

Original Articles

INTRAOPERATIVE FROZEN SECTION MONITORING OF NERVE SPARING RADICAL RETROPUBIC PROSTATECTOMY

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ABSTRACT

Purpose: We describe the clinical and pathological outcomes of intraoperative frozen sections performed on the posterolateral prostate margins during nerve sparing radical prostatectomy.

Materials and Methods: We developed a technique of bilateral nerve sparing, inking the posterolateral prostate margins and obtaining frozen sections. When tumor was seen on frozen section, the fascia and neurovascular bundle were widely excised before completing the vesicourethral anastomosis. We reviewed 142 radical retropubic prostatectomies performed by a single surgeon between 1992 and 1997. Patients were divided into group 1—nerve sparing procedure using our technique (48 patients), 2—planned unilateral nerve sparing without frozen sections (46) and 3—planned bilateral nerve sparing without frozen sections (48). Potency was measured implicitly by physician assessment and explicitly with the UCLA Prostate Cancer Index. Group comparisons were made for positive margins, biochemical recurrence and potency. Mean followup was 24.5, 43.8 and 39.4 months for groups 1, 2 and 3, respectively.

Results: Of the 48 group 1 patients 9 (18%) had adenocarcinoma in the frozen section specimen, prompting wide excision of the bundles. None of these patients had biochemical recurrence during a mean followup of 20.5 months. Both bundles were spared in the remaining 39 patients (82%). There was no difference in survival or time to biochemical recurrence between groups 1 and 2. Potency was significantly different between groups 1 and 2 (36 versus 13%, $p = 0.001$), even after age adjustment ($p = 0.05$). In contrast, potency did not differ between groups 1 and 3 (38 versus 40%). Preoperative stage, grade and prostate specific antigen level were similar among the 3 groups.

Conclusions: We found a significant difference in potency rates adjusted for age between patients with and without frozen sections. Our results indicate that this technique can enhance the ability of the surgeon to monitor the nerve sparing procedure without compromising cancer control.

KEY WORDS: prostatectomy, prostate-specific antigen, prostatic neoplasms, frozen sections

Since the inception of the nerve sparing technique for radical retropubic prostatectomy, the intraoperative assessment of the ability to preserve the neurovascular bundles safely has been difficult.^{1,2} Adherence of the neurovascular bundles to the prostate during dissection may indicate tumor involvement, although it can also be due to benign processes, such as chronic prostatitis, irritation from prostatic calculi or periprostatic bleeding following transrectal biopsy.^{3–5} Furthermore, since patients with clinical stage T2A/T2B tumors have a higher risk of ipsilateral nerve bundle involvement, it has been argued that those with a palpable nodule clinically confined to a single lobe should undergo resection of the ipsilateral prostatic pedicle, taking a margin of soft tissue along with the neurovascular bundle.

While erectile function can be preserved following unilateral nerve sparing, the likelihood that potency will be normal postoperatively is decreased compared to men undergoing bilateral nerve sparing. In published reports only 13 to 50% of men older than 50 years had normal erectile function

following unilateral nerve sparing radical prostatectomy.^{3,4,6,7} Furthermore, this loss of potency results in a marked reduction in quality of life, with many of these men willing to trade off an approximately 20% decreased chance of being cured in exchange for an increased chance of remaining potent.⁸

Thus, due to the significant impact that postoperative erectile dysfunction may have on quality of life, the adverse effect that nerve resection has on postoperative erectile function and the unknown impact that aggressive nerve sparing has on disease-free survival, we have focused on identifying the optimal circumstances in which bilateral nerve sparing can be performed safely. We describe a technique that allows for the intraoperative monitoring of the posterolateral margins during radical prostatectomy, using intraoperative frozen sections to assess the completeness of tumor resection. Since more younger men with normal sexual function are being diagnosed with prostate cancer, it has become increasingly important to provide them with the best possible outcomes in terms of quality of life and cancer control. By using an aggressive approach to nerve sparing in combination with thor-

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ough intraoperative assessment of the margins, the majority of patients who undergo radical prostatectomy should be able to undergo safely a bilateral nerve sparing procedure without added risk of cancer recurrence.

MATERIALS AND METHODS

Of 572 patients who underwent consecutive radical prostatectomy between 1989 and 1997, 142 underwent a radical retropubic procedure, and had normal preoperative potency and at least 6 months of followup. All surgeries were performed by a single surgeon (J. B. D.) using a modification of the anatomical dissection described by Walsh.¹ The men were divided into group 1—*intraoperative frozen section monitoring with removal of the bundle if tumor was seen in the ink* (48 consecutive patients), 2—*planned unilateral neurovascular bundle excision on the side of the tumor without frozen section monitoring* (46 consecutive age matched patients) and 3—*planned bilateral nerve sparing without frozen section monitoring* (48 consecutive age matched patients). The 3 groups were compared with respect to the preoperative Gleason score, clinical stage, pathological stage, incidence of positive lateral margins, biochemical recurrence as evidenced by detectable prostate specific antigen (PSA) and postoperative erectile function. Recurrence data were adjusted for duration of followup and potency data were adjusted for age. Radical retropubic prostatectomy was performed using a modified apical dissection.⁹ Indications for obtaining intraoperative frozen sections included adherence of the fascia to the prostate, palpable mass adjacent to the capsule and diffuse high grade tumor (clinical stage T1c).

