Prostate Cancer

Frozen Section for the Management of Intraoperatively Detected Palpable Tumor Lesions During Nerve-Sparing Scheduled Radical Prostatectomy


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Abstract

Objectives: The intraoperative finding of palpable tumor lesions has been described as a contraindication for nerve-sparing (NS) radical prostatectomy (RP). However, its evaluation is subjective. Especially in patients with a strong demand to regain postoperative erectile function, a surgeon might be reluctant to sacrifice neurovascular bundles (NVBs) based on this information. We investigated the use of frozen section (FS) analysis to monitor the safety and efficiency of NS during RP in patients with intraoperatively identified subcapsular tumor lesions.

Methods: In 83 of 608 patients, who underwent NS-RP, intraoperative FS was performed because of a lesion palpable close to the capsule. A wedge of 4 cm in diameter including the lesion was cut off and stained differently for capsule and intraprostatic margin. In case of presence of carcinoma adherent to the capsule, the NVB was resected; otherwise, the NVB remained in situ.

Results: Patients with palpable tumor lesions had pT3 tumors in 36% and 61% had Gleason 4 pattern, compared to 18% and 42% for the control group. Carcinoma was found in 93% of the FS specimens. In 42% of the FS samples, tumor had contact with the capsule and 14% of secondary resected NVB specimens demonstrated a carcinoma invasion. In 52% NVBs could be preserved despite an ipsilateral nodule without negatively affecting the margin status. However, the false-negative rate of the FSs was 6%. Conversely, FSs set the intraoperative decision to remove the NVB in 42% of FS patients, resulting in an additional 36% of negative margins.

Conclusions: In patients with intraoperatively detected tumor lesions during a NS planned RP, FS objectively supports the decision of secondary NVB resection as well as preservation.

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1. Introduction

Nerve-sparing radical prostatectomy (NS-RP), as introduced by Walsh et al. [1], marks the state-of-the-art therapy especially for younger and potent patients with localized prostate cancer [2].

With reported incontinence rates < 10% [3,4] and potency rates up to 96% [5–7], the specific major comorbidities of this procedure have become a predictable risk. To ensure the oncologic safety of the procedure, several models have been developed to identify patients with pathologically organ-confined carcinoma, who are therefore eligible for a NS procedure [8–10]. Most of these models are based on clinical stage, prostate-specific antigen (PSA) levels, and various analyses of transrectal biopsies.

Nevertheless, some authors consider intraoperative findings, such as ipsilateral palpable tumor nodules or adhesions, as a contraindication for ipsilateral nerve preservation [11,12]. Due to the fact that these findings are of a particular subjective nature and also can be the results of benign processes, a surgeon might be reluctant to sacrifice a preserved neurovascular bundle (NVB) based on these results. Evidently NS is an important issue in postoperative quality of life, inasmuch as some patients might even be willing to risk a trade off for their sexual function [13,14]. On the other hand, with respect to an oncologically safe procedure, every surgeon attempts to avoid positive surgical margins, which are reported to increase the risk of disease recurrence [15].

Although preoperative risk assessment has proven to be useful to plan NS in RP, a palpable tumor lesion detected during surgery might demand reconsideration. An objective instrument to determine the further procedure is therefore obviously needed.

As a tool to increase the rate of patients undergoing bilateral NS surgery while maintaining tumor-free surgical margins, Cangiano et al. [16] and later Goharderakhshan et al. [17] described the utility of intraoperative frozen section (FS) to monitor the safety of NS-RP. For the specific finding of a palpable tumor lesion detected during NS-RP we here report a single surgeon’s experience with intraoperative FS.

2. Methods

From May 2002 to May 2004, 608 NS-RPs were performed by a single surgeon (H.H.) applying the previously described technique [18]. Based on a validated computerized algorithm including information from transrectal ultrasonography, PSA values, number of positive biopsies, in general, and biopsies with single Gleason grade 4/5 separately for each prostatic lobe were used for the decision to perform a unilateral or bilateral NS-RP [8].

Intraoperatively, in patients scheduled for a NS procedure, an inspection of the complete specimen for a palpable tumor anywhere close to the surface was performed by the surgeon directly after the prostate was removed. In case of a positive finding, a tangential disc of about 3–4 cm in diameter, including the suspicious area, was cut off and stained with different ink colors for capsule and intraprostatic margin (Figs. 1 and 2).

This specimen was immediately sent to our Department of Pathology, where three to four incisions perpendicular to the color-marked surfaces were performed. Before rapid hematoxylin and eosin staining, these three or four “blocks” were completely frozen and finally progressed by 3–5-mm step section to 5–10 sections per FS specimen.

