Key Issues in Handling and Reporting Radical Prostatectomy Specimens

John R. Srigley, MD, FRCP

- Context.—Patients with prostatic adenocarcinoma commonly undergo radical prostatectomy, and it is often difficult and time consuming to handle the resulting specimens and to report the findings. Pathologic information derived from the radical prostatectomy specimen is used for selecting adjuvant therapy, such as radiotherapy and hormone therapy, and for determining a patient’s prognosis. The prostate specimen must be handled in a systematic fashion to derive the appropriate prognostic parameters.

Objective.—To review the prognostic factors of relevance in classifying radical prostatectomy specimens, using the College of American Pathologists categorization system, including a detailed survey of the morphologic-based factors but excluding other factors such as DNA ploidy and novel phenotypic and genotypic markers.

Conclusions.—Gleason score, pathologic stage, and margin status are considered category 1 prognostic factors, which are of proven prognostic significance and are useful in patient management. Factors such as tumor volume (intraglandular extent) and tumor subtype are considered category 2 prognostic factors, which show significant promise but require validation in multivariate analysis. Lymphovascular space invasion is a promising category 3 prognostic factor that needs additional study. Perineural invasion is an almost ubiquitous finding in radical prostatectomy specimens and is considered a category 3 prognostic factor.

After prognostic factors have been analyzed at the histologic level, it is critical to report the findings in a clear and unambiguous fashion. The synoptic style of reporting is ideal for describing complex cancer resection specimens. A synoptic report based on an evidence-based checklist, such as the one developed by the College of American Pathologists, effectively communicates complex cancer-related data, such as radical prostatectomy specimen findings. This information is used not only for individual case management with respect to treatment and prognostication but also for purposes such as education, research, quality monitoring, and system planning.

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Radical prostatectomy specimens are commonly encountered in the surgical pathology laboratory and often present challenges in terms of handling the samples and reporting the findings. Furthermore, these specimens have significant resource implications, especially if total specimens are submitted. In 2005, it was estimated that 232,000 new cases of prostate cancer would be diagnosed in the United States. More than 100,000 radical prostatectomies are likely to be performed.2

The pathologic information derived from radical prostatectomy specimens has important patient care implications. These prognostic data are used to predict patient outcome after surgery. Predictive tables such as the Kattan nomograms, which use information derived from the radical prostatectomy specimen, are used to predict an individual’s chance of having a prostate-specific antigen (PSA) recurrence at 7 years.5,6 In addition, the information obtained from the radical prostatectomy specimen, especially observations related to Gleason score, pathologic stage, and margin status, is used to decide if a patient is to receive adjuvant treatment such as radiotherapy or hormone therapy.7,8 Therefore, it is important to make accurate prognostic observations in radical prostatectomy specimens and to present this information to the urologist and other cancer physicians in a clear and unambiguous fashion.

In this article, the morphologic-based prognostic factors that can be determined from radical prostatectomy specimens will be reviewed. The practical aspects of assessing and reporting morphologic parameters will be emphasized. The classification of prognostic factors developed at consensus meetings sponsored by the College of American Pathologists (CAP) in 1994 and 1999 will be used (Table 1).9–11

Category 1 prognostic factors are those of proven prognostic significance and are useful in patient management. In radical prostatectomy specimens, Gleason score, pathologic stage, and margin status fall into this category. Category 2 prognostic factors are those that show promise as predictive or prognostic factors based on evidence from published studies but require validation in larger multivariate studies. The prognostic factors falling into this group include tumor volume (intraglandular extent) and
histologic subtype. Category 3 prognostic factors are those for which there is some scientific evidence to support their adoption as prognostic factors, but the data are too preliminary. These potential prognostic markers are not ready for "prime time." Vascular space invasion and perineural invasion are the morphologic-based prognostic factors that fit into this category. This review will not address prognostic factors that are not based on traditional morphologic parameters, including serum PSA (category 1), DNA ploidy (category 2), and markers of proliferation, apoptosis, and neuroendocrine status and other phenotypic and genotypic assays such as oncoproteins and their products (category 3).

**HANDLING THE RADICAL PROSTATECTOMY SPECIMEN**

To accurately assess prognostic factors in radical prostatectomy specimens, a systematic approach to specimen handling is required. The following reflects my approach to handling the radical prostatectomy specimen. The specimen is weighed and measured in 3 dimensions. Measurements of the seminal vesicles are also taken. In recent years, it has been common to see incompletely excised seminal vesicles in which parts of the bodies and tips are not removed with the main specimen.

