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REVIEW ARTICLE

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Evaluating radical prostatectomy specimens: therapeutic and prognostic importance

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Abstract The pathologic staging of prostate cancer involves determination of the anatomic extent and burden of tumor based on the best available data. Proper examination of radical prostatectomy specimens is critical in determining cancer stage, stratifying patient need for adjuvant treatment, and prediction of patient outcome. Differences exist in methods of handling and sampling specimens, although publication of practice protocols in recent years has led to convergence of opinion. In this report, we evaluate the current aspects of pathologic staging of prostate cancer and assessment of prostatectomy specimens. Recent international agreement on pathologic staging of prostate cancer should allow valid comparisons of surgical treatment from different institutions. The vanishing cancer phenomenon is also briefly discussed.

Key words Prostate · Prostatic neoplasms · Staging · Surgery · Pathology · Radical · Prostatectomy · Prognosis

Introduction

Prostate cancer is second only to lung cancer as a cause of cancer death in American men. In 1996, an estimated 41,400 Americans died of prostate cancer and 317,000 new cases were diagnosed [61]. For all men, the overall lifetime probability of developing clinically evident prostate cancer is about 16% (1 in 6), much lower than the 80% prevalence at autopsy by age 80 years. Consequently, most men die with prostatic carcinoma rather than of prostatic carcinoma.

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The incidence of prostatic adenocarcinoma has risen dramatically in the past decade, probably owing to early detection programs that employ digital rectal examination, serum prostate-specific antigen (PSA), and transrectal ultrasonography (TRUS). As competing causes of mortality such as lung cancer and heart disease decline, men are living longer and increasing their risk of developing clinically apparent prostate cancer.

This increase in cancer detection has evoked a sharp increase in the number of radical prostatectomies. The popularity of surgical treatment is due in part to improvements in technique that decrease the risk of impotence, including nerve-sparing prostatectomy. About one-third of American men diagnosed with prostate cancer in 1996 were treated by radical prostatectomy. At Mayo Clinic, more than 900 radical retropubic prostatectomies are performed annually.

Proper examination of radical prostatectomy specimens by the pathologist is critical in determining the need for adjuvant treatment and prediction of patient outcome. Routine protocol-based tissue sampling ensures consistent and thorough examination by trainees and consultants. This issue has been addressed recently by the College of American Pathologists (CAP) [41], the Association of Directors of Anatomic and Surgical Pathology (ADASP) [4], and a recent consensus conference sponsored by the American Cancer Society, World Health Organization, and Mayo Clinic [70]. In this report, we incorporate the conclusions of each of these contemporary statements to create a standardized approach to examination of radical prostatectomy specimens. Also included is a brief evaluation of pathologic staging and the vanishing cancer phenomenon. We begin with an evaluation of methods of sampling prostatectomy specimens (Fig. 1).

Assessment of radical prostatectomy specimens

Numerous methods for partial and complete sampling of prostatectomy specimens have been described, and the

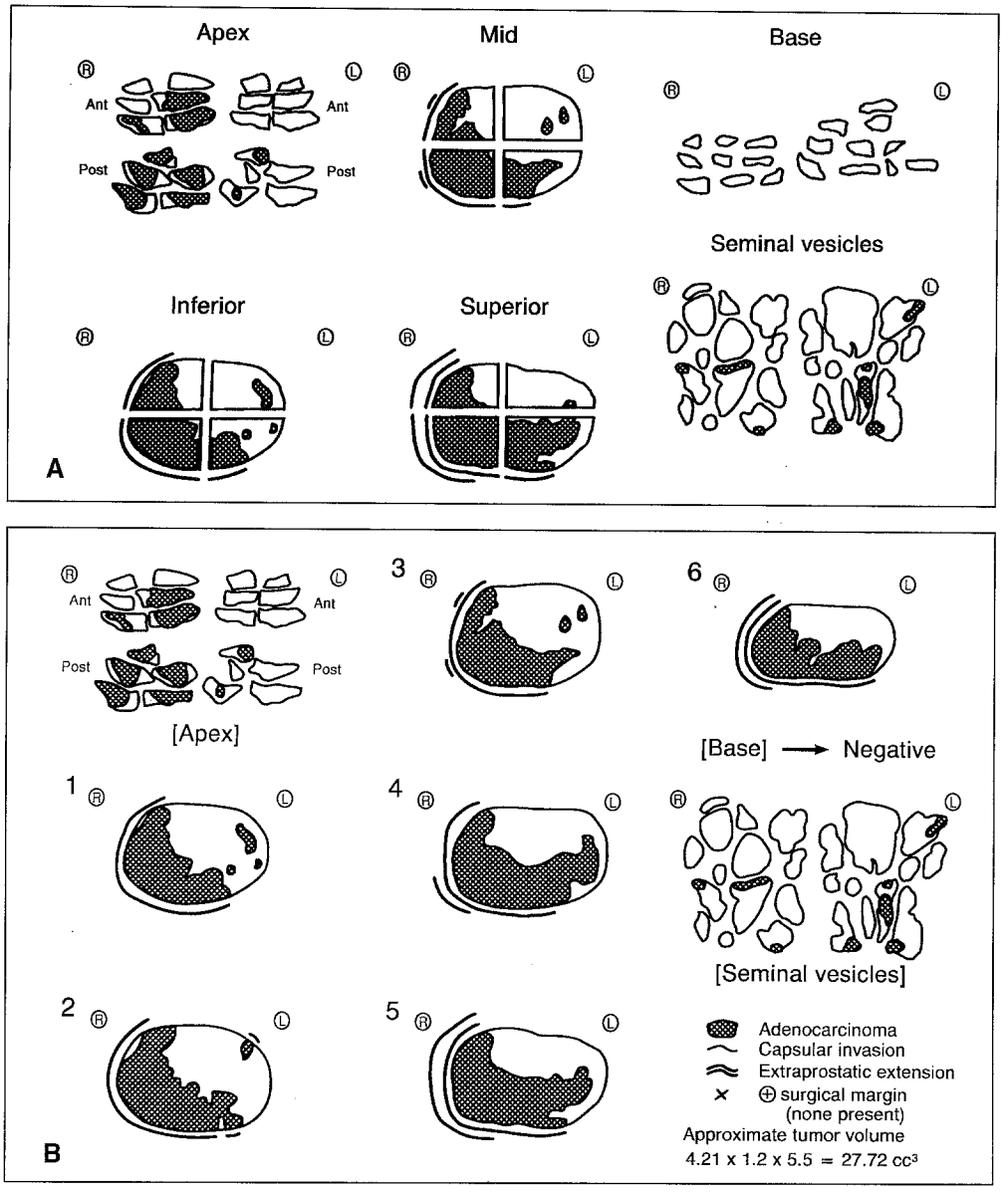

Fig. 1A, B Sample prostate cancer maps used at the Mayo Clinic for radical prostatectomy specimens. **A** Partial sampling; **B** complete sampling with whole-mount sections. [With permission from Bostwick DG, Eble JE (1997) Urologic surgical pathology. Mosby Yearbook, Philadelphia]

completeness of sampling influences the determination of pathologic stage [13, 37, 38, 41, 77]. Haggman and colleagues [37] compared the results of partial sampling (sections of palpable tumor and two random sections of apex and base) with complete sampling, and found a significant increase in positive surgical margins (12% vs 59%, respectively) and pathologic stage with complete sectioning. Others showed that the presence and extent of extraprostatic extension in clinical stage T2 adenocarcinoma (and hence clinical staging error) was directly related to the number of blocks processed [77]. Donahue and Miller [24] noted that 40% of patients had extraprostatic extension of cancer with standard study, compared with 60% with whole mount evaluation. Cohen et al. [21] found that partial sampling with alternate sections missed 15% of cases with extraprostatic extension which were identified by complete sampling. Partial sampling methods are reportedly equivalent to whole-mount sections for determining cancer volume [77], but we question this finding.