Simultaneously, the procedure continued until the suture placement for the vesicourethral anastomosis was completed.

In case of a focal or wide contact of tumor with the inked capsule, corresponding soft tissue as well as the ipsilateral NVB were resected and collected as a separate specimen for final pathologic examination. Accordingly, with no tumor contact on the outer stained margin or no tumor detection in the FS specimen at all, the NVB was saved and the procedure finished in the usual manner.

The remaining specimens were inked with three different colors to differentiate left and right prostatic capsule (green and blue) as well as the area corresponding to the FS sector (yellow).
For the final pathologic report, complete embedding by a 3-mm step-section technique (Stanford protocol) was applied at the main prostatic specimen together with possibly resected NVB and soft tissue.

Surgical margins were declared negative if no tumor contact was found at the green or blue inked external surface of the final prostatic specimen or the outer surface of the resected soft tissue and NVB, in case of a tumor contact with the green or blue ink in the intraoperatively resected wedge.

### 3. Results

FS analyses were performed in 83 (13.7%) of the 608 patients because of intraoperatively detected palpable tumor nodules (Table 1). In the group of FS-RP 31% of the patients had a suspicious preoperative digital rectal examination finding versus 19% of the non–FS-RP patients. In the FS-RP group, the pathologic report showed 36% pT3 prostate carcinoma (pCA). Moreover, 61% of all cancers contained Gleason 4/5 pattern. In the non–FS-RP group, the numbers were 18% and 42%, respectively.

Carcinoma was found in 93% of the investigated 83 FS specimens (Table 2). In 42% (35 of 83) of patients, carcinoma had focal or extensive contact with the inked capsule and consequently ipsilateral NVB and corresponding soft tissue were resected.

Due to FS evaluation in 58% (48 of 83) ipsilateral NVB was spared. However, eight of these patients had a positive margin in the final pathology. Of these eight patients, five had negative ipsilateral FSs and therefore had a NS procedure. They contributed to the overall margin positive rate at 6% (5 of 83). In 52% (43 of 83), the NVB was spared, without negatively affecting the ipsilateral margin.

In the permanent sections of the 35 resected soft tissues and NVBs, carcinoma could be found in only five cases (14%). All specimens were margin negative due to secondary resection, except for one case having a complete tumor infiltration of the NVB up to the outer margin. Consequently, this patient with four others, three with contralateral positive surgical margins and one with an ipsilateral positive margin outside the FS area (pT3a), were considered to be margin positive, despite secondary resection of the NVB after positive FS results.

For the complete FS-RP group, the positive surgical margin rate was 15.7% (13 of 83) compared to 14.3% (75 of 525) in the non-FS group. As for pT2 cancers, positive margins were present in 13.2% (7 of 53) of those in the FS-radical retropubic prostatectomy group.

### Table 1 – Comparison of clinical and pathologic features of FS-RP versus standard RP

<table>
<thead>
<tr>
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<th>FS-RP</th>
<th>Standard NS-RP</th>
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<tbody>
<tr>
<td>No.</td>
<td>83</td>
<td>525</td>
</tr>
<tr>
<td>Median procedure time (h)</td>
<td>2:40</td>
<td>2:26</td>
</tr>
<tr>
<td>Median blood loss (ml)</td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td>T1c in DRE</td>
<td>69%</td>
<td>81%</td>
</tr>
<tr>
<td>Median PSA (ng/ml)</td>
<td>6.02</td>
<td>5.90</td>
</tr>
<tr>
<td>Median free PSA</td>
<td>11.6%</td>
<td>13.9%</td>
</tr>
<tr>
<td>pT3</td>
<td>36.1%</td>
<td>17.7%</td>
</tr>
<tr>
<td>Gleason 4/5</td>
<td>61%</td>
<td>42%</td>
</tr>
<tr>
<td>Negative margin (all stages)</td>
<td>84.3%</td>
<td>85.7%</td>
</tr>
<tr>
<td>Negative margin pT2-stages</td>
<td>86.8%</td>
<td>89.4%</td>
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FS-RP = frozen section-radical prostatectomy; RP = radical retropubic prostatectomy; NS = nerve-sparing; DRE = digital rectal examination; PSA = prostate-specific antigen.

