The contemporary surgical management of prostate cancer has been shaped by two seminal events: (1) the description of the anatomic nerve-sparing radical prostatectomy,[5] and (2) the use of prostate-specific antigen (PSA) serology for prostate cancer screening.[7] Although seemingly disparate, these two milestones in urology are interconnected. As a result of early detection programs, younger men are diagnosed with, and treated for, prostate cancer. Consequently, there has been an enhanced effort to preserve sexual function during treatment. Fortuitously, Walsh's pioneering report on the anatomic radical prostatectomy preceded by several years the institution and acceptance of PSA-based screening programs.

In the year 2000, the National Cancer Institute reported that, for the first time, there was a significant diminution in prostate cancer–related mortality. This decrease was attributed, in part, to the success of PSA-based screening programs.[3] As a result of early detection, men are diagnosed with prostate cancer at a
younger age when they are still sexually active. This change in demographics has made preservation of erectile function at the time of surgery a paramount consideration. In a study performed at the authors' center, men undergoing treatment for prostate cancer were willing to exchange an approximate 20% chance of cure for an increased prospect of remaining potent after therapy. For many men, the emphasis of radical prostatectomy is no longer focused solely on cancer control but has expanded to include lifestyle issues. This trend has been reinforced by reports in the lay press and Internet on the overwhelming success of nerve-sparing operations. A similar paradigm shift has occurred in breast cancer treatment as sexuality issues have assumed a prominent position and radical and partial mastectomies have been replaced by combination lumpectomy and adjuvant therapy.

The anatomic nerve-sparing radical prostatectomy has improved understanding of the structures involved in urinary control and erectile function and how they are impacted by surgical manipulation. One controversy surrounding nerve-sparing surgery concerns the wide range of reported results. Potency and continence rates differ among surgeons and academic centers. Explanations for these inconsistencies have included differences in surgical skill and acumen, patient selection, and outcome measurement methodology. A thorough analysis regarding the fundamental issues of this debate is beyond the scope of this article. Suffice it to say that as a result of the modifications incorporated into the anatomic nerve-sparing radical prostatectomy, more patients are sexually potent after surgery, and continence tends to return more rapidly and more completely. Accordingly, quality of life studies indicate that most patients are satisfied with the outcomes of surgery.

ANATOMIC CONSIDERATIONS OF NERVE-SPARING SURGERY

Normal postprostatectomy erectile function depends on preservation of the autonomic cavernous nerves, which help comprise the neurovascular bundle. These nerves are located just outside the posterolateral margin of the prostatic capsule, within the periprostatic fascia at the junction of the lateral and posterior portions of the endopelvic (lateral pelvic) fascia. At this position, the lateral pelvic fascia is composed of two layers—the levator fascia and the prostatic fascia. The neurovascular bundle passes between these two layers. The bundle is separated from the prostatic capsule by approximately 1.5 mm at the base of the prostate and approximately 3 mm at the apex. Although it is in close apposition to the prostate, the neurovascular bundle can be dissected free of the prostate by entering the periprostatic fascia laterally and gently and meticulously dissecting the bundle off of the prostatic fascia.

If neither neurovascular bundle is preserved, the chance for potency postprostatectomy is essentially zero. The potency rate (defined as the ability to sustain an erection sufficient
to engage in sexual intercourse without the use of any aids other than sildenafil [Viagra] can be as high as 68% to 86% when both neurovascular bundles are saved. These results in men with favorable preoperative histologic, staging, and serologic factors reflect the highly selected patient populations common to most academic centers. When only one bundle is salvaged, potency rates can diminish substantially. Given the importance of sexual function to many men undergoing radical prostatectomy and the differences in erectile function when one bundle is spared instead of two, the authors believe that every effort should be made to preserve both neurovascular bundles whenever possible, as long as the potential for cure is not jeopardized.

**RISK THAT NERVE-SPARING SURGERY WILL COMPROMISE CANCER CONTROL**

Because the neurovascular bundle is located outside of the prostatic capsule, nerve-sparing radical prostatectomy should not compromise cancer control if the tumor is organ confined unless the prostatic capsule inadvertently is violated while attempting to mobilize the neurovascular bundle. Several studies confirm this premise and have demonstrated that preservation of sexual function does not compromise cancer control in the setting of pathologically organ-contained disease.