Current guidelines for the evaluation of radical prostatectomy specimens emphasize information that should be included in the pathology report, but leave the decision regarding partial or complete sampling to the individual pathologist [41]. Sampling methods for harvesting tissue for research purposes often vary from routine methods, and are beyond the scope of this review [14, 69, 90]. Regardless of which sampling method is employed, the initial handling of the specimen is similar or identical.

Initial handling of the prostatectomy

All methods begin with weighing the specimen when still fresh and measuring it in three dimensions. Weight may be more reproducible than linear dimensions because the resected prostate is an irregular structure [67, 86]. For ultrasonographic measurements, radiologists often describe the shape of the prostate as a prolate ellipsoid (length ×

height × width × 0.532) [47], but this is only a rough estimate that shows considerable variability. The attached seminal vesicles are measured separately.

Subsequent handling of the specimen can be performed when it is fresh or fixed. For fixation, the prostatectomy should be submerged in 5–10 volumes of 10% neutral buffered formalin. Care should be taken not to touch the sides of the container in order to avoid tissue compression and distortion. Some investigators cannulate the prostatic urethra with a tube attached to an aquarium pump that provides a constant gentle stream of formalin during fixation [77]; we find that simple immersion is usually sufficient. The fresh (or fixed) prostate is inked by brief immersion in a small container of india ink or by painting the surface with different colors of ink to allow unequivocal identification of left and right sides; subsequently, the wet specimen is briefly immersed in acetone or Bouin's fixative and air dried or blotted dry. Some pathologists use different colors of ink for the anterior and posterior prostate, apex, and base in order to ensure proper orientation.

Disruption of the attached periprostatic soft tissues by the surgeon or pathologist may cause ink to seep into tissue crevices. This creates the potential for misinterpretation of an inked surface as a true surgical margin (false-positive diagnosis of involved surgical margin). Consequently, it is important to note whether the attached tissue was disrupted and at which sites.

The apex and base are amputated at a thickness of 4–5 mm, and these margins are submitted as 3- to 4-mm-thick conization margins in the vertical parasagittal plane [5]; alternatively, some pathologists prefer 1- to 2-mm-thick shave margins. For conization, the apex usually requires sectioning into quadrants that we designate right anterior apex (RAX), left anterior apex (LAX), right posterior apex (RPX), and left posterior apex (LPX). Similarly, the base is sampled usually in left and right halves as left bladder base (LBB) and right bladder base (RBB). Although some protocols include circular "doughnut" sections of the urethra at the apex and base, we do not routinely submit these; unlike some cancers, prostate cancer rarely demonstrates pagetoid spread or submucosal spread without involving large areas of adjacent tissue.

The remaining specimen is serially sectioned at 3- to 5-mm thickness by knife to create transverse sections perpendicular to the long axis of the prostate from its apex to the tip of the seminal vesicles. Some investigators employ commercial meat slicers [5] or prostate slicing devices [77], but these are not widely used and are probably unnecessary [67]. Partial and complete sampling differ by the amount of prostate tissue submitted after this point. According to a 1994 survey, 88% of pathologists prefer partial sampling, probably due to time and cost considerations (Table 1) [86].

Table 1 Examination of radical prostatectomy specimens: practice survey by the American Society of Clinical Pathologists, 1994 [86]. *SV* seminal vesicles, *EPE* extraprostatic extension, *PIN* prostatic intraepithelial neoplasia

Practice characteristic	Respondents answering yes (%)
Processing and sampling	
Record weight	95
Record measurements	97
Cut specimen before fixing	40
Fix specimen overnight	53
Ink margins	86
Use different colors of ink	29
Section prostate coronally	82
Label each section by site	88
Describe size of lesions	97
Complete sectioning	12
Embed 1–4 blocks	5
Embed 5–8 blocks	19
Embed 9–12 blocks	29
Embed >12 blocks	34
Embed entire apex	64
Embed entire bladder base	62
Submit all lymph nodes	99
Reporting	
Assign Gleason score	73
Use other grading system	35
Assign nuclear grade	21
Report involvement of apex	83
Report involvement of SV	99
Report EPE	100
Report PIN	50
Report distance from margin[a]	61
Report vascular invasion	89
Report perineural invasion	90
Report multifocal cancer	90
Report non-neoplastic changes	81

[a] Distance of cancer from surgical margin of resection

Macroscopic identification of cancer

Macroscopic identification of prostatic adenocarcinoma may be difficult or impossible in some cases, and definitive diagnosis requires microscopic examination. Grossly apparent tumor foci are usually at least 5 mm in greatest dimension, and appear yellow-white with a firm consistency due to stromal desmoplasia. Some cancers appear as yellow granular masses which contrast sharply with the normal spongy prostatic parenchyma. Gross mimics of cancer include tuberculosis, granulomatous prostatitis, and acute and chronic prostatitis. One study noted that 92% of cases of clinically organ-confined biopsy-proven cancer were grossly identifiable in prostatectomy specimens [38], but most investigators, including us, find a much lower incidence.

Partial (limited) sampling

Partial sampling results in histopathologic submission of a fraction of the prostate, usually less than 50%, including all grossly apparent cancer. Given the limitations of gross identification of cancer, partial sampling protocols sometimes require submission of additional tissue in order to identify cancer (see Vanishing cancer phenomenon, below). The partial sampling protocol used at Mayo Clinic since 1968 is equivalent to that recently endorsed by consensus at the American Cancer Society meeting

[70]; this protocol fulfills all of the requirements of the CAP [41] and ADASP [4].

Complete (unlimited or totally embedded) sampling, including whole-mount sections

Complete sampling results in the entire prostate being submitted for histopathologic examination. However, even this method is subject to sampling error, since generation of a single 5-μm-thick section from each 3-mm tissue block still results in microscopic review of only 0.17% of all embedded tissue; theoretically, 15,600 slides would be required per case to review the entire specimen [42]. Two alternative methods exist for complete sampling: (1) routine sections and (2) whole-mount sections.

1. Complete sampling with routine sections means submitting the entire prostate after cutting tissue samples sufficiently small to fit into routine cassettes, obviating the need for special handling required of whole-mount sections. Sections are obtained by slicing each transverse section into four quadrants; larger prostates may require six or even eight sections to submit transverse sections, whereas smaller prostates may only require two sections. This method of complete sampling yields a mean of 26 routine slides per case [77]. In rare cases with very small prostates (fewer than 1 in 300 cases in our experience), intact transverse sections can fit into a cassette, thereby allowing routine sections of whole mounts.

2. Complete sampling with whole-mount sections involves submitting the entire prostate as intact transverse serial sections without subdivision. This is the method preferred by some investigators, but requires special handling of tissue samples that are larger than routine sections. This method may be optimal for teaching and research purposes, but is infrequently used in routine practice.

Diagnostic reporting of pathologic findings in radical prostatectomy specimens

Examination of radical prostatectomy specimens should include the information in Table 2.

Table 2 Examination of radical prostatectomy specimens: information to be included in the surgical pathology report

Histopathologic type of carcinoma
Histologic grade (Gleason score)
Location and size of cancer(s)
Extraprostatic extension: amount and location
Seminal vesicle involvement
Surgical margin status
Apex
Base
Neurovascular bundles
Posterior prostate
Anterior prostate
Lymph nodes
Sites, number, and status
pTNM

Histopathologic type

More than 95% of cases of prostatic carcinoma are acinar adenocarcinoma; in recent years, a number of new and unusual histopathologic variants of prostatic carcinoma have been identified. The biologic behavior of many of these variants may differ from typical adenocarcinoma, and proper clinical management depends on accurate diagnosis and separation from tumors arising in other sites. Unusual tumors arising in the prostate also raise questions of histogenesis. These variants represent the spectrum of changes which can occur in adenocarcinoma, and may not represent separate clinicopathologic entities, although data remain limited for many. The diagnostic features of different histopathologic types of carcinoma are beyond the scope of this review.