### Table 2 – Pathologic evaluation of frozen section and NVB specimen

<table>
<thead>
<tr>
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<th>FS analysis (n = 83)</th>
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<tbody>
<tr>
<td>Carcinoma detected in specimen</td>
<td>92.8% (n = 77)</td>
</tr>
<tr>
<td>Carcinoma contact with capsule</td>
<td>42.2% (n = 35)</td>
</tr>
<tr>
<td>Carcinoma in resected NVB and soft tissue (permanent section)</td>
<td>14.3% (n = 5/35)</td>
</tr>
<tr>
<td>Negative margin after secondary resection of NVB, all stages</td>
<td>30/35 = 85.7%</td>
</tr>
<tr>
<td>Negative margin after secondary resection of NVB, pT2 stages</td>
<td>16/17 = 94.1%</td>
</tr>
</tbody>
</table>

FS = frozen section; NVB = neurovascular nerve bundle.
(RRP) group and 10.6% (46 of 432) in non–FS-RP, respectively. Of all positive surgical margins, 46% (6 of 13) occurred on the prostatic lobe contralateral to the FS area. For the entire 608 patients investigated here, the overall positive margin rate was 14.5% (88 of 608) for all stages and 10.9% (53 of 485) for pT2 tumors (Table 3).

4. Discussion

The intraoperative finding of a palpable tumor lesion has been described as a possible contraindication for an ipsilateral NS procedure during RP [11,12]. Our analysis of this subgroup of patients reveals them as a risk group for capsular penetration with a proportion of 36% pT3 tumors; moreover, 61% of all tumors contain Gleason 4 or 5 patterns, compared to 18% and 42% in the group without intraoperatively palpable lesions.

However, according to our routinely analyzed preoperative algorithm with a positive predictive value of 86.6% [8], these patients were initially scheduled for a NS-RP. Conscientious surgeons might be reluctant to sacrifice the initially preserved, ipsilateral NVB when palpating a subcapsular tumor lesion intraoperatively, especially in a patient with a strong demand to regain normal sexual function postoperatively. Singer et al. reported that 68% of their investigated patients with prostate carcinoma were willing to trade off a >10% advantage in 5-yr survival to maintain sexual potency [13]. To avoid this dilemma, a quick and objective intraoperative evaluation of the resection site should aid in assessing the safety of an NS procedure if a tumor lesion is detected intraoperatively.

Cangiano et al. [16] first reported about FS analyses to monitor NS RRP in 48 patients, if intraoperative adherence of the NVB or palpable tumor mass adjacent to the capsule occurred or if a diffuse high-grade tumor was detected by preoperative biopsy. The authors found adenocarcinoma in 18% of the FSs and consequently resected the ipsilateral NVB. In contrast to our study, only three patients had an intraoperatively palpable tumor mass for which FS was performed. Their final positive margin rate in the FS-RP group was 24% compared to 28% and 20% for the control groups with planned unilateral and bilateral NS procedures.

Goharderakhshan et al. [17] also reported about the utility of intraoperative FS during RP. They performed FS in 101 patients with a high clinical suspicion of a positive margin. Intraoperatively detected tumor lesions were not explicitly investigated.

Tumor was detected in 15% of all FSs, although in permanent sections the detection rate dropped to 11%. The overall sensitivity, specificity, and positive and negative predictive values for predicting the margin status in the area of the NVB were 69%, 95%, 73%, and 94%, respectively.

The authors pointed out that in their FS group the positive surgical margin rate without the performed FS would have been 26.7% compared to 13.7% in the control group. By applying the intraoperative histologic analyses the final rate was reduced to 14.9%.

These data are comparable to our series. Overall positive surgical margin rate was reduced from 118 of 608 patients (19.4%) undergoing NS according to the preoperative nomogram without FS analysis and no secondary resection on palpable lesions to 88 (14.5%) by the use of intraoperative FS in case of palpable lesions and a subsequent ipsilateral NS procedure. As described for the pT3 tumors, positive margin rates dropped from calculated 38.2% to 28% (35 of 123), compared to the pT2 stages with 14.2% without and 10.9% (53 of 485) with intraoperative FS, respectively. Alternatively, a strict practice of a secondary nerve resection without FS analyses in case of a palpable lesion would have resulted in an only slightly better margin positive reduction of 13.7% for all 608 patients and 10.1% for pT2 stages (Table 3).

Moreover, in nearly half the patients (42 of 83) with an intraoperative palpable tumor nodule NS could be performed safely, without compromising the oncologic safety of the procedure due to an ipsilateral positive surgical margin. The more strict practice of a secondary nerve resection without FS analyses in case of a palpable lesion would have reduced the overall ipsilateral NS rate from an actual 94% to 87% (Table 3).
However, in 6% (5 of 83) of our patients, in which NS was performed due to negative FS, a positive ipsilateral margin to the side of the tumor nodule had to be diagnosed in the final histologic report, which must be seen as the failure rate of the method. The inherent risk of missing a positive margin on FS represents the major drawback for this method and is definitely a risk, which has to be thoroughly discussed with the patient beforehand.