The actuarial likelihood of postprostatectomy recurrence increases with pathologic stage, not with the preservation of potency. Unfortunately, the preoperative clinical staging of prostate cancer is inexact, and many men are placed in a higher stage at the time of prostatectomy. Although the ability to diagnose prostate cancer at an earlier and, theoretically, at a more curable stage has improved, clinicians still are limited by an inability to predict accurately the prognosis for a substantial proportion of tumors using conventional preoperative diagnostic methods. PSA serology is a poor predictor of pathologic stage, and needle biopsies can misrepresent the volume, histology, and behavior of a given tumor. Equally confounding is the fact that the presence of extraprostatic extension can be underappreciated by digital palpation, and conventional imaging studies can fail to detect metastatic spread. As many as 50% of men with clinically organ-confined lesions are discovered to have more extensive tumors at the time of surgery.

To compensate for these deficiencies, a combination of factors has been defined to help predict which men are at higher risk for recurrence after surgery. The authors use the following preoperative indicators to identify these men: a PSA level greater than 10 ng/mL, a Gleason grade 4 or 5 pattern or evidence of perineural invasion on biopsy, and the presence of tumor palpable beyond the prostatic capsule on digital rectal examination. Additional pathologic findings in the surgical specimen include tumor volume, vascular and perineural invasion, extensive capsular penetration, extension into the seminal vesicles, and positive surgical margins. Combining these factors, the authors have defined specific characteristics under which nerve-sparing prostatectomy might increase postoperative tumor recurrence. These criteria are used to counsel patients and to help
determine in which men nerve-sparing surgery can be performed safely with a minimal risk for leaving residual tumor within the prostatic fossa.

**RISK FACTORS FOR TUMOR RECURRENCE**

A positive surgical margin frequently denotes residual tumor and carries a high risk for treatment failure.[10][11] Clearly, differences will exist as to whether the positive margin is focal or extensive, with the former having a better prognosis. Conversely, extracapsular extension does not necessarily predict a poor outcome.[7][61] To achieve a surgical cure in the presence of extracapsular disease, a sufficiently wide excision of periprostatic tissue is necessary to produce negative margins.

Men with palpable tumors on digital rectal examination have a higher risk for ipsilateral neurovascular involvement. Studies by Partin and associates at Johns Hopkins University demonstrated that the positive surgical margin rate was increased significantly in men with unilateral palpable disease when the ipsilateral neurovascular bundle was preserved instead of widely excised. Follow-up studies on these patients confirmed that men who had a wide excision of the neurovascular bundle had a disease-free survival advantage when compared with men who underwent attempted nerve-sparing procedures.[51] These findings suggest that nerve-sparing radical prostatectomy should not be performed if extracapsular disease is apparent preoperatively because of an increased possibility of cancer recurrence.

Several pathologic studies have concluded that nerve-sparing surgery can be performed safely in men with extraprostatic extension. Epstein and co-workers studied patients with positive surgical margins present in the posterolateral region only and determined that postprostatectomy relapse was uncommon. In 507 men with stage T1c and T2c tumors, the most common sites of positive margins were distal (22%), posterior (17%), and posterolateral (14%). In a study of 144 men undergoing radical prostatectomy, Rosen and co-workers confirmed these findings, demonstrating that, when positive margins were present, fewer than 10% of men had involvement in the region of the neurovascular bundles. These findings suggest that, in cases of extraprostatic extension, involvement of the posterolateral margin is less common than in other locations.

Epstein and co-workers examined paired specimens from men with prostate tumors that were highly suspicious for posterolateral involvement who underwent nerve-sparing prostatectomy followed by excision of the neurovascular bundles on the suspect side. Cancer was found in the bundles in 17.5% of the men. In men with clinically suspicious but pathologically negative posterolateral margins, no tumor was found in the resected bundles. These findings suggest that intraoperative frozen-section analysis of the posterolateral margin can be used to predict tumor involvement of the neurovascular bundle in men in whom there is clinical suspicion of extracapsular extension. If extraprostatic tumor is noted, the bundle should be resected.
CONTRAINDICATIONS TO NERVE-SPARING PROSTATECTOMY

The authors have developed criteria by which patients unsuitable for nerve-sparing radical prostatectomy can be identified based on an increased potential for having positive margins. As is true regarding most issues in prostate cancer, there are few unambiguous factors, and the whole gestalt of the patient must be considered before a decision can be made to proceed with nerve preservation. Contraindications for nerve-sparing prostatectomy are as follows:

Absolute contraindications

Locally advanced disease (T3c lesions)
Palpable disease at the apex
Gleason grade 5 disease
PSA >20 ng/mL
Preoperative impotence