Histologic grade

Grade is one of the strongest and most useful predictors of pathologic stage, according to numerous univariate and multivariate studies. This predictive ability applies to virtually every measure of pathologic stage, including extraprostatic extension, seminal vesicle invasion, lymph node metastases, and bone metastases. Some investigators claim that a Gleason score of 8 or higher is strongly predictive of lymph node metastases and suggest dispensing with the staging of lymph node dissections in these cases. Despite the optimism for grading to predict stage, the predictive value is not high enough to permit its application for individual patients, particularly in those with moderately differentiated adenocarcinoma.

Location of cancer

The site of origin appears to be a significant prognostic factor. Adenocarcinoma arising in the transition zone of the prostate appears to be less aggressive than typical acinar adenocarcinoma arising in the peripheral zone (Table 3) (Fig. 2). The majority of cases of transition zone adenocarcinoma arise adjacent to nodules of hyperplasia, with one-third actually originating within nodules. These adenocarcinomas are better differentiated than those in the peripheral zone, accounting for the majority of Gleason primary grade 1 and 2 tumors. The volume of low-grade tumors tends to be smaller than that of those arising in the peripheral zone, although frequent exceptions are seen. The confinement of transition zone adenocarcinoma to its anatomic site of origin may account in part for the favorable prognosis of clinical stage T1 tumors. The transition zone boundary may act as a relative barrier to tumor extension, as malignant acini appear to fre-

Table 3 Prostatic carcinoma: Comparison based on anatomic site of origin (central zone cancers, 5–10% of total, were excluded). *BPH* Benign prostatic hyperplasia, *TURP* transurethral resection of the prostate, *AAH* atypical adenomatous hyperplasia, *PIN* prostatic intraepithelial neoplasia. (From [11] with permission)

	Transition zone cancer	Peripheral zone cancer
Incidence		
Stage T1a	75%	–
Stage T1b	79%	–
All stage T1	78%	–
All stages	24%	70%
Origin		
In or near BPH	Yes	No
Near apex Yes	Yes	
Detection rate by TURP	78%	–
Pathologic features		
Tumor volume	Usually small	Small to large
Tumor pattern	Alveolar-medullary	Tubular-scirrhous
Tumor grade (Gleason)	Usually 1 or 2	Usually 2, 3, or 4
Clear cell pattern	Most cases	Rare
Stromal fibrosis	Uncommon	Common
Associated putative		
Premalignant changes	AAH or PIN	PIN
Aneuploidy	6%	31%
Clinical behavior		
EPE	11%	44%
Site of EPE	Anterolateral and apical	Lateral
Average tumor volume with EPE	4.98 cc	3.86 cc
Risk of seminal vesicle invasion	0%	19%
Risk of lymph node metastases	Low	High

quently fan out along this boundary before invasion into the peripheral and central zones.

Cancer volume

Cancer volume has been proposed as an adjunct to digital rectal examination-based staging of prostatic adenocarcinoma because of its powerful prognostic ability [12, 36, 42, 43, 49]; this approach may be feasible in the future with improvements in imaging techniques such as (TRUS). A cancer volume-based prognostic index has been proposed as an adjunct for staging based on the evidence linking adenocarcinoma volume with patterns of progression (extraprostatic extension, seminal vesicle invasion, and lymph node metastases) [36]. For organ-confined cancer, three main categories were recognized: V1, cancer less than 1 cc; V2a, cancer 1–5 cc; V2b, tumor more than 5 cc. The goal of the prognostic index is to achieve greater precision in predicting outcome for individual patients [12].

Several studies have found a positive correlation between cancer volume and serum PSA concentration, suggesting that PSA can serve as a surrogate of volume [9, 62, 81]. However, the additive and confounding effect of nodular hyperplasia limits the usefulness of PSA in estimating preoperative cancer size and extent [62]. As adenocarcinoma enlarges, it usually becomes less differentiated and may lose some of its capacity for PSA production. PSA concentration increases with increasing Gleason grade, but, when tumor volume is held constant, PSA decreases (PSA concentration declines as Gleason grade increased) [62]. This finding is due to less production of PSA per cell in poorly differentiated tumors [9]. No accepted standard exists for reporting cancer volume in prostatectomy specimens; the easiest and most practical approach is an estimate of the percentage of cancer in the entire specimen. After accounting for pathologic stage, tumor volume may not provide significant additional prognostic information, but this observation has not been confirmed [28].

Cancer stage

Extraprostatic extension

The term "extraprostatic extension" (EPE) was accepted at a recent consensus conference to replace other terms, including capsular invasion, capsular penetration, and capsular perforation [70]. To define extraprostatic extension, it is first necessary to understand the anatomy of the capsule of the prostate.

Anatomy of the prostatic capsule. The capsule is an extension of the prostatic parenchyma, consisting of transversely oriented fibers of compressed smooth muscle and collagen, with some variability in the relative amounts in different areas (Fig. 3). The mean thickness of the capsule varies from 0.5 to 2 mm, and the mean percentage of smooth muscle fiber is 31%, similar to that within the prostate [72]. At the outer edge of the apex and bladder base, the acinar elements are often sparse, and the capsule is thin and ill-defined, precluding reliable evaluation. Anteriorly, the smooth muscle and fibrous stroma of the prostate interdigitate with the smooth muscle and skeletal muscle of the pelvic wall; although this constitutes a useful surgical plane of dissection, it does not

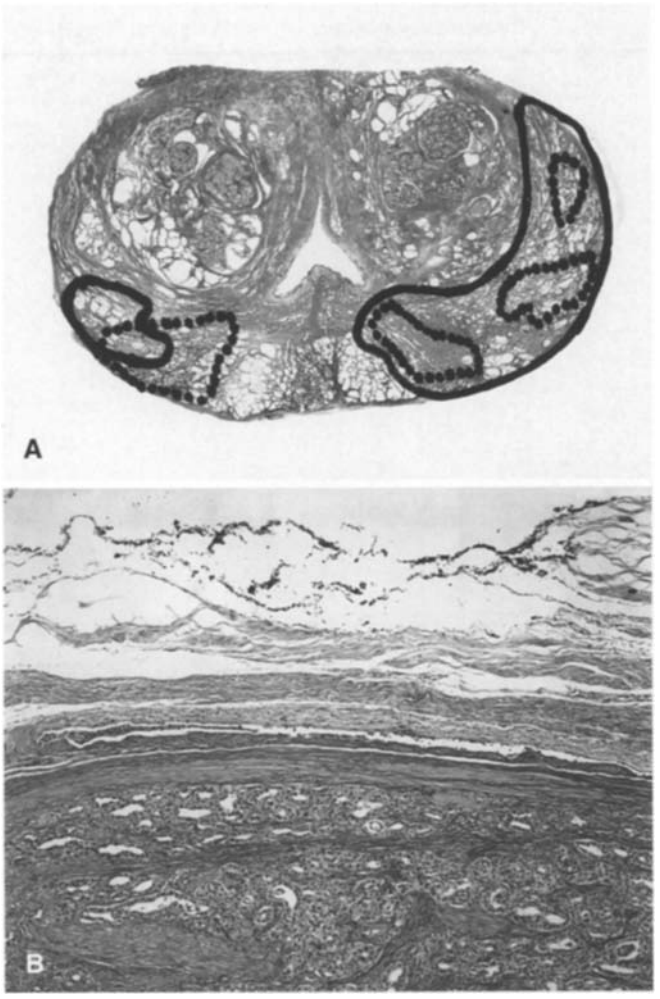

Fig. 2A, B Organ-confined prostate cancer. **A** In this whole-mount section, there is extensive bilateral cancer in the peripheral zone (outlined with *solid lines*) accompanied by high-grade prostatic intraepithelial neoplasia (outlined with *dotted lines*). **B** The cancer was confined to the prostate (stage T2c), but was present within the compressed fibromuscular stroma of the capsule

provide the sharp line of microscopic demarcation usually expected from a capsule (Fig. 3). As a result, the prostatic capsule is not regarded as a well-defined anatomic structure with constant features [5, 72]. We use the term "capsule" to refer to the surface or edge of the fibromuscular stroma of the prostate, a stable and reproducible anatomic landmark, and consider the capsule as an extension of the parenchymal stroma which is compressed. The capsule at the apex and bladder base is difficult or impossible to identify (Fig. 3). Consequently, it is not possible to reliably and consistently determine the presence of extraprostatic extension of cancer at these sites, and we limit our evaluation to surgical margin status.