Of note, Goharderakhshan et al. could detect carcinoma in only 20% of their secondary resected soft tissues and NVBs, and Cangiano et al. did not find any tumor in NVBs at all, when the FS of the capsule was positive. This is corroborated in our cohort, where carcinoma was found in 14% of the additionally excised material.

In the search to explain the reason the relationship between positive margins and PSA relapse in NS-RRP is not straightforward, but only true for 36–58%, Epstein et al. [19] reported that in a group of patients, margin was positive or equivocally positive in the region of the NVB, only 39% demonstrated residual tumor in the separately resected NVB [11].

One limitation of our study surely is that we cannot yet provide sufficient follow-up data. The question whether the lowered rate of positive margins due to secondary resection following positive FS also results in a lower rate of biochemical recurrence (BCR) is therefore not answered by this study.

Several authors have demonstrated that NS itself is not a risk factor for BCR after RP even in T3 tumors [20,21]. This and the low detection rate of carcinoma in resected NVBs might raise doubts about the necessity of a secondary abandonment of first preserved NVBs.

Nevertheless, because BCR was clearly related to positive margins especially in extracapsular and high-grade tumors [21,22] we think the oncologic principle of an utmost complete resection of tumor is especially valid for the here-investigated risk group with a palpable lesion and the described high rates of these adverse factors.

In a recent study by Fromont et al. [23], a relationship between the positive margin size and the probability for a positive tumor finding in secondary resected NVB was reported. Of 487 FSs performed during laparoscopic RP, tumor was detected at the outer margin in 17.2%, but only 29.7% of secondary resected NVBs revealed carcinoma. The authors indicated that residual tumor finding in NVBs is strongly related to a positive margin size in FS >0.2 cm, but was not detected at all in margins of <0.1 cm.

Although we did not observe this factor in our series, it might be an additional option to further improve the number of patients in whom NVB could be spared. However, with respect to a certain lack of comparability of the mentioned study due to the absence/presence of the specific finding of a palpable lesion, and our false-negative rate of 6% of FS analysis in this cohort, we generally would be hesitant to further extend indications for a “secondary preservation” of NVB in this particular risk group. Obviously, the intraoperative detection of a palpable lesion undermines the predictive value of the applied nomogram. Incorporating features of intraoperative findings into a nomogram and consecutive “online” re-evaluation of NS safety during RP might present a possible way to circumvent the highly cost-intensive and, moreover, not universally available method of intraoperative FS analysis.

However, even the latest published nomograms with slightly higher predictive values do not include this feature but also are based on preoperative variables [24,25].

Therefore, we consider intraoperative FS to date as the most reliable method for the safe management of the particular finding of an intraoperatively detected palpable lesion during an intended NS-RP.

5. Conclusions

According to our results, the intraoperatively detected tumor lesion is not necessarily a contraindication for ipsilateral NS during RP because intraoperative FS offers an objective and useful tool to handle this specific finding. By applying it, we were able to protect the ipsilateral NVB in 52% of cases with palpable lesions, without compromising the radical intention in this risk group.

In contrast, FS set the intraoperative decision to secondarily remove the NVB in 42% of investigated patients and helped reduce the overall rate of positive surgical margins, especially in patients with pT3 grade tumors.

However, even in patients with a strong desire for postoperative potency, the surgeon must be aware of a failure rate of 6% and discuss this risk with the patient preoperatively.

References

Radical nerve-sparing prostatectomy (RP) represents a standard surgical treatment for clinically localized prostate cancer (pCA). Preservation of continence and potency are important quality of life issues that have to be considered carefully in every individual patient undergoing RP. However, RP represents an oncologic surgery that primarily should focus on the long-term cure, especially of young patients, and on avoiding positive surgical margins associated with a high risk for biochemical recurrence. In the past, intraoperative findings such as palpable tumor nodules and adhesion of the neurovascular bundle to the prostate have been considered as contraindications for nerve-sparing RP [1].

In the current paper, the authors report on a single surgeon’s experience with regard to the use and efficacy of intraoperative frozen section analysis of palpable tumor nodules during nerve-sparing RP for clinically localized pCA in a cohort of 608 consecutive patients. Fourteen percent of the patients...
demonstrated palpable nodules suspicious for extraprostatic extension, making an intraoperative adaptation of the surgical strategy necessary. Most interestingly, 93% of all nodules contained cancer but only one third of the nodules were associated with pT3 pCA, demonstrating that even in cases with palpable lesions a nerve-sparing approach can be attempted without negatively affecting the frequency of positive surgical margins. Especially for pT3 tumors the frequency of positive surgical margins dropped by nearly 25%—a finding that has also been demonstrated by two other groups [2,3].