Unless fresh tissue is being harvested for research purposes, specimens are generally fixed in 10% neutral buffered formalin for 18 to 24 hours. To reduce fixation time, a microwave-assisted technique may be used. The outer surface of the prostate, with associated extraprostatic tissue and margins, along with a left and right mid-anterior transverse block of the prostate or prostatic urethra, the distal urethral margin is of critical importance.

The apical margin should not be considered a "ure-thral" margin where urothelium needs to be assessed. The urothelium commonly retracts into the apical segment, and it is not necessary to analyze this tissue, as prostatic carcinoma does not typically spread along the urethra proper but involves the peripheral connective tissue of the apical cone. By contrast, when urothelial carcinoma involves the prostate or prostatic urethra, the distal urethral margin is of critical importance.

The basal (bladder neck) aspect should also be handled in a fastidious fashion. The bladder neck is often irregular and commonly is doughnut-shaped. The basal margin can be submitted using a shave (en face) approach or using perpendicular sectioning. In my laboratory, perpendicular sectioning is the preferred method.

The seminal vesicles can be handled in different manners. It is not necessary to block all of the body and the tip of each seminal vesicle, and as already mentioned, these portions of the seminal vesicle may not be present. It is important to always include the junction between the seminal vesicle and the prostate proper. Some urologic pathologists prefer to obtain a longitudinal section of the seminal vesicle and to submit both halves in 1 or 2 blocks. Some also include cross sections from the margins of each vas deferens, but this is not mandatory.

After handling the apical and basal portions, including the seminal vesicles, the middle portion of the prostate gland is left, which should be serially sectioned transversely at 3- to 5-mm intervals perpendicular to the rectal surface. The transverse sections are then carefully analyzed for the presence of grossly identifiable tumor (Figure 1). A decision is made regarding total or partial submission of the remaining specimen. A survey conducted by the American Society of Clinical Pathologists indicated that only 12% of laboratories in the United States submitted total radical prostatectomy specimens. A systematic partial submission strategy can provide almost as much prognostic information as a total submission. A variety of partial submission methods have been described in the literature, and the preferred method depends to a great extent on whether the specimen represents palpable (stage T2) or impalpable (stage T1c) disease. In stage T2 disease, submission of the palpable grossly obvious tumor with associated extraprostatic tissue and margins, along with the mandatory apical, basal, and seminal vesicle sections, provides accurate prognostic information. When a tumor is neither palpable nor visible, several possible submission strategies may be used. Approaches include submission of alternate transverse slices or, preferably, submission of the posterior aspect of each transverse slice along with a left and right mid-anterior transverse block to pick up the 15% to 25% of stage T1c cancers that involve the anterior gland. In very large glands with marked nodular hyperplasia, the peripheral aspect of each transverse slice can be submitted and only a small amount of the nodular transition zone sampled.

In my laboratory, a Plexiglas orientation board is used for specimen handling. All gross slices of the radical prostatectomy specimen are laid out on the board (Figure 2), and a photocopy is obtained. The photocopy is used to record the block legend and to document microscopic observations related to prognostic factors.

In some laboratories, a whole-organ sectioning technique is used, and this provides aesthetically pleasing sections but is expensive and requires additional technical expertise (Figure 3). Furthermore, there is some loss of

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**Table 1. College of American Pathologists Working Classification of Prognostic Factors**

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Well supported by the literature; generally used in patient management</td>
</tr>
<tr>
<td>II</td>
<td>Extensively studied biologically and/or clinically</td>
</tr>
<tr>
<td>A</td>
<td>Tested in clinical trials</td>
</tr>
<tr>
<td>B</td>
<td>Biological and correlative studies done; few clinical outcome studies</td>
</tr>
<tr>
<td>II</td>
<td>Currently do not meet criteria for category I or category II</td>
</tr>
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Table 2. Morphologic-Based Prognostic Factors in Radical Prostatectomy Specimens