Definition of EPE. Extension of cancer beyond the edge or capsule of the prostate is considered EPE. There are three criteria for EPE, depending on the site and composition of the extraprostatic tissue: (1) Cancer in adipose tissue; (2) cancer in perineural spaces of the neurovascular bundles; (3) cancer in anterior muscle (Fig. 4).

1. EPE is easily diagnosed when malignant acini are in contact with adipose tissue. There is no adipose tissue within the prostate, so this constitutes unequivocal EPE; it is useful in biopsy specimens and in poorly oriented sections from a prostatectomy. Adipose tissue is usually present adjacent to the lateral, posterolateral, and posterior surfaces of the prostate. Difficulty is occasionally encountered when cancer has provoked a dense desmoplastic response in the extraprostatic tissue, particularly in cases treated by androgen deprivation therapy. We resolve this uncommon problem by scanning the smooth rounded external contour of the prostate to determine whether the focus of concern has breached this contour and is enmeshed within an extraprostatic nodule of fibrous tissue.

2. The neurovascular bundles act as a path of least resistance for cancer to escape from the prostate. These bundles are clustered in the posterolateral corners of the prostate (at about 5 o'clock and 7 o'clock in transverse sections) and are best appreciated at scanning magnification in whole-mount sections of non-nerve-sparing radical prostatectomies. Although cancer may not be in contact with adipose tissue, involvement of perineural spaces of the neurovascular bundles represents EPE. Perineural invasion alone does not constitute EPE, and there are often large nerve twigs within the prostate that may be mistaken for neurovascular bundles. Accordingly, it is best to diagnose cancer within the neurovascular bundles (and thus EPE) only when the malignant acini are present beyond the reasonable contour (edge) of the prostate.

3. Anterior muscle is a very uncommon site of EPE only observed with large bulky cancers within the transition zone. The anterior fibromuscular stroma of the prostate interdigitates with external smooth muscle and skeletal muscle adjacent to the pubic bone, and there is little or no adipose tissue in this area to define the extraprostatic tissue; consequently, it may be difficult to identify EPE. We diagnose EPE at this site only when there is unequivocal evidence of cancer extending beyond the reasonable confines of the prostatic edge into skeletal muscle and beyond the rounded interface between the fibromuscular stroma and skeletal muscle.

Frequency of EPE. In patients treated by radical prostatectomy for clinically localized cancer, the frequency of EPE (stage T3) is 23% [85], 41% [10], 43% [60], 45% [50], and 52% [92]. There is a strong association of tumor volume and extraprostatic extension, including seminal vesicle invasion [13]. An autopsy study showed EPE in 2% of cancers less than 0.46 cc in volume, compared with 52% of larger cancers [49].

Clinical significance of EPE. Patients with EPE have a worse prognosis than those with organ-confined cancer [30, 50]. Cancer-specific survival 10 years after radical prostatectomy in patients with pT3 cancer is 54% [76], 62% [83], 70% [63], or 80% [46]; at 15 years, the sur-

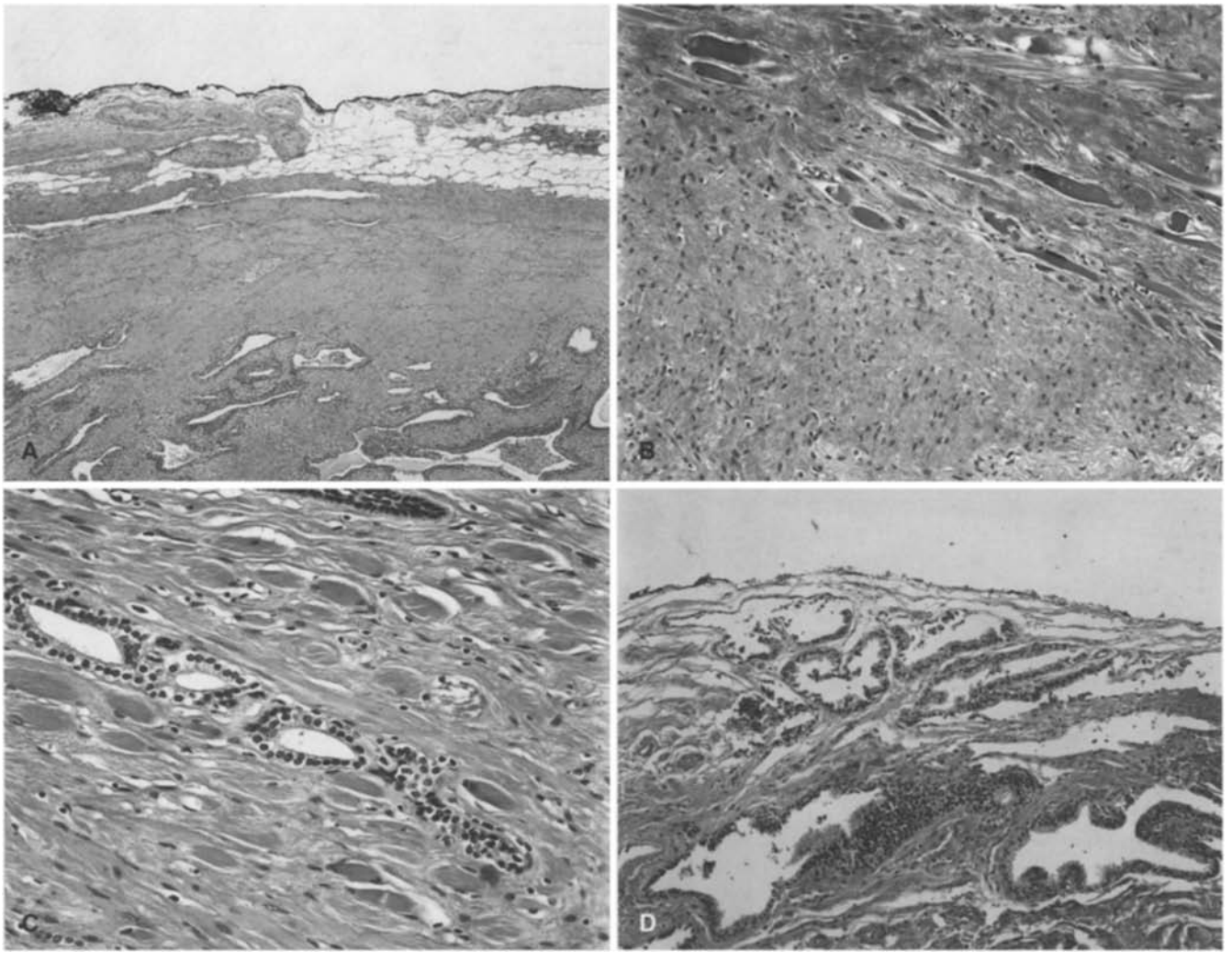

Fig. 3A–D Prostatic capsule (or external border) at different sites. **A** Lateral prostate with abundant fibromuscular stroma at the periphery. **B** Anterior prostate, with interdigitation of smooth muscle and skeletal muscle. **C** Anterior prostate skeletal muscle with benign prostatic acini. **D** External edge of the apex following conization; the benign acini extend to the edge of the sections with no apparent fibromuscular stroma, precluding assessment of the capsule at this site

vival rate is 69% [46]. Cancer-specific survival 10 years after definitive radiation therapy in patients with clinical stage T3 is 44% [74] or 59% [75]; at 15 years, the rate is 36% [74], 33% [6], or 39% [75]. Cancer-specific survival after expectant management (watchful waiting or observation) in patients with clinical stage T3 cancer is 70% [2]. Direct comparison of these studies may be inaccurate due to significant differences in methods of staging and patient selection and evaluation; further, no prospective comparative study has been performed to settle the debate regarding optimum treatment.