Despite this innovative approach and the encouraging results, points of caution have to be raised before applying intraoperative frozen section monitoring of nerve-sparing RP into daily routine:

1. All patients undergoing nerve-sparing RP had been diagnosed with clinically organ-confined pCA according to a validated preoperative strategy developed by the Hamburg group [4]. This strategy, however, is unique in that the majority of the patients undergo a repeat ultrasound-guided transrectal prostate biopsy the day before surgery. Therefore, there might be a certain bias as compared to those institutions that rely on the biopsy results of the referring urologist. Furthermore, the reliability of this algorithm has been assessed by prospective internal, but not by external, validation.

2. Nearly two thirds of the patients demonstrated a Gleason 4 pattern and 17% of the patients demonstrated false-positive findings during frozen section analysis. Both findings are associated with an increased risk for biochemical recurrence. As has been demonstrated in a recent paper of the Hamburg group [5], surgical margin status and Gleason pattern of the RP specimen are significant prognosticators for early biochemical recurrence, so that the oncologic follow-up data have to be awaited before final conclusions with regard to frozen section monitoring of nerve-sparing RP can be drawn.

3. As has been demonstrated nicely with the described surgical approach, the use of preoperative nomograms is of utmost importance to reliably identify patients with organ-confined pCA in nonscreened populations who are candidates for a nerve-sparing procedure. Recently, Ohori et al. [6] reported a logistic regression-based nomogram to predict the presence and side of extracapsular extension, with a predictive accuracy of 0.806. As compared to the tree-regression model presented by the Hamburg group [4], the predictive accuracy of the Ohori model was superior with 0.84 versus 0.70, respectively. However, independent of the applied nomogram, intraoperative frozen section analysis should be obtained in any case with a high likelihood of local extension to save the neurovascular bundle in about 50% of all patients.

In conclusion, frozen section monitoring of RP should be considered more often in patients with potential extracapsular extension to save the neurovascular bundles whenever oncologically indicated to optimize postoperative potency and continence thereby improving quality of life.

References


Editorial Comment

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The authors address a very practical problem that has significant implications for the younger patient who undergoes a total radical prostatectomy (RP) for prostate cancer. The priorities for most of our patients are similar: cure, continence, and regaining potency (in that order). The vast majority have excellent continence and thus the emphasis is on eliminating the primary tumor while preserving as
many of the nerves and vessels adjacent to the prostate as possible. Many of us, I believe, base our decision on whether to resect the neurovascular bundles on several factors: the location and grade of the positive biopsies and preoperative and intraoperative alterations in the texture of the prostate. Unfortunately, this information is far from perfect. In my view the biggest unknown is whether the cancer is localized. In our experience, consistent with most others, local recurrence is unusual.

The authors have chosen to enhance their intraoperative decision-making with frozen sections in 14% of men who were candidates for a nerve-sparing RP. The primary criterion was a palpable nodule. Most, but not all, had some Gleason 4 or 5 patterns. In 42% of the 83 patients who had an intraoperative frozen section the bundle was resected based on the frozen section report that there was tumor at the margin. Interestingly and not surprising to me cancer was found in the resected adjacent tissue in only 5 of the 35 cases (14%).

My approach has been to attempt a bilateral nerve-sparing procedure in virtually all cases in which the man is potent preoperatively, the clinical stage is T1 or T2, and the Gleason score is <8. A very high prostate-specific antigen (PSA) level and intraoperative findings that indicate resection of periprostatic tissue may alter this approach. I do not rely on frozen sections, however. As noted by the authors (their ref. [20]) we compared the biochemical recurrence rate in patients who did and did not have a nerve-sparing RP. The recurrence rates were similar. At 5 yr the relapse rate (PSA >0.4) was 14% in nerve-sparing versus 21% in those where the bundles were resected. Admittedly those who did not have the bundles spared had poorer prognostic factors, yet the low recurrence rate in those who had nerve sparing suggests that few were harmed with this approach. In addition, only 19% of my patients with a positive margin have had a biochemical recurrence [1]. Tumor at the margin does not mean there is tumor remaining in the prostatic fossa.

For the occasional patient who has not had a curative procedure solely because a nerve-sparing procedure was performed, there is a very reasonable chance that radiation will provide an opportunity for eradicating small-volume residual tumor in the prostate fossa.

I applaud the authors on their careful analysis. As they state in the article, they do not have sufficient follow-up data to state that their approach in those selected cases results in a lower rate of biochemical recurrence.

Reference