<table>
<thead>
<tr>
<th>Factor</th>
<th>CAP Category*</th>
</tr>
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<tbody>
<tr>
<td>Gleason score</td>
<td>I</td>
</tr>
<tr>
<td>pTNM</td>
<td>I</td>
</tr>
<tr>
<td>Margin status</td>
<td>II</td>
</tr>
<tr>
<td>Volume (intraglandular extent)</td>
<td>II</td>
</tr>
<tr>
<td>Tumor subtype</td>
<td>II</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>III</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>III</td>
</tr>
</tbody>
</table>

* Based on the 1999 College of American Pathologists (CAP) Consensus Statement.11

prognostic information, especially in regard to extraprostatic extension (EPE) and margin positivity due to the thickness of the sections.19,22

ASSESSING MORPHOLOGIC-BASED PROGNOSTIC FACTORS

Much of the discussion herein on the assessment and reporting of morphologic-based prognostic factors reflects the consensus developed at a 2004 World Health Organization–sponsored international consultation.23 Table 2 lists the morphologic-based prognostic factors along with their CAP prognostic categories.

Gleason Score

In the radical prostatectomy specimen, Gleason score is an important prognostic factor, arguably the most powerful predictor of disease progression.23 The Gleason score is the sum of the most predominant Gleason grade (primary pattern) based on the surface area of involvement and the second most predominant Gleason grade (secondary pattern)24-26 (Figure 4). In cases in which only a single pattern is present, the primary grade is doubled to derive the Gleason score. Potential scores range from 2 to 10, but radical prostatectomy specimen Gleason scores are usually in the range of 5 to 8. Tumors with low Gleason scores of 2 to 4 are uncommon, accounting for only 2% of specimens in one series of radical prostatectomies27 (Figure 5). These low-grade tumors are generally located in the transition zone. Gleason scores of 6 and 7 are the most common scores in radical prostatectomy cases.28 Because Gleason score 7 tumors behave significantly worse than Gleason score 6 tumors, it is important to identify even small amounts of Gleason grade (pattern) 4 tumor.29 Gleason grade 4 tumor is generally characterized by glandular fusion or by complex cribriform structures. In some instances, poorly formed glands that may be admixed with

Figure 1. Transverse slice of prostate gland showing white-gray tumor nodule on the right side. This specimen is from a patient with stage T2 cancer.

Figure 2. Picture of Plexiglas orientation board used for handling radical prostatectomy specimens. The board has labels for base, apex, left, and right. The apex, base, seminal vesicle, and transverse midsections of the prostate are laid out on the Plexiglas board. This allows the specimen to be photocopied. Photocopies are used for block designation and for recording histologic findings related to the presence of cancer and to prognostic factors.

Figure 3. Whole-mount transverse section of prostate gland showing nodule of adenocarcinoma in the right posterolateral aspect (hematoxylin-eosin).
better-differentiated acinar structures are also considered Gleason pattern 4. The amount of Gleason pattern 4 tumor appears to be important in predicting prognosis. Gleason score 4+3 tumors are associated with a worse prognosis than Gleason score 3+4 tumors. Tumors with high Gleason scores of 8 to 10 account for less than 10% of tumors seen in radical prostatectomy specimens, with most of these being Gleason score 8. Tumors with high Gleason scores are generally aggressive and commonly display extraprostatic spread and margin positivity. Stamey et al advocate measuring the percentage of high-grade tumor (Gleason patterns 4/5) present within a specimen. Although this is of value in predicting outcome, grade reproducibility and calculation of the percentage of high-grade tumor can be problematic, and this measure is considered investigational.

The Gleason score along with the primary and secondary grades should be determined in all radical prostatectomy specimens, with occasional exceptions. If a patient has received neoadjuvant hormone therapy, the Gleason score is often artifactualy altered, and Gleason grading in...
Figure 8. Low-power photomicrograph showing extraprostatic extension characterized by tumor involving periprostatic fat and connective tissue (hematoxylin-eosin, original magnification ×150).

Figure 9. Extraprostatic extension in the region of the neurovascular bundle. Note the large nerve encircled by adenocarcinoma (hematoxylin-eosin, original magnification ×600).

Figure 10. Extraprostatic extension manifested by a bulging nodule beyond the normal contour of the prostate gland (hematoxylin-eosin, original magnification ×150).

Figure 11. Extraprostatic extension (EPE) in the anterior region. Note the tumor extending beyond the limit at which nonneoplastic glands (dilated on the left) are seen. This type of EPE is sometimes difficult to discern (hematoxylin-eosin, original magnification ×150).

