Intraoperative frozen section monitoring during nerve-sparing radical prostatectomy: evaluation of partial secondary resection of neurovascular bundles and its effect on oncologic and functional outcome

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Abstract

Purpose Intraoperative frozen sections (IFS) of the prostate have demonstrated to be effective in reducing positive surgical margins (PSM) and biochemical recurrence (BCR). The aim of this study was to assess partial secondary resection of neurovascular bundles (NVB) and report for the first time corresponding functional results.

Methods A total of 500 consecutive patients were included in this prospective series. All patients underwent open nerve-sparing radical prostatectomy. Intraoperatively, both posterolateral aspects of the prostate were sent for IFS. In case of PSM, additional tissue was partly resected from the prostatic bed along the NVB. BCR was the oncologic endpoint (PSA $\geq$ 0.2 ng/ml). The impact of IFS on PSM and BCR-free survival, and the effect of secondary partial resection of NVB on continence and erectile function (EF) recovery were analyzed by Kaplan–Meier analyses.

Results Twenty-nine patients were excluded because of neoadjuvant treatment/lymph node positive disease. PSM were detected in 137/471 patients (29.1 %). After secondary resection. 127/137 patients (92.7 %) converted to definitive negative surgical margins (NSM). Out of 137 patients, ten (7.3 %) showed persistent PSM. False-negative rate was 3.3 % (11/334). Out of 471 patients, two (0.4 %) showed PSM outside the IFS area. Overall, final PSM rate was 4.9 % (23/471). Five-year BCR-free survival did not differ significantly in patients with primarily and converted NSM. Continence and EF recovery after 12 months were 95.8 versus 94.3 %, and 65.7 versus 56.1 %, respectively (all $p > 0.05$).

Conclusion IFS are highly effective in reducing PSM and avoiding compromised oncologic outcome. Partial secondary resection of the NVB ensures ns status and consequently preserves continence and EF.

Keywords Biochemical recurrence · Continence · Erectile function · Frozen section · Radical prostatectomy · Surgical margins

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Introduction

Radical prostatectomy (RP) is standard surgical treatment in patients with localized prostate cancer (PCa) and life expectancy >10 years, and should preferably be performed using a nerve-sparing (ns) technique, whenever possible [1]. Positive surgical margins (PSM) in RP occur in 11–43 %, leading to increased risk of biochemical recurrence (BCR), secondary cancer treatment and worse prognosis [2, 3]. In nsRP, PSM mainly occur at the posterolateral aspects which are adjacent to the neurovascular bundles (NVB) [2]. Importantly, PSM at this site confer the greatest probability of relapse [4]. PSM are acknowledged an adverse outcome and should be avoided [2, 5]. In this regard, several studies have investigated intraoperative frozen sections (IFS) to reduce PSM [6–8]. However, different IFS techniques were used, and moreover, the decision for IFS was mainly made by preoperative clinical parameters/nomograms or subjective judgement during surgery. Unfortunately, accurate preoperative and intraoperative assessment of NVB involvement with tumor is difficult. Moreover, preoperative risk assessment of tumor extent by rectal examination, sonography or cross-sectional imaging is not accurate enough to select patients suitable for ns [9–13].

Regarding functional outcomes after RP, it is known that nerve-sparing status is a major predictor, especially for erectile function (EF) recovery. According to the literature, EF recovery rates in nsRP vary between 54 and 90 %. However, this rate decreases in non-nerve-sparing procedures. The same issue might also apply for continence rates [14, 15]. By means of IFS monitoring during nsRP, the nerve-sparing status could be ensured and consequently functional outcomes (continence/EF recovery) can be preserved. However, there is lack of data regarding functional outcomes associated with the IFS procedure in the literature.

We report our results of a prospective study analyzing IFS in a consecutive series of patients undergoing nsRP, aiming to detect PSM and subsequently reduce PSM and BCR rates. Moreover, we assessed the effect of secondary partial NVB resection and provide for the first time functional results on continence and EF recovery associated with this technique.

Materials and methods

Study population and design

The population of this prospective series consisted of consecutive, non-screened and non-selected patients with histopathologically confirmed PCa. All patients underwent open retropubic nsRP by one high-volume surgeon (JEG, >2500 RP). An attempted ns approach and pelvic lymph node dissection were routinely performed in all patients, regardless of preoperative risk classification and EF. Patients with neoadjuvant treatment were excluded from the analysis. The principles of the Helsinki Declaration were followed. All patients were informed about the specific surgical approach and signed written informed consent.