Most patients with EPE also have positive surgical margins, with a frequency of 57% [28] to 81% [92]. The combination of EPE and positive margins predicts a worse prognosis than EPE alone [28, 63].

Recent studies have questioned the value of substaging of stage T3 adenocarcinoma in patients treated by radiation therapy. In two studies, there were no differences in relapse rates for those with clinical stage T3a and T3c adenocarcinoma [23, 91]. Conversely, substaging is useful for prediction of outcome in patients treated by radical prostatectomy [28]. Consequently, substaging based on digital rectal examination alone (used in radiation therapy studies) does not distinguish meaningful prognostic substages among patients with T3 cancer [23].

Surgical margins

Definition of positive surgical margins. Positive surgical margins are defined as cancer cells touching the inked surface of the prostate (Fig. 5). Care must be taken to avoid interpreting ink within tissue crevices created by postoperative handling of the specimen as true margins; careful handling of the specimen and awareness of this potential problem is usually sufficient for avoidance.

Surgical margins are not included in pathologic staging. However, many studies have erroneously equated positive margins and EPE, particularly in cases in which

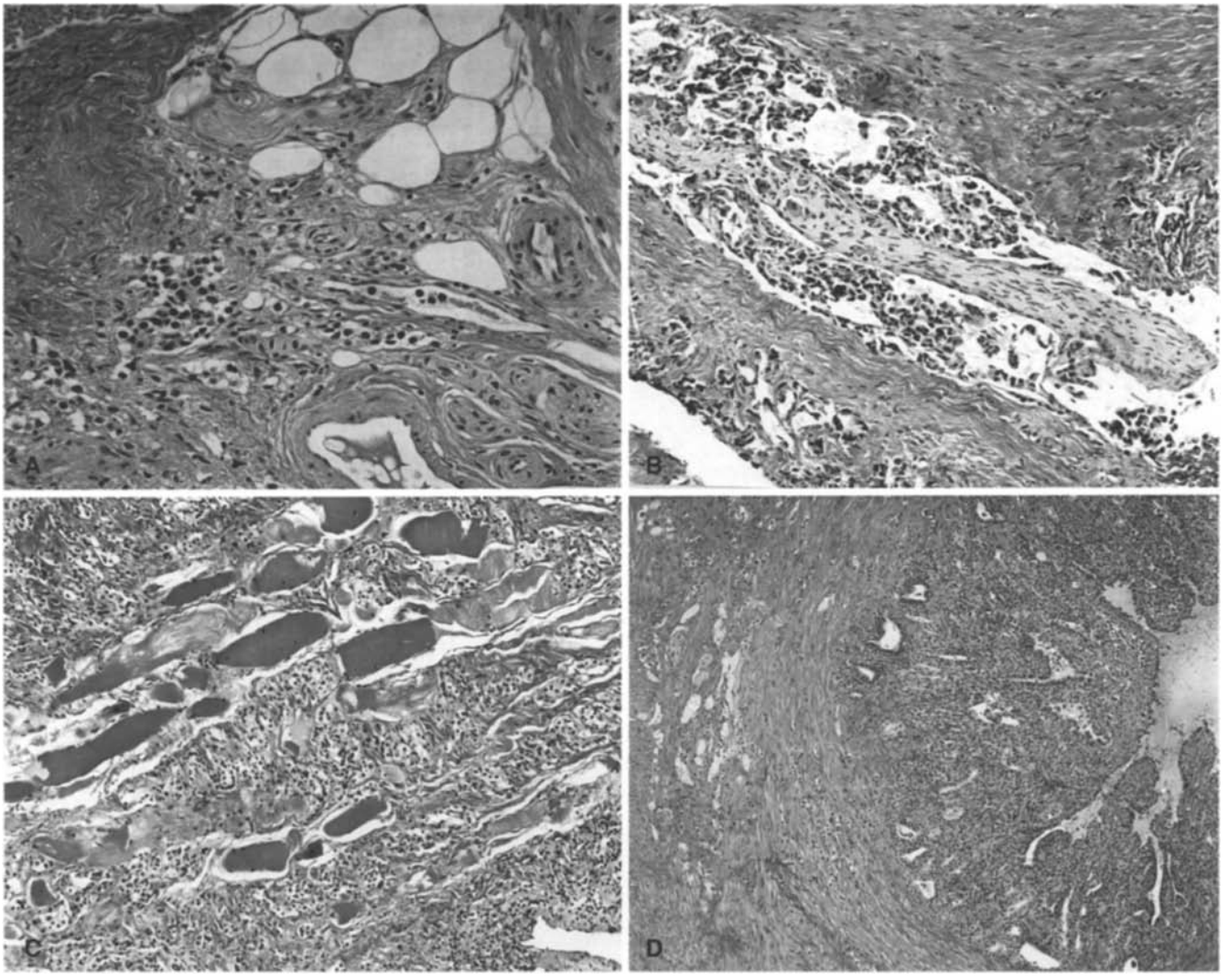

Fig. 4A–D Extraprostatic extension. **A** Cancer in adipose tissue; **B** cancer in perineural spaces of the neurovascular bundles; **C** cancer in the anterior muscle above the urethra; **D** cancer in the wall of the seminal vesicles. All of these cases show histopathologic changes of androgen deprivation therapy (see text)

the surgeon has cut into the prostate and intraprostatic cancer. The recent Mayo Clinic consensus conference emphasized this distinction and called upon investigators to carefully describe surgical margin status separately from EPE [70].

Confusion may persist in interpretation of prostatectomies in which there is focally no extraprostatic tissue for examination. At such sites, the surgical resection margin corresponds exactly with the outer surface of the prostate or cuts into the prostatic capsule or parenchyma. If the surgical margin at this site contains cancer, does this represent EPE? Participants at the recent Mayo Clinic consensus conference agreed these foci should be considered T2+ rather than T3 (the plus sign is a "telescopic ramification" of the TNM staging system which is added to emphasize that the available evidence indicates T2 cancer but there may be cancer outside of the prostate which cannot be evaluated in the specimen submitted) [70] (Fig. 6).

Frequency of positive surgical margins. The frequency of positive surgical margins has steadily declined in the past decade, probably owing to refinements in surgical technique and earlier detection of cancer at smaller volume (Table 4). Ohori et al. [60] found positive surgical margins in 24% of whole-mount radical prostatectomies obtained at their hospital prior to 1987, usually in the posteriolateral region near the neurovascular bundles. By approaching the neurovasular bundles laterally and widely dissecting the apex of the prostate, they observed a positive surgical margin rate of only 8% by 1993, despite similar volume grade and pathologic stage of cancer. Earlier reports noted a frequency of positive surgical margins of 33% [82], 46% [44], and 57% [18], with no difference in specimens from nerve-sparing and non-nerve-sparing surgery [44]. Positive surgical margins are strongly correlated with cancer volume [10, 60, 63, 65, 82, 87, 88] and number of needle biopsies containing cancer [1, 78]. Most positive surgical margins in prostates with cancer smaller than 4 cc are caused by surgical