Relative contraindications

Intraoperative difficulties with mobilization of the neurovascular bundles
Palpable localized disease (T2c, other than at the apex)
PSA serology between 10 and 20 ng/mL
Greater than 50% Gleason grade 4 on biopsy
Perineural invasion on biopsy
Presence of cancer in three needle cores from the same lobe of the prostate on sextant biopsy

Absolute Contraindications to Nerve-Sparing Prostatectomy

Locally Advanced Disease

Patients with T3c disease (whether diagnosed on preoperative digital rectal examination or on palpation at the time of surgery) are not candidates for nerve-sparing surgery, and the indications for radical prostatectomy are also questionable. Because many patients with T1c or T2c tumors who are classified as having T3c disease at surgery can experience durable cancer remissions, if extraprostatic disease is discovered in these
patients by intraoperative palpation, every attempt should be made to remove the tumor completely and to forego nerve preservation.

Of particular importance is palpable disease at the prostatic apex. The presence of a nodule on digital rectal examination at the apex is often indicative of extraprostatic extension at that location; however, intraoperative examination of an apical nodule underestimates its magnitude, and an accurate assessment can be made only after gross inspection of the operative specimen. If nerve preservation is attempted and a wide excision of the apex is not performed, there is a significant chance of leaving residual tumor.

**Gleason Grade 5 Disease, Prostate-Specific Antigen Greater Than 20 ng/mL, or Both**

The high risk for recurrent and metastatic disease in men with high PSA values, high-grade disease, or both precludes them from nerve-preservation surgery. Some authorities would contend that, because many of these men are predestined to fail surgical management, attempts at nerve preservation are justified to maximize quality of life for the remainder of the patient's limited life. The authors believe that, because of PSA screening, many of these men are diagnosed with cancer when the tumors still potentially are localized within the prostate. Although there is a high chance of treatment failure, every attempt should be made to remove the tumor completely and to forego nerve preservation.

**Preoperative Impotence**

Because there is no need for nerve preservation in men who have preoperative impotence, there is no need to risk leaving residual disease by performing nerve-sparing surgery. This recommendation applies only to men with complete erectile dysfunction. In men using sildenafil (Viagra), attempts should be made to salvage the neurovascular bundles because there remains the possibility of postoperative potency, albeit, less than for men with normal preoperative erectile function. Recently, the authors have started performing simultaneous radical prostatectomy and artificial prosthesis placement in impotent men and in men who are not candidates for nerve preservation, as described by Khoundary and associates. Although early work by Walsh suggested that nerve-preservation surgery may improve postoperative continence, this success has never been demonstrated conclusively.

**Relative Contraindications to Nerve-Sparing Prostatectomy**

Risk factors associated with extraprostatic disease have been described previously and can portend treatment failure postprostatectomy. Although the presence of any of these factors does not preclude a man from undergoing nerve-sparing radical prostatectomy, a patient with such findings must be evaluated intraoperatively to determine whether it is safe to proceed with preservation of the neurovascular bundles. As more of these factors are present, the authors' threshold for performing nerve-sparing surgery decreases. In addition to palpation at the time of surgery, the authors recommend frozen-section
analysis of the posterolateral margin to identify possible areas of neurovascular bundle involvement. In addition, patients must be counseled before surgery that they have risk factors for neurovascular involvement, and that nerve preservation may not be feasible.

Intraoperative Difficulties with Mobilization of the Neurovascular Bundles

Adherence of the neurovascular bundles to the prostatic fascia during prostatectomy may indicate tumor involvement; however, this adherence also can result from benign processes, including postbiopsy inflammation, benign prostatic hypertrophy (BPH); and prostatitis. Because of the concern that the adherence represents a desmoplastic reaction to the tumor, the following situations are indications for a wide excision: induration detected in the region of the neurovascular bundle before opening the lateral pelvic fascia, fixation of the neurovascular bundle to the prostate after releasing the lateral pelvic fascia, and inadequate appearing soft tissue surrounding the prostate on examination of the removed specimen.

If any doubt remains that the adherence is the result of a benign process (postbiopsy inflammation, BPH, or prostatitis), intraoperative frozen sections of the posterolateral margin can be obtained to assess the completeness of tumor resection, with subsequent excision of the neurovascular bundle should tumor be present at the margin. Similarly, if a violation of the prostatic capsule occurs during mobilization of the neurovascular bundle, the removed specimen must be scrutinized to ensure that there is sufficient periprostatic tissue to allow for adequate negative surgical margins. Once again, if there is any doubt regarding the integrity of the tissue after visual inspection, intraoperative frozen sections can be obtained to evaluate the posterolateral border.