All patient information was prospectively entered into our institutional review board-approved PCa database. Follow-up was done by PSA measurements, assessment of number of pads, and International Index of Erectile Function (IIEF-5) score. BCR was defined as PSA $\geq$0.2 ng/ml and rising after RP. Continence recovery was defined using a no pad or one safety pad (dry at the end of the day) definition. Like in other studies, EF recovery was defined as IIEF-5 score $\geq$17 [14–16]. In patients with negative surgical margins (NSM) in final examination, adjuvant radiation or hormone therapy was not initiated without evidence of BCR. Patients with definitive PSM were treated according to international guidelines and offered adjuvant versus salvage radiation [17]. However, patients with lymph node positive disease (pN+) were excluded from the study analyses.

Frozen section technique and pathological examination

Upon prostatectomy, the prostatic lobes were ink-marked (right: black, left: yellow). The complete posterolateral aspects were dissected from apex to base (large-area section). The resulting inner surgical margins were ink-marked with red color, and the basal directions marked with a 3-0 Vicryl® suture to facilitate orientation. These two ink-marked posterolateral aspects were sent for IFS.

In the pathology department, each specimen was sectioned into 4 mm slices and allocated to basal, central and apical clusters. This resulted in three frozen section blocks per specimen. Two cryosections were cut from each block, hematoxylin and eosine stained, and viewed by a pathologist. In total, the frozen section analyses were performed by 5 board-certified pathologists experienced with this technique. PSM were defined when malignant glands touched the inked surgical margin (black/yellow).

The IFS procedure required an average of 30 min. During this time, surgery continued with lymph node dissection, hemostasis, bladder neck reconstruction, catheter insertion, and anastomotic suture placement between bladder neck and urethra. Thus, the IFS did not prolong total operating time.

In case of PSM, additional tissue was resected from the prostatic bed along the NVB corresponding to the PSM. In order to resect the additional tissue from the exact location of the PSM, the secondarily resected tissue was taken from the basal and/or central and/or apical part of the prostatic bed along the NVB, according to the IFS result obtained intraoperatively by the pathologist. However, secondary resection was routinely performed partially without resecting the NVB completely, whenever possible. Partial resection means the resection of a tangential lamella at the site corresponding to the PSM. This lamella is approximately 1–2 cm in length and 3–5 mm in thickness, which is sufficient for conversion from positive to negative margins in almost all cases. The secondary resected neurovascular structures were submitted separately for permanent section analysis after ink-marking of new surgical margins to facilitate orientation. According to the literature, only a small percentage of patients will show a microscopic detectable

Table 1 Characteristics of patients with primarily and converted negative surgical margins

	Total	Primarily NSM	Converted NSM	*p* value
Number of patients	458	321 (70.1 %)	127 (27.7 %)	
Patient median age with range (years)	66 (39; 80)	66 (46; 78)	67 (39; 80)	0.55
Preoperative PSA (ng/ml)				0.23
≤4	71 (15.5 %)	53 (16.5 %)	18 (14.2 %)	
4–10	312 (68.1 %)	220 (68.5 %)	84 (66.1 %)	
≥10	75 (16.4 %)	48 (15.0 %)	25 (19.7 %)	
Pathological tumor stage				$<10^{-3}$
pT2a/b/c	373 (81.4 %)	287 (89.4 %)	84 (66.1 %)	
pT3a	53 (11.6 %)	20 (6.2 %)	29 (22.8 %)	
pT3b	31 (6.8 %)	14 (4.4 %)	14 (11.0 %)	
pT4	1 (0.2 %)		0	
Pathological Gleason score				$<10^{-3}$
≤6	180 (39.3 %)	145 (45.2 %)	34 (26.8 %)	
7a	197 (43.0 %)	129 (40.2 %)	65 (51.2 %)	
7b	61 (13.3 %)	36 (11.2 %)	23 (18.1 %)	
≥8	20 (4.4 %)	11 (3.4 %)	5 (3.9 %)	

PSA prostate-specific antigen; *NSM* negative surgical margins

tumor remnant in secondarily resected tissue (0–33 %) [6]. Therefore, we did not perform additional IFS of the secondarily resected specimen. The definitive surgical margin status was determined on the RP specimen, including the two dissected parts for IFS, and possibly secondary resected neurovascular tissue.