After incision of the periprostatic fascia meticulous preservation of the nerves along the posterolateral margin of the prostate was performed. Following removal of the specimen colored india ink was applied to the posterolateral margin of the prostate in the areas where the periprostatic fascia was excised. A generous portion of ink was used to cover the entire posterolateral region of the prostate along the course of the spared nerve bundles (see figure). Once the ink was dry a wedge of tissue was cut along the entire inked section of the prostate and sent for frozen section analysis. The entire process required about 20 minutes. The specimen was sent immediately upon removal before bladder neck closure, in-

section of sutures and so forth. Approximately 10 minutes of anesthesia time was added by the process.

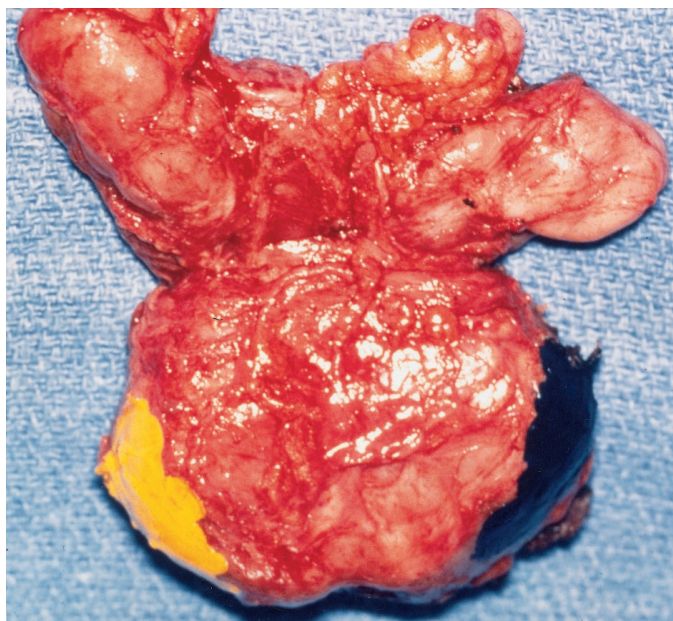
If no tumor was seen at the inked margin, the vesicourethral anastomosis was performed and the procedure was completed. If adenocarcinoma was detected at the inked margin, the corresponding neurovascular bundle was widely resected by identifying and ligating it at the urogenital diaphragm, and resecting it proximal to the level of the bladder neck. The entire bundle and all of its attached soft tissue were then sent as a separate specimen to the pathologist.

Patients were evaluated every 6 months after surgery with PSA and digital rectal examination. Implicit qualitative assessment of sexual function was performed during each followup visit by direct questioning from the surgeon (J. B. D.). Potency was strictly defined as ability to maintain an unassisted erection sufficient for penetration, intercourse and orgasm. If the patient was unable to maintain an erection sufficient for completion of intercourse, he was considered to be impotent. Any patient who needed to use devices or medications for stimulating an erection was classified as impotent. Partial potency was defined as the ability to achieve but not maintain an erection long enough for satisfactory intercourse without the use of a device or medication. The accuracy of this implicit assessment was measured in a subset of 28 patients by administering a validated, written self-reported measure of potency, namely the sexual function and sexual bother scales of the UCLA Prostate Cancer Index.¹⁰

Statistical analysis was performed using Fisher's exact or chi-square test when comparing sample proportions with 2 or 3 groups, respectively, and the 2-tailed Student t test was used when comparing continuous outcome variables. Survival analysis was performed using Kaplan-Meier curves with log rank tests for comparing groups, and multivariate survival analysis was performed using the Cox proportional hazards model. The subjective physician potency evaluation was compared to the sexual function scale of the UCLA Prostate Cancer Index using a nonparametric rank sum test.