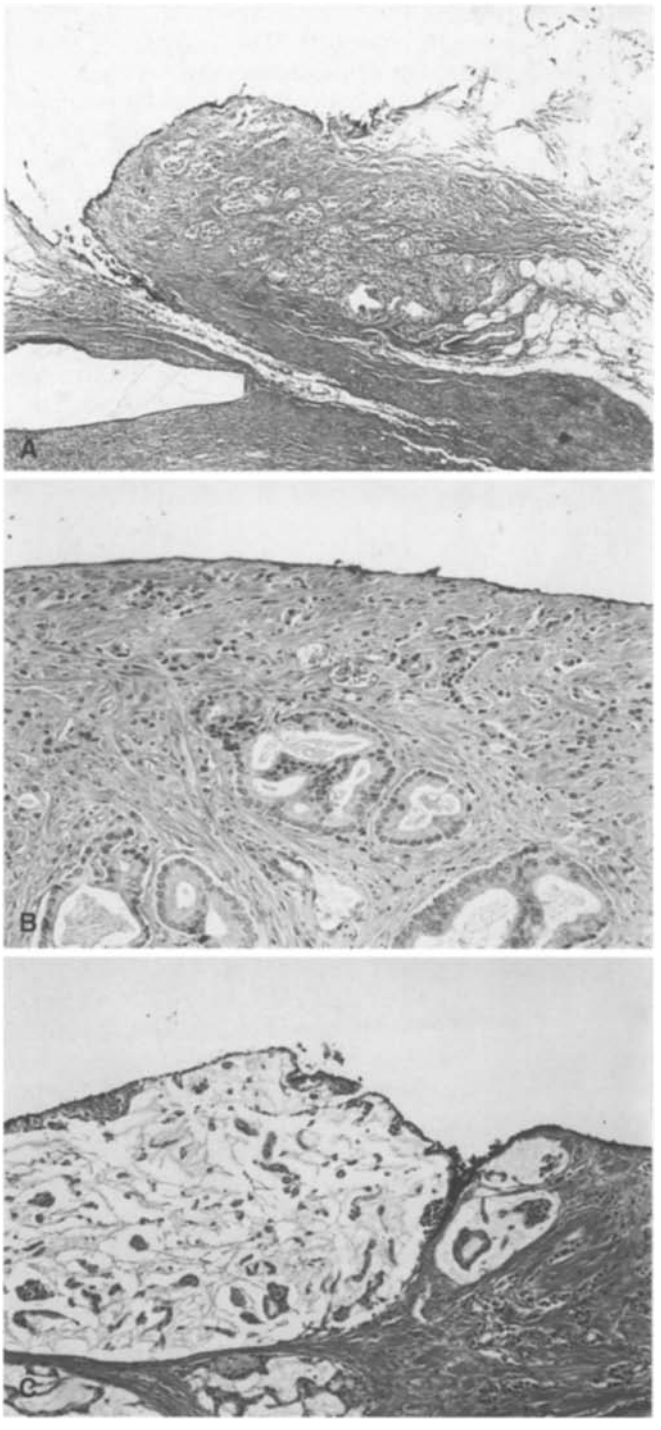

Fig. 5A–C Positive surgical margins. **A** Margin involvement and extraprostatic extension of cancer; note the presence of cancer in the extraprostatic soft tissue with extension to the inked surface (stage T3 cancer with positive surgical margins). **B** Positive surgical margins, with surgical incision into the prostatic parenchyma (stage T2+). **C** Mucinous carcinoma showing positive surgical margins with surgical incision into the prostatic parenchyma (stage T2+)

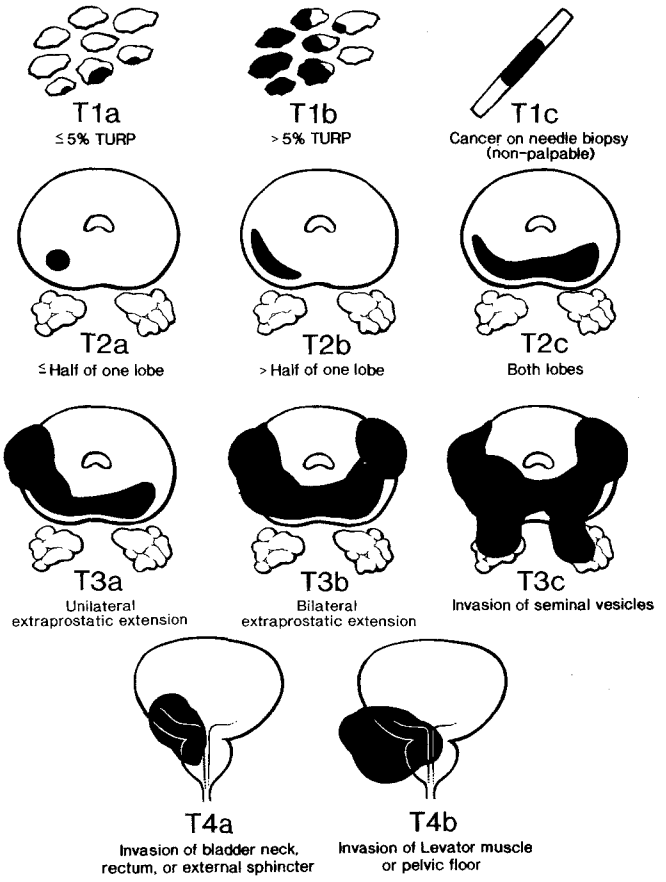

Fig. 6 Prostate cancer staging using the TNM system, 1992 revision, for the T (tumor) category. *Black* indicates extent of cancer. [With permission from Bostwick DG, Eble JE (1997) Urologic surgical pathology. Mosby Yearbook, Philadelphia

Table 4 Incidence of positive surgical margins in totally embedded radical retropubic prostatectomies according to pathologic stage

Reference/stage	No. of cases with positive margins/total no. of cases
[28]	
Less than pT3c (stages not provided)	100/185 (54%)
[65]	
pT3a+b	17/26 (65%)
pT3c	14/19 (74%)
All pT3	31/45 (69%)
[60]	
pT1 and pT2	23/247 (9%)
pT3a+b	33/150 (22%)

incision [87]. Positive margins are located at the apex (48%), rectal and lateral surfaces (24%), bladder neck (16%), and superior pedicles (10%) [82] (Table 5).

Clinical significance of positive surgical margins. The significance of positive surgical margins in patients treated by prostatectomy is uncertain (Table 6). Paulson et al.

[63] noted that patients with organ-confined cancer and positive surgical margins have a 60% possiblity of death from cancer, significantly greater than 30% possibility in patients without positive surgical margins. Epstein et al. [28, 29] found that surgical margin status was the only predictor of cancer progression other than Gleason score in patients without seminal vesicle invasion or lymph node metastases. Conversely, Ohori and colleagues [59, 60] found that positive surgical margins had no effect on prognosis. Currently, there is no consensus on the utility of postoperative adjuvant therapy in patients with positive surgical margins, probably due to the uncertainty regarding the clinical significance of this finding [52].

Lymph nodes

Staging pelvic lymph node biopsy is usually performed prior to prostatectomy, and most urologists discontinue surgery if metastases are identified. Lymph node dissection may be an open or laparoscopic procedure. Radical perineal prostatectomy and lymph node dissection are performed as separate procedures because the surgical approaches are different, whereas radical retropubic prostatectomy and lymphadenectomy are often performed as a single procedure. The pathologist should carefully evaluate the fibroadipose tissue obtained by lymphadenectomy and submit all lymph nodes for pathologic examination. It may not be necessary to submit obvious adipose tissue, although it is our policy to do so. Sampling error by frozen section accounts for a false-negative rate for lymph node metastases of 2–3% in our experience (D. Bostwick, unpublished observations). Surgeons at Wayne State University and some other centers do not undertake frozen section evaluation of pelvic lymph nodes that are not palpably enlarged due to the potential for histopathologic sampling error (D. Grignon, personal communication). The surgical pathology report should include the number and site of all submitted lymph nodes, as well as sites of involvement and the size of cancer foci.

There is a low incidence of micrometastatic occult prostatic carcinoma in pelvic lymph nodes which cannot be detected by routine hematoxylin and eosin staining [56]. Using immunohistochemical studies directed against cytokeratin, Moul et al. [56] found lymph node micrometastases in 3% of patients with clinically localized prostatic adenocarcinoma, similar to the results of Gomella et al. [35].