Statistical analysis

Primary endpoint was BCR-free survival. Secondary endpoints were maintenance of continence and EF. Only potent patients (preoperative IIEF-5 ≥17) were included in the analysis regarding EF recovery. For descriptive statistics, quantitative data are given as mean or median and range, whereas qualitative data are given as relative and absolute frequencies. Comparison between primarily and converted NSM groups with respect to median age is due to the Mann–Whitney *U* test. For between-groups comparisons of frequencies, χ^2 tests were used. Estimation of diagnostic measure is given with respective 95 % confidence intervals. Survival analyses are due to the Kaplan–Meier method, the log-rank test and Cox regression. Any *p* values are two-sided with significance level of 0.05. Analyses were performed with IBM-SPSS statistics version 22 and NCSS version 9 (NCSS, Kaysville, Utah, USA).

Results

From April 2008 to May 2012, five hundred consecutive patients were included. All patients underwent systematic IFS and attempted ns procedure. Seven and 22 patients were excluded from final analysis because of neoadjuvant treatment and lymph node positive disease, respectively.

Impact of IFS on surgical margin status and BCR-free survival

Intraoperative PSM were detected in 137/471 patients (29.1 %), resulting in secondary neurovascular tissue resection. T stage and Gleason score in final pathology of those patients were pT2: 86/137 = 62.8 %, pT3/pT4: 51/137 = 37.2 %; Gleason score <7b: 103/137 = 75.2 %, Gleason score ≥7b: 34/137 = 24.8 %. After secondary resection. 127/137 patients (92.7 %) converted to definitive NSM, without evidence of PSM elsewhere around the prostate. Out of 137 patients, ten (7.3 %) had persistent PSM (in final pathology: pT2: 2/10 = 20 %, pT3/pT4: 8/10 = 80 %; Gleason score <7b: 4/10 = 40 %, Gleason score ≥7b: 6/10 = 60 %). The IFS results of PSM (137/471 patients) were confirmed in all cases by final pathologic examination. False-negative rate was 3.3 % (11/334). Additionally, 2/471 patients (0.4 %) showed PSM outside the IFS area (1× seminal vesicle, 1× ventral aspect of prostate). Thus, the overall PSM rate in final pathology was 4.9 % (23/471 patients).

In order to provide clear data regarding IFS, and the effect of partial secondary NVB resection on oncologic and functional results, the two latter patient groups with PSM ($n = 13$) were excluded from the following analyses. This resulted in an evaluable total study cohort of $n = 458$ patients. However, regarding oncological outcomes, $n = 94$ patients were lost to follow-up and therefore are not included in the analysis of BCR-free survival.

Table 2 Cox regression univariate analysis of evaluable total study cohort ($n = 364$) with respect to biochemical recurrence

Parameter	HR	95 % CI	*p* value
SM (pNSM vs. cNSM)	0.83	0.23 to 3.08	0.78
Preoperative PSA (ng/ml)			
4–10 versus ≤4	1.85	0.23 to 14.75	0.56
≥10 versus ≤4	2.00	0.67 to 6.01	0.22
Pathological tumor stage			
pT3a versus pT2	0.99	0.12 to 8.07	0.99
pT3b versus pT2	2.65	1.43 to 4.89	0.002
pT4 versus pT2	3.64	1.80 to 7.36	$<10^{-3}$
Pathological Gleason score			
≤6 versus ≥8	$<10^{-3}$	$<10^{-3}$ to $>10^{3}$	0.95
7a versus ≥8	0.27	0.05 to 1.32	0.10
7b versus ≥8	0.60	0.11 to 3.28	0.56

SM surgical margins, *pNSM* primarily negative surgical margins, *cNSM* converted negative surgical margins, *PSA* prostate-specific antigen, *HR* hazard ratio, *CI* confidence interval

Characteristics of patients with primarily and converted NSM are shown in Table 1. Cox regression univariate analysis of this cohort with respect to BCR is depicted in Table 2.