RESULTS

Patient characteristics are summarized in table 1. Groups did not differ in regard to operative time, intraoperative complications, estimated blood loss, tumor stage, tumor grade, patient age or preoperative PSA. Of 48 group 1 patients 9 had prostatic adenocarcinoma in the frozen section of the inked margin, and the fascia and neurovascular bundle were subsequently resected, while 39 (82%) the neurovascular bundles were preserved. None of the 9 patients with positive frozen sections and resection of the nerve bundle had PSA recurrence (mean followup 23.5 months), while 5 of 39 (13%) with negative frozen sections had recurrence (mean followup 31 months) ($p > 0.05$). None of the 9 men with positive posterolateral frozen sections had other positive margins, while 24% of the 39 men with negative posterolateral frozen sections had positive margins elsewhere in the specimen. Indications for frozen sections in the 9 patients



Technique of intraoperative frozen section inking of prostate. Ink covers posterolateral portion of prostate. Different colored ink is used if bilateral frozen section is required as depicted.

TABLE 1. Stratification of patients undergoing radical prostatectomy

	Group 1	Group 2	Group 3
Mean age (range)	59.5 (38–71)	63.8 (47–75)	60.0 (41–72)
Mean ng./ml. PSA (range)	9.4 (1.4–30)	11.4 (0.5–90)	10.2 (0.8–48)
Gleason sum:			
3–6	32	30	36
7	13	12	11
8–10	3	2	1
% Pathological stage:			
T1/T2	52	57	66
T3/T4	48	43	35
% Pos. margin rate	24	28	20
Mean mos. followup (range)	24.5 (6–78)	43.8 (6–111)	39.4 (9–99)

with tumor in the inked margin were palpable mass in 3, adherence of the periprostatic fascia in 4 and high grade clinical stage T1c in 2. The final margins in all patients with frozen section monitoring were negative in the ipsilateral posterolateral region. Other positive margin areas included the contralateral posterolateral margin, apex (mid or contralateral) and bladder neck. No patients in group 1 or 2 had clinical recurrence during followup. In addition, when adjusted for the duration of followup, no statistically significant difference was seen in the incidence of PSA relapse between groups 1 and 2 ($p = 0.94$).

In terms of erectile function group 1 (intraoperative frozen section 18% unilateral, 82% bilateral nerve sparing) did better than group 2 (100% unilateral nerve sparing). According to our criteria 36% of group 1 patients were potent versus 13% in group 2 ($p = 0.001$ rank sum test, table 2). This difference remained statistically significant when adjusted for age ($p = 0.05$). Furthermore, postoperative potency in group 1 patients was equivalent (38 versus 40%) to those with normal preoperative potency and planned bilateral nerve sparing (group 3). The incidence of partial potency was also improved in group 1 compared to groups 2 and 3, although these differences were not statistically significant (45, 33 and 33%, respectively). Patients classified as potent by the interviewing physician had significantly better average sexual function ($p = 0.008$) and sexual bother ($p = 0.034$) scores than those classified as impotent. Significant agreement was seen between the implicit physician assessment of potency and the explicit, validated, self-reported measures of sexual function and bother (table 3).

DISCUSSION

Classically, when the neurovascular bundle is adherent to the prostate, or when there is suspicion of tumor involvement based on clinical stage, it has been suggested that the nerve bundle should be sacrificed given the increased risk that tumor will be left behind and the historical inability to assess accurately the status of the lateral margins during prostatectomy. When the neurovascular bundle is adherent or fixed to the prostate it is assumed that the desmoplastic reaction is secondary to locally advanced prostate cancer.³⁻⁵ Nonetheless, inflammation, stones and changes associated with a transurethral resection of the prostate and/or biopsy can mimic cancer and produce misleading impressions. Furthermore, attempts to detect extracapsular prostate cancer and neurovascular bundle involvement using imaging techniques, such as transrectal ultrasound and magnetic resonance imaging, have been limited by low sensitivity and specificity.^{11,12} If unilateral nerve sparing during radical prostatectomy yielded similar potency rates to bilateral nerve sparing, this would not be an issue. However, since the results of unilateral nerve sparing are generally poor, there is a need to improve the ability to define the circumstances in which bilateral nerve sparing can be safely performed without compromising tumor resection.

We use frozen sections to evaluate the lateral margins during nerve sparing radical prostatectomy. When frozen section analysis was used to determine the advisability of sparing the nerves, despite suspicion of unilateral tumor

TABLE 3. Cross tabulation of item and total scores from the UCLA Prostate Cancer Index Sexual Function scale between men who were potent or impotent by subjective physician assessment

Sexual Function Items	Mean Score	
	Subjectively Potent	Subjectively Impotent
Sexual desire	43	44
Ability to have erection	45	6
Ability to reach climax	80	38
Quality of erections	73	25
Frequency of erections	52	19
Morning erections	28	0
Frequency of intercourse	25	25
Overall sexual function	38	13
Mean sexual function score	48	21 ($p=0.008$)

Items and scale from 0 to 100, with higher scores representing better outcomes.