Figure 12. A, Focal extraprostatic extension. Note the small amount of tumor just touching the cluster of adipocytes (hematoxylin-eosin, original magnification ×600). B, Nont focal (established) extraprostatic extension. Note the tongue of tumor extending well into periprostatic fibroadipose connective tissue (hematoxylin-eosin, original magnification ×150).
these situations is not recommended. Adjuvant hormone therapy can alter acinar morphologic structure so that Gleason grade 3 patterns can appear as collapsed cords or as individual cells resembling Gleason grade 5 patterns. In cases in which the patient has received neoadjuvant hormone therapy, a comment should be included on the pathology report indicating why a Gleason score is not being rendered.

An important aspect of Gleason grading in radical prostatectomy specimens is the issue of tertiary Gleason patterns. One study showed that more than 50% of radical prostatectomy specimens contained at least 3 different Gleason grades, which contrasts with a needle biopsy series in which tertiary patterns were present in less than 10% of cancer specimens. Recent studies have shown that even small amounts of Gleason pattern 5 can have an adverse effect on outcome (Figure 6); for instance, Gleason score 7 (grades 3+4) tumors with minute amounts of Gleason pattern 5 behave worse than tumors with pure Gleason score 7 (grades 3+4) tumors.

Recommendations from the 2005 International Society of Urological Pathology Consensus Conference on Gleason Grading of Prostatic Carcinoma suggest that, in radical prostatectomy specimens in which Gleason grades 3, 4, and 5 are present and Gleason grade 5 is a tertiary pattern, the presence of the high-grade element should be noted but not necessarily included in the Gleason score. For instance, a tumor is recorded as Gleason score 7 (grades 3+4) with a tertiary grade 5 element. This contrasts with the recommendation for reporting a tertiary grade 5 element in a needle biopsy specimen in which the predominant and the worst grades comprise the Gleason score. A similar situation exists for Gleason score 5 (grades 3+2) tumor with a tertiary pattern 4. These tumors behave worse than the pure Gleason score 5 (grades 3+2) cancers.

Another issue is dealing with minor elements of a secondary pattern when only 2 Gleason patterns are present. For instance, in a case in which greater than 95% of the tumor displays Gleason grade 3 and less than 5% displays Gleason grade 4, it is generally recommended to acknowledge the minor higher-grade component in the Gleason score. Conversely, if greater than 95% of the tumor is Gleason grade 4 and less than 5% is Gleason grade 3, the lower-grade secondary pattern can be ignored in the Gleason score.

Gleason grading of separate tumor nodules within radical prostatectomy specimens is also problematic. The identification of completely separate tumor nodules is dependent to some extent on sampling techniques. As noted earlier, the radical prostatectomy specimen, whether it be from a patient with clinical stage T2 or stage T1c disease, should be handled in a systematic fashion. In stage T2 disease, the palpable and grossly identified nodule is generally considered the dominant one. In stage T1c disease, carcinoma is often multifocal, with an irregular serpentine distribution. It is often difficult to determine whether there is a single tumor or multiple tumors. In the setting in which topographically separate tumors are seen, each “dominant” nodule should be separately graded. In many situations, however, this has no practical significance because each tumor displays Gleason score 6 (grades 3+3) or Gleason score 7 (grades 3+4 or grades 4+3). Occasionally, a small peripheral zone tumor with a high Gleason score of 8 (grades 4+4) and a low-grade transition zone tumor with a Gleason score of 4 (grades 2+2) are encountered. In that situation, it is important to separately grade each tumor because the high-grade peripheral zone carcinoma, although smaller in volume, is of greater biologic significance than the larger-volume low-grade transition zone tumor. Application of a mean Gleason score of 6 (grades 2+4 or grades 4+2) across these 2 neoplasms is misleading. However, this scenario is uncommon, and in most radical prostatectomy specimens, a single Gleason score is applied to the irregular multifocal disease in which a dominant nodule cannot be determined, or the dominant and other secondary nodules have the same Gleason scores.

Pathologic Stage (TNM)

Lymph Node Status (pN).—The presence of metastatic prostate cancer in pelvic lymph nodes is a significant adverse prognostic factor. During the last 20 years, the rate of pelvic lymph node positivity at the time of radical prostatectomy has significantly decreased to 1% to 2% of cases. The advent of PSA testing and the use of nomograms for better patient selection are the major factors leading to the low lymph node positivity rates.