Five-year BCR-free survival for pT2 PCa was 96.9 and 100 % in patients with primarily and converted NSM, respectively ($p = 0.146$). For pT3 disease, this was 91.2 and 92.1 %, respectively ($p = 0.811$). After a mean PSA follow-up of 26.2 months (median 24.0 months; range 3–60), BCR rates were 3.3, 2.9 and 20 % in patients with primarily NSM, converted NSM and persistent PSM after secondary resection, respectively. BCR rates between the former two groups did not differ significantly ($p = 0.78$). Due to the low patient number in the latter group ($n = 10$), statistical comparison with the former two groups was not feasible. Figure 1 shows Kaplan–Meier analyses of BCR-free survival in patients with primarily and converted NSM.

Impact of IFS and secondary partial NVB resection on ns status and functional results

All patients with PSM in IFS (137/471 = 29.1 %) underwent partial secondary resection of the affected NVB. Therefore, total ns frequency was not reduced by secondary resection; however, these patients showed a partial ns status at the end of surgery. Out of 137 cases, 22 (16.1 %) in this group did actually display a microscopic detectable tumor remnant in secondary resected tissue during final pathologic examination.

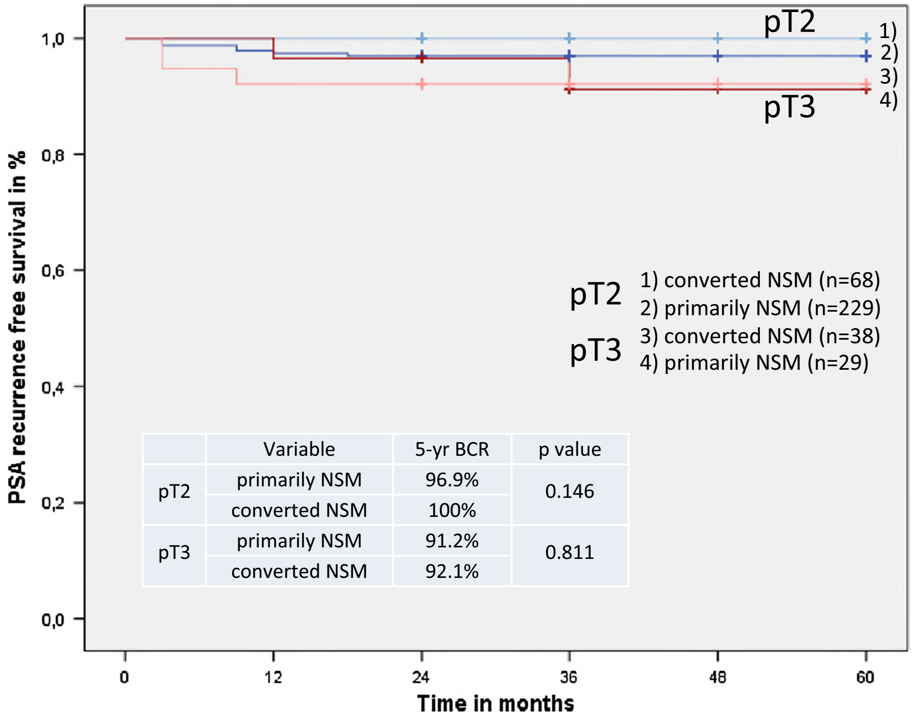
All patients from the study cohort were continent before surgery. Regarding preoperative EF, 40.9 and 39.6 % of patients with primarily and converted NSM were potent, respectively (IIEF-5 ≥ 17). Only those patients were included in the analysis regarding EF recovery. Patients using phosphodiesterase-type-5 inhibitors were excluded. Continence and spontaneous EF recovery rates in these cases with primarily and converted NSM were 95.8 versus 94.3 %, and 65.7 versus 56.1 %, at 12 months, respectively (all $p > 0.05$). Associated Kaplan–Meier analyses are shown in Figs. 2 and 3. All patients suffering from urinary incontinence after surgery showed stress urinary incontinence problems. Urge problems or neurological comorbidities were not present.

Discussion

Complete cancer resection, urinary continence and EF recovery are the most important outcomes after RP [18]. We demonstrated that IFS are effective in reducing PSM and BCR, while partial secondary resection ensures ns status and consequently preserves continence and EF. Schlomm et al. [6] showed that PSM were less frequent by applying IFS (overall 15 vs. 22 %). Twenty-five percent of patients had PSM in IFS and underwent secondary complete NVB resection. This resulted in conversion to definitive NSM in 86 %. Regarding BCR-free survival, there was no difference in patients with primarily and converted NSM. Von Bodman et al. [19] reported an intraoperative PSM rate of 22 %. After secondary resection. 92.3 % of patients converted to NSM. However, the authors did not report oncologic outcomes.