Palpable Localized Disease (T2c, other than at the apex)

Digital rectal examination understages organ-confined disease. In a series of 601 men undergoing radical prostatectomy at Johns Hopkins, of the 565 men with T2c disease, only 52% had organ-confined tumors. Of the 36 men with T3c disease, 19% had organ-confined lesions. With increasing clinical stage, there is a corresponding increase in understaging; hence, any patient with palpable disease preoperatively must be examined thoroughly intraoperatively to exclude the chance of T3 disease. If, after intraoperative palpation, a T2c lesion is clearly without extraprostatic extension, attempts can be made to save the neurovascular bundle. In such situations, the authors recommend the use of intraoperative frozen sections of the posterolateral margin to evaluate for the presence of tumor near the nerves.

Prostate-Specific Antigen Serology Between 10 and 20 ng/mL

Prostate-specific antigen serology is a poor predictor of pathologic stage. Because PSA values vary widely within a given stage and overlap between different stages, the predictive value of PSA in determining pathologic stage is weak. Even with the combined use of digital rectal examination, serum PSA, and transrectal ultrasonography, it is not feasible to estimate reliably the stage of an individual tumor before surgery. Nevertheless,
as PSA levels rise, the chance of extracapsular disease increases correspondingly. Partin and co-workers demonstrated that 70% to 80% of men with a PSA less than 10 ng/mL will have organ-confined disease. This rate decreases to approximately 50% for men with a PSA greater than 10 ng/mL and to approximately 25% for men with a PSA greater than 50 ng/mL. Sanwick and co-workers showed that 37.5% of patients with PSA values between 10 and 15 ng/mL and all patients with PSA values greater than 15 ng/mL had evidence of extracapsular extension.

Greater Than 50% Gleason Grade 4 on Biopsy

The presence of Gleason grade 4 or greater histology carries a significantly worse prognosis. Stamey and co-workers have demonstrated that Gleason score 7 tumors can be stratified based on the amount of grade 4 disease. Tumors with less than 50% grade 4 disease behave similarly to Gleason score 6, whereas tumors with greater than 50% grade 4 act like Gleason score 8 cancers.

Oesterling and co-workers demonstrated the importance of Gleason grade in prostate needle biopsy as a predictor of final pathology. Gleason score 6 tumors were associated with a 24% risk for capsular penetration and a 29% probability of positive surgical margins. Gleason score 7 cancers were associated with a 62% risk for capsular penetration and a 48% probability of positive surgical margins, whereas Gleason score 8 to 10 tumors had an 85% and 59% risk, respectively. Of 72 men with Gleason score 8 to 10 tumors, extraprostatic disease was noted in 92%.

In an attempt to identify patients who would be good candidates for nerve-sparing surgery, Sanwick and associates evaluated the accuracy of digital rectal examination, PSA, and prostate biopsy to predict extracapsular tumor extension. Because the chance of capsular perforation increased with tumor grade, they concluded that patients with Gleason grade 4 or higher disease should undergo wide excision of the bundle on the side of disease. In this study, all patients with Gleason score 8 to 10 tumors had extraprostatic extension; however, an analysis could not discriminate whether the location of extraprostatic extension was at the posterolateral margin or other locations.

Perineural Invasion on Biopsy

Perineural invasion on needle biopsy correlates strongly with capsular penetration in the corresponding radical prostatectomy specimen. In addition, a relationship between perineural invasion and Gleason grade 4 disease has been observed. Nonetheless, perineural invasion on the final pathology specimen does not portend a worse outcome.

Men with perineural invasion on prostate biopsy have a 17.5% risk for positive margins when nerve-sparing surgery is performed. Holmes and colleagues reviewed the pathology findings in 80 patients with perineural invasion. Fourteen patients (17.5%) had tumor in the neurovascular bundle, which would have remained in situ in these men had nerve-sparing surgery been performed.
de la Taille and co-workers determined that perineural invasion was an independent predictor of pathologic stage. Of 371 patients, 77 (24%) were identified to have perineural invasion, which had an 83% specificity and 40% sensitivity for predicting pT3 disease (with an odds ratio of 3.49). Perineural invasion, along with PSA and Gleason score, was predictive of extracapsular extension.