The gold standard technique for assessing pelvic lymph nodes is routine microscopy. The identification of a positive lymph node using routine hematoxylin-eosin microscopy indicates pN1 disease, and this observation should be noted in the pathology report (Figure 7). In the case of lymph nodes that are negative by light microscopy, some authors have used immunohistochemistry and molecular techniques, in particular reverse transcription–polymerase chain reaction, but these methods are considered experimental.

In addition, the relevance of isolated tumor cells (defined as single cells or small clusters of tumor cells ≤0.2 mm in diameter) is unknown. Isolated tumor cells are usually detected by immunohistochemistry but may be seen by routine microscopy as well. The rules of TNM suggest that such cases be classified as N0 disease. In contrast, micrometastases (defined as tumor cell clusters >0.2 mm and <0.2 cm in greatest diameter) should be reported as stage pN1 disease.

The role of intraoperative assessment of pelvic lymph nodes at the time of radical prostatectomy is controversial. Some urologists will abort the procedure in cases in which positive lymph nodes are found at surgery. In that situation, it is reasonable for the pathologist to analyze frozen sections. However, a selective approach to cases for intraoperative assessment is important. The tables by Partin et al can be used to identify the likelihood of lymph node metastases and can help the urologist determine the value or the futility of intraoperative assessment. In particular, in stage T1c disease in which the Gleason score is less than 7 and the PSA level is between 4.1 and 10 ng/mL, the rate of pelvic lymph node positivity is about 1%. In this setting, frozen section analysis of lymph nodes is probably unwarranted. There are practical problems with the assessment of lymph nodes because pelvic lymph nodes are often fatty and it is difficult to get good-quality sections. Furthermore, only a small amount is being sampled at the time of frozen section analysis, and tumor deposits are sometimes found in deeper permanent sections.

Some urologists proceed with radical prostatectomy for local control even in the setting of positive lymph nodes, especially when there is a long projected survival period. The Gleason score in these situations is the major deter-
minant of outcome. In patients with Gleason scores less than 7, it is generally not necessary to freeze lymph nodes because the urologist will proceed to radical prostatectomy for local control anyway. In patients with high Gleason scores of 8 to 10, the likelihood of distant disease is high, and it is reasonable to have the patient undergo lymph node dissection (laparoscopic or otherwise) before deciding on radical prostatectomy or to freeze all lymph nodes at the time of radical prostatectomy. In the case of positive lymph nodes, the radical prostatectomy should probably be aborted.

Occasionally, lymph nodes are identified in the peri-prostatic compartment or in soft tissue around the seminal vesicles. Pelvic lymph node involvement is also usually seen in this setting. The presence of isolated positivity in lymph nodes in the periprostatic or periseminal vesicle regions should be considered pN1 disease. In regard to the handling of lymph node specimens, all grossly identified lymph nodes should be submitted in their entirety. In high-grade disease (Gleason scores 8–10), some investigators have submitted all adipose tissue as well because a small percentage of positive cases are identified within fatty lymph nodes that are not grossly recognized as such.

### Primary Tumor (pT)

The assignment of pathologic stage is dependent on accurate observations in the radical prostatectomy specimen. The pathologic TNM categories are given in Table 3. There is no stage pT1 category. Stage T1 is a clinical category that uses pathologic information derived from transurethral resectate or needle biopsy observations. Although subdivision of clinical stage T2 disease into stage T2a, stage T2b, and stage T2c categories makes some sense, a similar approach to stage pT2 disease is problematic. In particular, the stage pT2c category is used for several different scenarios ranging from 2 microscopic foci, 1 involving each side of the gland, to a large-volume tumor with bilateral involvement. The subdivision does not give a clear indication of the intraglandular disease extent or the disease volume. In organ-confined disease, it makes more sense to use the generic stage pT2 category, with a comment recorded about the amount and distribution of intraglandular disease.

Tumor that extends beyond the confines of the prostate gland is considered stage pT3 disease. This can occur as extraprostatic extension (EPE; stage pT3a), seminal vesicle involvement (stage pT3b), or both.