In our study, PSM were detected by IFS in 29.1 % of patients in a cohort with mixed risk features. After secondary resection. 92.7 % converted to definitive NSM. Without the IFS approach, those patients would have had persisting PSM in final pathology, which could have led to additional treatment [5]. The final overall PSM rate was 4.9 %, independent of known adverse pathologic factors (e.g., Gleason score, Biopsy cores, PSA). This final PSM rate is low compared to the literature, showing that IFS is a good tool to achieve optimal cancer control. Noteworthy, this is a series of a high-volume surgeon which might influence the low final PSM rate, as surgical experience is a main determining factor of treatment success [2, 20, 21].

In regard to our ns approach, we do not rely on preoperative clinical data/nomograms or intraoperative subjective findings [1]. We rather perform IFS in all patients undergoing attempted nsRP and decide individually according to IFS. Performing an attempted ns technique in all patients irrespective of clinical stage and Gleason score might be the reason for the high number of PSM during IFS in our study. However, the major advantage of IFS is the availability of a real-time result during surgery which then directly allows further decision making

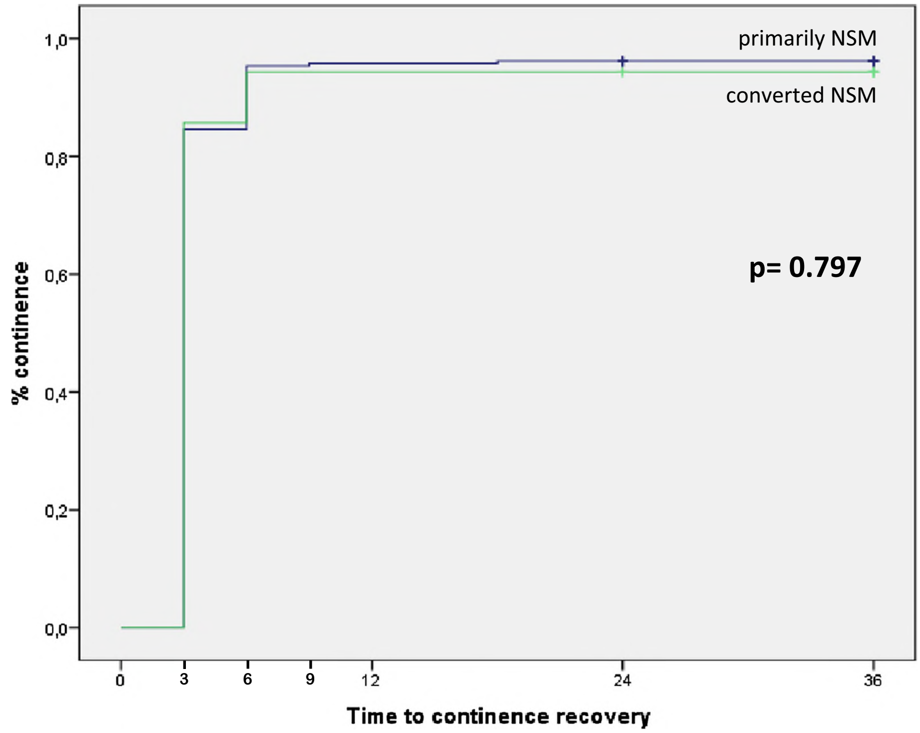


pT2	BCR primarily NSM	0	6	7	7	7	7
	BCR converted NSM	0	0	0	0	0	0
	At risk primarily NSM	229	223	221	147	90	69
	At risk converted NSM	68	67	67	44	18	8
pT3	BCR primarily NSM	0	1	1	2	2	2
	BCR converted NSM	0	3	3	3	3	3
	At risk primarily NSM	29	28	27	17	4	3
	At risk converted NSM	38	35	34	17	9	3