Table 5 Frequency of positive surgical margins by location in prostate cancer treated by radical prostatectomy[a]

Location	Reference	
	[82][b]	[1]
Apex	21%	23%
Superior pedicle	4%	
Lateral surface	4%	
Rectal surface	7%	
"Mid-portion"	22%	
Bladder neck	7%	6%
Anterior fibromuscular stroma	1%	
Total no. of cases with positive surgical margins/total no. of cases	63/189 (33%)	37/101 (37%)

[a] Frequencies are percentage of positive surgical margins by location among all cases; consequently, the cumulative frequencies do not add up to 100% because more than one margin is often involved.
[b] Used totally embedded specimens

TNM staging

Current TNM staging of early prostatic adenocarcinoma separates patients into two groups: those with palpable tumors and those with nonpalpable tumors [13, 53, 79]. This reliance on palpability of the tumor as determined by digital rectal examination is unique among organ staging systems and is hampered by the low sensitivity, low specificity, and low positive predictive value of digital rectal examination [33]. Recent refinements in staging have led to the introduction of a new stage of nonpalpable adenocarcinoma detected by elevated serum PSA level, referred to as stage T1c; however, this new stage was introduced without supportive clinical evidence, and recent studies show that it does not identify a distinct group of patients [29, 32, 58, 73]. The question remains whether those patients who will benefit from early detec-

Table 6 Correlation of positive surgical margins and progression in totally embedded radical prostatectomies

Reference/stage	Mean duration of follow-up in Months (range)	No. progressing/total no. of cases
[65]		
pT1c and T2	24 (6–48)	6/7 (86%)
pT3a+b	"	14/26 (54%)
pT3c	"	18/19 (95%)
All pT3	"	32/45 (71%)
[60]		
pT1 and pT2	39 (1–126)	0/23 (0%)
pT3a+b	"	14/33 (42%)
[28]		
Less than pT3c (stages not provided)	Minimum of 5 years (range not provided)	40/85 (47%)

tion and intervention can be separated from those who will not.

The 1992 revision of the TNM system is the international standard for prostatic adenocarcinoma staging [13, 16, 53, 79]. The Commission on Cancer of the American College of Surgeons has required it for accreditation since 1995 [25]. Efforts directed toward standardization of staging, including guidelines for pathologic evaluation of specimens, allow comparison of results from different centers [41]. The 1992 revision of the TNM system included four significant changes from the 1987 version [79]. First, a new category (T1c) was introduced to recognize nonpalpable nonvisible adenocarcinomas identified by random biopsy following detection of elevated serum PSA level (see discussion below). Second, palpable adenocarcinoma confined to the prostate (T2) was subdivided into three groups rather than two based on relative involvement of the prostate (involvement of half a lobe or less, more than half a lobe but not both lobes, and both lobes) instead of absolute tumor size by digital rectal examination. Third, adenocarcinoma with local extraprostatic extension (T3) was subdivided into three groups rather than two based on laterality and seminal vesicle invasion (unilateral, bilateral, and seminal vesicle invasion) (Fig. 6). Finally, the concept of "telescopic ramification" was introduced to allow the introduction of additional prognostic factors without altering existing categories.

Limitations of the TNM system.

The TNM staging system is limited by a number of factors, including: (1) clinical understaging with transurethral resection; (2) clinical understaging with digital rectal examination; (3) limited ability of imaging studies to evaluate the presence and extent of prostatic adenocarcinoma; (4) heterogeneity of stage T1c adenocarcinoma; (5) variability in pathologic staging of stage T1 adenocarcinoma; and (6) variability in examination of radical prostatectomy specimens.

Clinical understaging with digital rectal examination

Current staging of palpable organ-confined adenocarcinoma relies on digital rectal examination to separate unilateral from bilateral tumors or small from large tumors (less than half of one lobe, between one half and one lobe, and more than one lobe). However, there is a high level of inaccuracy and interobserver variability of digital rectal examination in determining tumor size and pathologic stage. Prostatic adenocarcinoma staging is unique among organ staging systems in relying on the presence or absence of palpability and in substaging T2 adenocarcinomas based upon the proportion of organ induration identified.

Bostwick [10] identified clinical understaging in 59% and clinical overstaging in 5% of cases in a series of 311 serially sectioned radical retropubic prostatectomies removed for clinically localized prostatic adenocarcinoma (excluding stages T1a, T1b, and T1c; note that there is no equivalent pathologic stage for clinical stage T1c, so this group will always be re-staged pathologically). These results are similar to those reported by others who have also undertaken careful pathologic sectioning of prostatectomy specimens. This substantial error rate must be accounted for when evaluating recurrence and survival rates, especially when comparing studies of clinically staged patients followed with active surveillance (watchful waiting) and surgically (pathologically) staged patients. There was considerable overlap in the volume of adenocarcinoma in clinical stages T2a + b and T2c, with tumors measuring up to 41 and 43 cc, respectively. These data indicate that digital rectal examination is inaccurate for preoperative assessment of tumor volume.

Limitations of imaging studies

Imaging studies to assess tumor volume and extent would be invaluable in clinical staging. However, the current accuracy of such methods limits the utility of these methods. The rate of correct identification of EPE is 63% with TRUS [68], 71% with body coil magnetic resonance imaging (MRI) [68], and 83% with endorectal and surface coil MRI [64].

Pathology of PSA-detected adenocarcinoma (clinical stage T1c)

Prior to widespread clinical use of PSA, most organ-confined adenocarcinoma was discovered by digital rectal examination (clinical stage T2) or at the time of transurethral resection (clinical stage T1). Routine use of serum PSA increases the detection rate of prostatic adenocarcinoma and discovers some adenocarcinomas which cannot be detected by digital rectal examination [15, 19, 22, 45, 51]. There was a substantial increase in the number of adenocarcinomas detected by means of PSA at Mayo Clinic between 1988 (14 cases) and 1991 (118 cases) [58].

There is no pathologic stage equivalent for clinical stage T1c, and such tumors are invariably upstaged at surgery, usually to pathologic stage T2 or T3 (Table 7). Oesterling et al. [58] found that clinical stage T1c adenocarcinoma and clinical stage T2a + b adenocarcinoma had similar maximum tumor diameters, frequencies of multifocality, tumor grades, DNA content results, pathologic stages, and tumor locations; interestingly, they had different serum PSA values, tumor volumes, positive surgical margins, and prostate gland sizes, with the T1c tumors having higher values for each feature. These findings indicate that PSA detects adenocarcinoma which is clinically important and potentially curable. Also, PSA-detected tumors which are visible on TRUS have similar pathologic features to those which are not visible [32].

Table 7 Staging of prostatic adenocarcinoma

	American	TNM[b, c]
Non-palpable cancer		
≤5% of TURP tissue[a]	A1	T1a
>5% of TURP tissue[a]	A2	T1b
Cancer detected by biopsy (e.g. elevated PSA)	BO	T1c
Palpable or visible cancer clinically confined within the prostate		
≤Half of one side	B1	T2a
>Half of one side, but not both sides	B1	T2b
Both sides	B2	T2c
Cancer with local extra-prostatic extension		
Unilateral	C1	T3a
Bilateral	C1	T3b
Seminal vesicle invasion	C2	T3c
Invasion of bladder neck, rectum, or external sphincter	C2	T4a
Invasion of levator muscle or pelvic wall	C2	T4b
Metastatic cancer		
Single regional lymph node, ≤2 cm in greatest dimension	D1	N1[d]
Single regional lymph node, 2–5 cm, or multiple regional lymph nodes ≤5 cm	D1	N2
Single regional lymph node, >5 cm	D1	N3
Distant metastasis	D2	M1[e]
Non-regional lymph node(s)	D2	M1a
Bone(s)	D2	M1b
Other sites	D2	M1c

Stage 0	T1a	N0	M0	G1
Stage I	T1a	N0	M0	G2,3,4
	T1b	N0	M0	Any G
	T1c	N0	M0	Any G
	T1	N0	M0	Any G
Stage II	T2	N0	M0	Any G
Stage III	T3	N0	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1,2,3	M0	Any G
	Any T	Any M	M1	Any G

[a] Different definitions exist for substaging T1a and T1b cancers
[b] No or Nx Mo for T1-T4
[c] Stage groupings for TNM staging system (G=grade on 1–4 scale)
[d] Nx: regional lymph nodes are not assessable
[e] Mx: distant metastasis is not assessable

Further long-term follow-up of PSA-detected prostatic adenocarcinoma is necessary to establish the prognosis of these tumors and determine whether they warrant a separate staging category.