Vargas and associates evaluated the radical prostatectomy specimens of 340 men. Perineural invasion was noted in 57 men (17%). The sensitivity for predicting extraprostatic extension was 32%, the specificity 88%, and the positive predictive value 42%. Biopsy specimens with perineural invasion had significantly more core specimens involved with tumor and higher biopsy-determined Gleason scores.

Presence of Cancer in Three Needle Cores from the Same Lobe of the Prostate on Sextant Biopsy

McNeal and associates have demonstrated that tumor volume on prostatectomy specimens correlates with extracapsular extension; however, they have found that an accurate measurement of tumor volume based on biopsy findings is technically difficult. McNeal and Stamey have proposed further that the biologic aggressiveness of prostate cancer is a direct function of the tumor volume. It can be implied that the more volume on biopsy, the worse prognosis for extracapsular disease. This rationale has been confirmed in several studies, suggesting that the tumor extent on prostate biopsies can predict T3 disease.

Using multivariate analysis models, Goto and co-workers determined that the length of cancer in needle biopsies could predict extraprostatic disease, and Sebo and co-workers demonstrated that the percentage of needle biopsy cores and the surface area positive for cancer were strong predictors of pathologic stage and tumor volume of the pathologic specimen. Once the percentage of positive cores was known, the percentage of tumor surface area involved with tumor added no additional information.

INTRAOPERATIVE FROZEN-SECTION ANALYSIS OF THE POSTEROLATERAL PROSTATIC MARGIN

Cangiano and associates demonstrated that intraoperative frozen sections following nerve-sparing radical prostatectomy could be used effectively to evaluate whether cancer was present at the posterolateral margins of the resected prostate. If tumor was found, the corresponding neurovascular bundle was excised. These investigators were able to distinguish local tumor extension from benign processes that involved the neurovascular bundle and could distinguish patients whose nerves could be spared safely from patients in whom resection was indicated. When these patients were compared with patients who underwent radical prostatectomy with preoperatively planned unilateral neurovascular bundle resection, the rates of cancer control were equal. The potency rates for men in whom intraoperative frozen sections were obtained were identical to the rates for patients
who underwent preoperatively planned bilateral neurovascular bundle preservation, with minimal differences in regard to the positive margin rate. The authors have been using a similar technique at their center in men who may be candidates for nerve-sparing surgery but who have risk factors for extracapsular extension.

The authors use a modification of the anatomic nerve-sparing prostatectomy described by Walsh. After completion of the apical dissection, the lateral periprostatic fascia is incised, and the neurovascular bundle is dissected meticulously off the prostatic fascia. The nerves are spared throughout the surgery from the level of the urethra to proximal of the seminal vesicles. If any doubt remains that nerve preservation might compromise cancer eradication, introperative frozen-section analysis of the posterolateral margin is performed.

When the prostate is removed, the posterolateral margins are marked with three number 4-0 Prolene sutures in a line adjacent to the location of the neurovascular bundles. The specimen is sent promptly to a genitourinary pathologist who inks the margins and performs frozen-section analysis. The results are reported to the operating room by the time that the bladder neck is repaired and the mucosa everted. If no tumor is noted in the frozen section, the authors proceed with the vesicourethral anastomosis and completion of the surgery. If tumor is present at the marked margin, the entire neurovascular bundle is resected en bloc with a margin of soft tissue from the urogenital diaphragm to the bladder neck and sent as a separate specimen.

SUMMARY

Nerve-sparing radical prostatectomy can be performed safely in most men undergoing radical prostatectomy. As is true in many aspects of prostate cancer diagnosis and therapy, the key element is patient selection. With many prostate tumors diagnosed at an earlier stage, the authors have seen a shift toward more favorable pathologic findings at the time of surgery. Concomitant with the success of early detection of prostate cancer is the realization that men are younger at the time of diagnosis and more interested in preserving sexual function.

This article has described factors associated with an increased risk for extraprostatic tumor and, subsequently, an increased possibility of postprostatectomy cancer recurrence. Except for the previously mentioned absolute contraindications, none of these factors, by themselves, should be used to exclude a patient from nerve-sparing prostatectomy. Instead, meticulous attention must be given to the surgical dissection. If any doubt remains regarding residual tumor, the surgeon should err on the side of caution and remove the neurovascular bundle. The use of standardized intraoperative frozen-section analysis can help guide these decisions. The patient must be informed before surgery regarding the risks of nerve-sparing surgery, the potency rates of the surgeon, and the possibility that, to ensure adequate cancer control, the nerves may be sacrificed despite any preoperative optimism favoring the potential for their salvage.
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