Fig. 1 Kaplan–Meier curve of biochemical recurrence-free survival in patients with primarily and converted negative surgical margins, subdivided in pT2 and pT3 subgroups. Inset table presents 5-year biochemical recurrence-free survival (5-yr BCR) and *p* values of the log-rank test. *PSA* prostate-specific antigen, *NSM* negative surgical margins

regarding secondary resection of affected areas. This is reflected by the low number of PSM in final pathologic examination (overall 4.9 %). In particular, the IFS technique is most valuable in patients with high-risk features in preoperative risk assessment (cT3/cT4, Gleason score ≥8, PSA ≥20), as otherwise these cases would have undergone a strict wide-margin resection without any attempt to spare the NVB. In our study, the NVB could be partly preserved successfully by IFS in 37.2 % of patients even with pT3 PCa. Noteworthy, 62.8 % of patients with PSM in IFS had still organ-confined disease in final pathologic examination, which is attributed to an aggressive ns approach. However, by means of IFS, the intraoperative status can safely be converted to clear margins in final examination. As an important consequence, BCR-free survival in patients with primarily and converted NSM was not statistically different, which underlines the value and oncologic safety.

The major difference of our approach, when compared to the formerly mentioned study groups, is that we performed only a partial secondary NVB resection in case of PSM in IFS, whenever this seemed to be justified instead of complete NVB resection. Consequently, ns frequency itself is not reduced, with the limitation that only a partial ns status remains. In this context, the question may arise whether partial secondary resection is sufficient to achieve clear final margin status and low BCR. By means of partial secondary resection. 92.7 % of our patients were converted to definitive NSM. Furthermore, BCR-free survival was not statistically different in patients with primarily and converted NSM. This demonstrates that partial secondary resection of NVB is sufficient and does not compromise midterm oncologic outcome. Another important factor arguing for performing only a partial secondary resection is the low rate of persisting tumor detected in secondary resected specimens by means of pathology. In the literature,



		3 mon	6 mon	9 mon	1 year	2 years	3 years
primarily NSM	C recovery	84.6%	95.4%	95.8%	95.8%	96.1%	96.1%
	No at risk	258	39	11	11	9	6
converted NSM	C recovery	85.7%	94.3%	94.3%	94.3%	94.3%	94.3%
	No at risk	104	14	14	14	5	3

Fig. 2 Kaplan–Meier curve of continence recovery in patients with primarily and converted negative surgical margins. *NSM* negative surgical margins, *C* continence

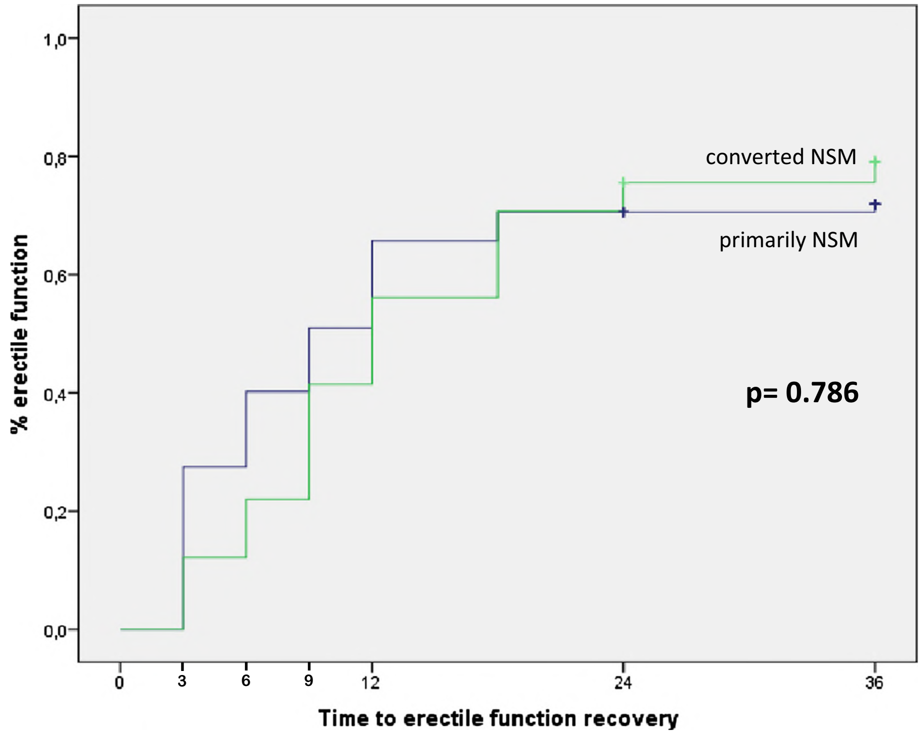
this ranges from 0 to 33 % [6]. Reasons for detecting cancer cells in this small percentage only include the following: when focal extension of tumor cells is present, it may not be identified because of sampling variation, or small tumor areas can become undetectable due to cauterization artefacts [6, 22]. In our study, tumor was confirmed in only 16.1 % of patients in the secondary resected specimen. Therefore, it seems neither necessary nor justified to resect the complete NVB. Moreover, in terms of continence and EF recovery, it is crucial to preserve as many neurovascular structures as possible [14, 23].