Problems with TNM staging (1992 revision) of radical prostatectomy specimens

Three practical problems have been described for pathologic staging using the TNM system in radical prostatectomy specimens. First, separation of substages T2a (less than half of one lobe) and T2b (more than half of one lobe) is difficult, particularly in specimens that are partially sampled rather than whole-mounted; this problem is resolved by reporting such cases as T2a + b, an approach which necessarily compresses data. Second, the pathologist rarely if ever has access to clinical information pertaining to distant metastases at the time of histologic evaluation of the prostatectomy specimen, and thus cannot accurately report the "M" of TNM; this problem is resolved by reporting all cases as "Mx" with a brief qualification which refers to the clinical record. The third problem is pathologic "upstaging" of adenocarcinoma which usually occurs with prostatectomy following transurethral resection; as noted above, transurethral resection-detected adenocarcinomas are T1a and T1b, yet additional adenocarcinoma identified on prostatectomy frequently results in upstaging to T2 and T3. This problem is resolved by reporting both TNM stages (transurethral resection and prostatectomy) with a brief note describing this issue; alternatively, it may be better to exclude the T1 category from pathologic staging of radical prostatectomy specimens.

Perineural invasion

Perineural invasion is common in adenocarcinoma, and may be the only evidence of malignancy in biopsy specimens. This finding is strong presumptive evidence of malignancy, but is not pathognomonic because it occurs rarely with benign acini [8, 40, 48]. Complete circumferential growth, intraneural invasion, and ganglionic invasion are found only with cancer.

Perineural invasion indicates tumor spread along the path of least resistance, and does not represent lymphatic invasion. When present in needle biopsy specimens,

perineural invasion indicates a high likelihood of EPE [8]; however, it does not appear to have independent prognostic value after other factors are evaluated, and we no longer include this in our surgical pathology reports [17] (M. Egan, A. Lopez-Beltran, D.G. Bostwick, unpublished observations).

Vascular/lymphatic invasion

Microvascular invasion is a strong indicator of malignancy, and its presence correlates with histologic grade, although it is sometimes difficult to distinguish from fixation-associated retraction artifact of acini [7, 71]. Microvascular invasion may also be an important predictor of outcome, and carries a four times greater risk of tumor progression and death. The CAP [41] recommends reporting microvascular invasion in all prostatic specimens, presumably using routine light microscopic examination, but this suggestion is largely ignored. Despite this recommendation, microvascular invasion is not measured in prostatic biopsies by most laboratories, including ours. Immunohistochemical stains directed against endothelial cells, such as factor VIII-related antigen or *Ulex europaeus*, may increase the detection rate [71].

Microvascular invasion is defined as the unequivocal presence of tumor cells within endothelium-lined spaces. We do not require the presence of a cellular reaction in the adjacent stroma with hemosiderin and fibrin deposition to diagnose microvascular invasion. Also, we do not differentiate vascular and lymphatic channels because of the difficulty and lack of interobserver reproducibility by routine light-microscopic examination [71].

Microvascular invasion is most often confused with perineural invasion and cell clusters within empty spaces without a lining due to retraction artifact. Equivocal foci and spaces without an identifiable endothelial lining are not considered evidence of perineural invasion. Microvascular invasion is present in 38% of radical prostatectomy specimens and is commonly associated with EPE and lymph node metastases (62% and 67% of cases, respectively) [7, 71]. However, it is not an independent predictor of progression when stage and grade are included in the multivariate analysis [7].

Studies of circulating PSA-positive cells may also assist with staging [39, 55]; discussion of this potentially useful factor is beyond the scope of the present review.

The vanishing cancer phenomenon

In some thoroughly studied radical prostatectomy specimens, there is minimal or no residual cancer within the specimen. This "vanishing cancer phenomenon" is probably increasing in incidence as more low-stage cancers are being treated by radical prostatectomy [34]; the use of preoperative androgen deprivation therapy is also a contributory factor (see below). The inability to identify cancer in a prostate removed for needle biopsy-proven carcinoma does not necessarily indicate technical failure, although it is important to exclude the possibility of improper patient identification. DNA "fingerprinting" has been used as a research tool to compare the formalin-fixed paraffin-embedded biopsy and prostatectomy tissues [34], but is not recommended for routine use.

Substantial resources may be needed to identify minimal residual cancer, and even exhaustive sectioning may fail. How many sections is it reasonable to obtain in such cases? When can one stop sectioning if no cancer is found? We believe that it is appropriate for the pathologist to submit routine sections of the entire prostatectomy for histologic evaluation in such cases; however, after submission and examination of the entire prostate, further levels and block-flipping are probably not necessary, as any residual cancer at that point is likely to be extremely small and of no clinical significance.

Preoperative androgen deprivation therapy

Hormonal treatment such as androgen deprivation alters the prostatic epithelium, causing glandular atrophy and apoptosis (programmed cell death) [54]. This therapy also induces significant histologic changes in prostatic adenocarcinoma, which poses diagnostic difficulty for the pathologist (Table 8) (Fig. 4) [3, 20, 26, 31, 57, 80, 84]. This pattern consists of sheets and ribbons of cells with clear cytoplasm and an infiltrative pattern reminiscent of lobular carcinoma of the breast. Tumor cell nuclei and nucleoli are frequently small, with condensed hyperchromatic chromatin further obscuring the nucleoli, creating a "nucleolus-poor" appearance in many areas. Recognition of this pattern may be particularly difficult in needle biopsies and lymph node metastases due to its subtle infiltrative pattern and inconspicuous nucleoli.

Androgen deprivation is used for preoperative tumor shrinkage and treatment of benign prostatic hyperplasia, and may be effective for cancer prophylaxis, although

Table 8 Androgen deprivation therapy: histologic features in the prostate[a]. [With permission from Bostwick DG, Dundore PA (1997). Biopsy pathology of the prostate. Chapman and Hall, London (in press)]

Architecture
Prominent acinar atrophy
Decreased ratio of acini to stroma
Basal cell hyperplasia in benign epithelium
Foci of epithelial hyperplasia
Stromal edema in early stages; fibrosis in late stages
Squamous metaplasia
Decrease in extent of PIN
Cytology
Prominent clear cell change
Nuclear shrinkage
Nuclear hyperchromasia
Nucleolar shrinkage

[a] These changes affect benign, hyperplastic, and neoplastic epithelium. There is some variability depending on the method of therapy

this remains speculative. It causes a marked reduction in the presence and extent of high-grade prostatic intraepithelial neoplasia (PIN), the most likely precursor of prostatic adenocarcinoma [31].

What is the the biologic potency of treated prostate cancer? Does the consistent high-grade pattern noted by all observers reflect aggressive androgen-insensitive clones, or, conversely, collapsed carcinoma of low viability? The results of DNA ploidy examination before and after treatement have been contradictory [3, 26]. Most investigators explain the high-grade appearance of residual carcinoma as therapy-induced morphologic alteration rather than truly a biologically high grade, and grading after therapy was considered potentially misleading and not recommended [3]. The mechanism of action varies among the different androgen deprivation agents, and further study is needed to assess subtle differences beyond those noted here and to establish the possible biologic significance of these changes.

Conclusion

Significant progress has been made in recent years in standardizing the handling of radical prostatectomy specimens, with most practitioners utilizing select partial sampling rather than whole-mount sectioning. Practice protocols have been published by multiple authoritative groups, with similar suggestions about which information should be included in pathology reports. Definitions of EPE and positive surgical margins are also standardized, although methods of quantitating EPE and the clinical significance of positive margins remain uncertain. The 1992 revision of the TNM system is now the international standard for staging, but future refinements may increase its prognostic accuracy for the individual patient.

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