extension, bilateral nerve sparing was feasible in more than 80% of patients without increased risk of tumor recurrence. Some believe that nerve sparing can result in iatrogenic positive margins but the effect of these margins on outcome is unclear.¹³ The overall impact of positive margins on cancer recurrence is probably related to degree to which the tumor penetrates the capsule (extensive versus focal capsular). In a study by Partin et al patients with a palpable abnormality on 1 side of the prostate were treated with wide excision of the ipsilateral neurovascular bundle.¹⁴ Of these patients 42% had positive surgical margins, which was significantly lower than the positive margin rate seen in patients when the neurovascular bundle on the side of the tumor was left intact. However, during long-term followup patients with extensive capsular penetration who underwent wide excision of the neurovascular bundles had a disease-free survival advantage compared to those with nerve sparing in the presence of extensive capsular penetration and positive surgical margins.¹⁵

Since patients with extensive capsular penetration may also have micrometastatic disease, some would contend that wide excision of the neurovascular bundles does not benefit cancer control and in fact results in a decreased quality of life due to diminished sexual function.^{8,16} Thus, if no survival benefit is obtained from nerve resection it might be reasonable to spare the neurovascular bundles, especially in patients for whom potency is extremely important.

Of 40 patients with clinically suspicious posterolateral borders of the excised prostate Epstein noted that only 7 (17.5%) had residual tumor in the separately resected ipsilateral nerve bundles.⁵ The 22 patients with clinically suspicious but pathologically negative posterolateral borders of the prostate had no tumor in the separately resected neurovascular bundles. Also, Quinlan et al showed that when the neurovascular bundles were resected based on intraoperative suspicion of tumor involvement, the tumor was found to penetrate no more than 2 mm. into an excised bundle in 75% of patients.⁴ These results suggest that complete nerve resection may be unnecessary even when clinical suspicion of involvement exists. Therefore, frozen section analysis of the tissue margins might be a reasonable option to preserve the neurovascular bundle in these patients. Although we found no tumor in the resected bundle when the frozen section was positive, we still considered it important to achieve a clear surgical margin based on sound surgical principle. Indeed, it is still possible that several tumor cells are hidden in the removed tissue and not seen in the permanent sections.

Thus, our frozen section technique allows more patients to undergo bilateral nerve sparing without any apparent increased risk of cancer recurrence. Our followup was relatively short but in the majority of groups 2 and 3 PSA recurred within 2 years. While it is possible that patients with intraoperative frozen section monitoring might have a higher

TABLE 2. Potency rates for all ages by subjective physician assessment

	Group 1	Group 2	Group 3
	% Frozen Section Nerve Sparing	% Planned Unilat. Nerve Sparing	% Planned Bilat. Nerve Sparing
Impotent	19	54	27
Partially potent	44	33	33
Potent	38 (rank sum test $p = 0.001$.)	13	39

relapse rate with longer followup, it is doubtful in view of the current experience with this significant number of patients. Furthermore, frozen section monitoring influences only decisions regarding margins which might become positive secondary to the nerve sparing itself and, as noted elsewhere, will have no impact on other areas or on distant foci. Selection of patients with these other adverse factors could result in a higher risk of recurrence but this would not have changed with preservation of the neurovascular bundle. In the study by Epstein 22 patients with clinically suspicious but pathologically negative posterolateral borders had no tumor in the corresponding neurovascular bundle. In more than 80% of our patients with suspicion of neurovascular bundle involvement by tumor, we were able to spare both neurovascular bundles, which resulted in significantly improved potency rates compared to unilateral nerve resection.

The relatively low potency rates in our study reflect the large number of elderly patients and the more critical response achieved by rigorous data collection through third-party questionnaire surveys. Potency in patients between 50 and 60 years old in all 3 groups averaged 80% compared to 18% in those 68 years old or older. When potency is strictly defined as the ability to have unassisted intercourse, we obtained results similar to those of Geary et al who also treated a large group of older men.⁷ They reported that 32% of patients who underwent bilateral nerve sparing remained potent. If only 1 nerve was spared, the rate dropped to 13%. Our potency rates were similar (38% bilateral versus 13% unilateral). Several other series also indicated a marked decline in potency rates by 20 to 50% after resection of 1 neurovascular bundle.^{4,6,17} Hence, when data were adjusted for age and tumor stage, we found that the likelihood of recovering potency postoperatively was largely determined by the number of spared neurovascular bundles. Given the impact of nerve resection on postoperative sexual function, it seems ideal to try to preserve both bundles in patients who are concerned with potency.

CONCLUSIONS

Our technique can help distinguish local tumor extension from other benign processes that can involve the neurovascular bundle. The surgeon can readily use this technique to help monitor the status of the posterolateral border of the prostate when a nerve sparing technique is contemplated. When suspicion exists due to the preoperative clinical examination or intraoperative fixation of the neurovascular bundles to the prostate, frozen section analysis can be used to discriminate between patients whose nerves can safely be spared versus those whose nerves should be resected.

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