In addition to oncologic outcomes, functional results in terms of continence and EF recovery after RP are important issues, especially regarding patient's quality of life. Our study represents the first report of functional results in correlation with IFS of the whole posterolateral prostate surface.

Continence recovery rates in patients with primarily and converted NSM did not differ significantly. Our continence rates are similar compared to Tasci et al. The corresponding continence rates in patients undergoing nsRP were 88 % after 26 months in this study [24]. These data also underline our approach to preserve as much functional tissue as possible to improve functional outcome.

Interestingly, spontaneous EF recovery rates in patients with primarily and converted NSM did also not differ significantly. The similar EF recovery rates in these two groups are presumably attributed to the fact that a partial ns status is still ensured after partial secondary NVB resection. The overall EF recovery rate after RP in a recent meta-analysis was 58 % [16]. This is similar to our results in a mixed population exhibiting also high-risk factors that are usually regarded a contraindication for ns. In a recent review, EF recovery rates after 12 months were 54–90 %, regardless of surgical approach (open, laparoscopic, robot-assisted) [14]. However, assessment of EF was not homogenous and objective in the included studies. In contrast, we used the validated IIEF-5 questionnaire to assess EF recovery and report spontaneous recovery rates, without any medical help.

The IFS technique offers two major benefits: First, it provides an oncologically safe resection of PCa which is reflected by the low final PSM and BCR rate in our study. Second, it allows the preservation of the NVB, thus ensuring nerve-sparing status and consequently preserving EF in a lot of cases, including high-risk PCa, as otherwise these cases would have undergone a wide-margin resection without sparing the NVB. As described above, it should be



		3 mon	6 mon	9 mon	1 year	2 years	3 years
primarily NSM	EF recovery	27.5%	40.2%	51.0%	65.7%	70.6%	71.9%
	No at risk	101	73	60	49	29	22
converted NSM	EF recovery	12.2%	22.0%	41.5%	56.1%	75.6%	79.1%
	No at risk	40	35	31	23	11	6

Fig. 3 Kaplan–Meier curve of spontaneous erectile function recovery in patients with primarily and converted negative surgical margins. *NSM* negative surgical margins, *EF* erectile function

emphasized that, in contrast to results in the literature, we used only objective parameters to assess EF (IIEF-5) and do report only spontaneous EF recovery rates.

In summary, functional results of our series underline the value of IFS, and our concept of partial secondary NVB resection in case of PSM detected in IFS.

There are some limitations which should be considered: The IFS technique requires a pathologist nearby which is not given in all areas. Moreover, we report midterm results. This is a major limitation of our study as oncologic outcomes in terms of BCR, progression, metastases and survival require additional long-term assessment. In this regard, we will continue the follow-up of our patients and report on 5- and 10-year follow-ups in the future. Furthermore, pad usage as definition of continence is not validated. However, pad testing provides an objective form of incontinence assessment [23, 25, 26]. The lack of a control group is another limitation. However, IFS of the prostate has already been investigated by a large controlled study [6]. The main aim of our study and the real novelty is the concept of partial secondary resection, and of capital importance, the analysis and presentation of functional results associated with this technique. In future attempts to further investigate IFS during nsRP, a preferably multicenter validation may be necessary to evaluate its definitive added value.

Conclusion

IFS are highly effective in reducing PSM in nsRP independent of known adverse pathologic factors. Secondary partial NVB resection in case of PSM is safe in terms of BCR-free survival. IFS avoid compromised oncologic outcome, while partial secondary resection ensures ns status and consequently preserves continence and EF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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