**Extraprostatic extension** is the recommended term to be used when the tumor extends beyond the normal confines of the prostate gland. Extraprostatic extension replaces terms such as capsular invasion, capsular penetration, and capsular perforation, which are somewhat ambiguous. The prostatic capsule is not a well-defined structure like the renal capsule. In the lateral and posterior aspects, the so-called prostatic capsule is a condensed band of fibromuscular connective tissue that blends imperceptibly with the prostatic stroma. In other areas such as the apex and the anterior and basal (bladder neck) regions, the capsule is lacking, and the connective tissue in these regions is often not clearly separable from the surrounding extraprostatic connective tissue.

Descriptors of EPE are listed in Table 4. In radical prostatectomy specimens, involvement of peri-prostatic fat indicates EPE (Figure 8). There are rare instances of intraprostatic fat, but for all practical purposes, involvement of

### Table 3. 2002 TNM Staging of Prostatic Adenocarcinoma

<table>
<thead>
<tr>
<th>Pathologic Primary Tumor (pT)</th>
<th>Clinical Primary Tumor (T)</th>
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<tbody>
<tr>
<td>pT1a Tumor incidental histologic finding in ≤5% of tissue resected</td>
<td>T1a Clinically inapparent tumor not palpable or visible by imaging</td>
</tr>
<tr>
<td>pT1b Tumor incidental histologic finding in &gt;5% of tissue resected</td>
<td>T1b Tumor incidental histologic finding in &gt;5% of tissue resected</td>
</tr>
<tr>
<td>pT1c Tumor identified by needle biopsy (eg, because of elevated prostate-specific antigen)</td>
<td>T1c Tumor identified by needle biopsy (eg, because of elevated prostate-specific antigen)</td>
</tr>
<tr>
<td>T2a Tumor involves ≤½ of 1 lobe</td>
<td>T2 Clinor confined within prostate*</td>
</tr>
<tr>
<td>T2b Tumor involves &gt;½ of 1 lobe but not both lobes</td>
<td>T2a Tumor involves ≤½ of 1 lobe</td>
</tr>
<tr>
<td>T2c Tumor involves both lobes</td>
<td>T2b Tumor involves &gt;½ of 1 lobe but not both lobes</td>
</tr>
<tr>
<td>T3 Tumor extends through the prostatic capsule†</td>
<td>T3a Extracapsular extension (unilateral or bilateral)</td>
</tr>
<tr>
<td>T4 Tumor is fixed or invades adjacent structures other than seminal vesicles, bladder neck, external sphincter, rectum, levator muscles, or pelvic wall</td>
<td>T4 Tumor is fixed or invades adjacent structures other than seminal vesicles, bladder neck, external sphincter, rectum, levator muscles, or pelvic wall</td>
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### Table 4. Descriptors of Extraprostatic Extension

- Involvement of fat and/or loose connective tissue in plane of fat or beyond
- Involvement of perineural space in large neurovascular bundles
- Bulging tumor beyond the normal contours of the prostate gland, sometimes with desmoplastic stromal reaction

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fat indicates spread beyond the gland. Tumor involving large nerve bundles in the region of the neurovascular bundles even in the absence of fat involvement is considered EPE (Figure 9). In addition, tumor that is beyond the normal contour of the prostatic edge involving connective tissue that is typically looser than prostatic stroma is an indicator of EPE (Figure 10). In some instances, bulging tumors are associated with desmoplastic stromal response, and generally this is an indication of EPE. In the absence of fatty involvement, the best way to assess the presence of EPE is to look at the prostate sections on scanning magnification to see whether the smooth rounded contour of the gland is distorted by any tumor protrusion. This is particularly important in looking at the anterior region, where the anterior fibromuscular stroma blends into the extraprostatic connective tissue. In this location, tumor that extends beyond the confines of the normal glandular portion of the prostate is considered EPE (Figure 11).

