA, Schulze M, Teber D, Rassweiler JJ. Complications in 2,200 consecutive laparoscopic radical prostatectomies: standardised evaluation and analysis of learning curves. Eur Urol 2010; 58: 733-741.

15) Zarbo RJ, Hoffman GG, Howanitz PJ. Interinstitutional comparison of frozen-section consultation. A College of American Pathologists Q-Probe study of 79,647 consultations in 297 North American institutions. Arch Pathol Lab Med 1991; 115: 1187-1194.

16) Gal AA, Cagle PT. The 100-year anniversary of the description of the frozen section procedure. JAMA 2005; 294: 3135-3157.

17) Lavery HJ, Xiao GQ, Nabizada-Pace F, Mikulasovich M, Unger P, Samadi DB. 'Mohs surgery of the prostate': the utility of in situ frozen section analysis during robotic prostatectomy. BJU Int 2011; 107: 975-979.

18) Schlomm T, Tennstedt P, Huxhold C, Steuber T, Salomon G, Michl U, Heinzer H, Hansen J, Budäus L, Steurer S, Wittmer C, Minner S, Haese A, Sauter G, Graefen M, Huland H. Neurovascular structure-adjacent frozen-section examination (NeuroSAFE) increases nerve-sparing frequency and reduces positive surgical margins in open and robot-assisted laparoscopic radical prostatectomy: experience after 11,069 consecutive patients. Eur Urol 2012; 62: 333-340.

19) Heinrich E, Schön G, Schiefelbein F, Michael MS, Trojan L. Clinical impact of intraoperative frozen sections during nerve-sparing radical prostatectomy. World J Urol 2010; 28: 709-713.

20) Gillitzer R, Thüroff C, Fandel T, Thomas C, Thüroff JW, Brenner W, Wiesner C, Jones J, Hansen T, Hampel C. Intraoperative peripheral frozen sections do not significantly affect prognosis after nerve-sparing radical prostatectomy for prostate cancer. BJU Int 2011; 107: 755-759.

21) Wolanski P, Chabert C, Jones L, Mullavey T, Walsh S, Gianduzzo T. Preliminary results of robot-assisted laparoscopic radical prostatectomy (RALP) after fellowship training and experience in laparoscopic radical prostatectomy (LRP). BJU Int 2012; 110 (Suppl 4): 64-70.

22) Patel VR, Tully AS, Holmes R, Lindsay J. Robotic radical prostatectomy in the community setting–the learning curve and beyond: initial 200 cases. J Urol 2005; 174: 269-272.

23) Ploussard G, de la Taille A, Moulin M, Vordos D, Hoznek A, Abbou CC, Salomon L. Comparisons of the perioperative, functional, and oncologic outcomes after Robot-Assisted Versus Pure Extraperitoneal Laparoscopic Radical Prostatectomy. Eur Urol 2012; Dec 1. pii: S0302-2838(12)01424-8. doi: 10.1016/j.eururo.2012.11.049.

24) Atug F, Castle EP, Srivastav SK, Burgess SV, Thomas R, Davis R. Positive surgical margins in robotic-assisted radical prostatectomy: impact of learning curve on oncologic outcomes. Eur Urol 2006; 49: 866-871.

25) Dogra PN, Javali TD, Singh P, Kumar R, Seth A, Gupta NP, Nayyar R, Saxena V, Nayak B. Perioperative outcome of initial 190 cases of robot-assisted laparoscopic radical prostatectomy - A single-center experience. Indian J Urol 2012; 28: 159-163.

26) Ahlering TE, Eichel L, Edwards RA Lee DI, Skarecky DW. Robotic radical prostatectomy: a technique to reduce pT2 positive margins. Urology 2004; 64: 1224-1228.

27) 27-Shah A, Okotie OT, Zhao L, Pins MR, Bhalani V, Dalton DP. Pathologic outcomes during the learning curve for robotic-assisted laparoscopic radical prostatectomy. Int Braz J Urol 2008; 34: 159-162.

28) Yuh BE, Ruel NH, Mejia R, Novara G, Wilson TG. Standardized comparison of robot-assisted limited and extended pelvic lymphadenectomy for prostate cancer. BJU Int 2013; In press

29) Jo JK, Autorino R, Chung JH, Kim KS, Lee JW, Baek EJ, Lee SW. Randomized controlled trials in endourology: a quality assessment. J Endourol 2013; 27: 1055-1060.