The assessment of EPE at the apex is often problematic. In this location, benign prostatic glands are often admixed with skeletal muscle bundles of the urogenital diaphragm, and many pathologists believe that EPE cannot be assessed at this site. The presence of tumor beyond the level where normal prostatic acini are seen at the apex is considered an indication of EPE by some. Others consider EPE to be present when the tumor involves the inked perpendicular (radial) apical margin if benign glands are not present at that site (capsular incision is discussed in the next subsection). Extraprostatic extension is most commonly seen in peripheral zone tumors in the posterolateral aspect, and a perineural pathway is the most common mechanism of spread. In transition zone tumors, EPE usually occurs anteriorly by direct infiltration of the extraprostatic connective tissue. The degree of EPE can be subdivided into focal and nonfocal amounts. In focal EPE, there are only a few neoplastic glands outside the prostate, whereas more substantial involvement of the extraprostatic tissue is seen in nonfocal EPE (Figure 12). Not uncommonly, a distinct tongue of tumor extending well into periprostatic connective tissue is seen. There is no standardized method of subdividing EPE into focal versus nonfocal types, but the designation of focal versus nonfocal EPE appears to have prognostic significance. Some authors have advocated the assignment of levels of capsular invasion as a prognostic measure; however, this is not widely accepted given the histoanatomic vagaries of the so-called capsule. Other more quantitative approaches to EPE are considered investigational, including counting the number of blocks involved by EPE and measuring the depth of penetration or the linear extent (width) in millimeters.

Seminal vesicle involvement (stage pT3b) is a major adverse factor predicting biochemical failure after radical prostatectomy. Seminal vesicle invasion is defined as tumor infiltrating the muscular coat of the seminal vesicle (Figure 13). Seminal vesicle invasion is commonly associated with EPE.

The possible routes of seminal vesicle invasion have been well elucidated by Ohori et al and include the following: (1) spread along the ejaculatory duct into the seminal vesicle, (2) extension into the perimesimal vesicle soft tissue and then into the wall of the seminal vesicle, (3) direct invasion of the seminal vesicle at the base of the prostate, and (4) discontinuous metastases. The discontinuous pathway is uncommon. The first 2 routes are more commonly seen. There is some anatomic variation in the amount of seminal vesicle that appears to be within the prostate gland (so-called intraprostatic portion). Diagnosis of seminal vesicle invasion is usually restricted to involvement of structures that are exterior to the prostate gland, and invasion of the intraprostatic portion is viewed as being essentially ejaculatory duct involvement.

Seminal vesicle involvement is considered an independent adverse prognostic factor. It is especially significant in the case of margin positivity, and the presence of seminal vesicle involvement and margin positivity can often influence a radiation oncologist to offer a patient adjuvant radiotherapy.

The involvement of adjacent structures other than seminal vesicle, including bladder and rectum, is considered pT4 disease. Some controversy exists with respect to bladder involvement, especially in the region of the basal (bladder neck) aspect of a radical prostatectomy specimen. If there is a clinical mass extending into the bladder or if the pathologist grossly identifies a tongue of tumor extending into the basal tissue, often with margin positivity, little controversy exists as to the stage pT4 designation. However, the more common situation is microscopic involvement of the bladder neck musculature (Figure 14). Some data suggest that microscopic bladder neck invasion has a prognosis equivalent to that of seminal vesicle invasion, and this issue should be addressed in future modifications to the TNM system.

<table>
<thead>
<tr>
<th>Table 5. Causes of Margin Positivity</th>
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<tbody>
<tr>
<td>• Artifacts</td>
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<tr>
<td>• Macroscopic handling of specimens in operating room or after surgery</td>
</tr>
<tr>
<td>• Histology of en face (shave) margins</td>
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<tr>
<td>• Capsular invasion (pT2+)</td>
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<tr>
<td>• Inability to resect extraprostatic disease</td>
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Margin Status

The presence of positive margins in a radical prostatectomy specimen adversely affects outcome, and margin status is considered a category 1 prognostic factor. A positive margin is defined as one where the tumor extends to the inked surface of the specimen, presumably representing the site across which the surgeon has cut (Figure 15). Because of the numerous vital structures in close proximity to the prostate gland, the radical prostatectomy specimen is typically surrounded by only a small amount of periprostatic connective tissue, often less than a few millimeters. The tumor has to involve the inked surface, and a closely approaching margin should be considered negative. A description such as “tumor is close to margin of resection” implies uncertainty and has no clinical meaning unless the tumor is on the inked surface.

There are 3 major causes of margin positivity: (1) artifactual positivity resulting from specimen handling, (2) transection of intraprostatic tumor (capsular incision), and (3) inability to excise extraprostatic tumor (Table 5). Spurious margin positivity can result from handling the radical prostatectomy specimen in the operating room or from transporting or processing it in the laboratory. Delicate strands of periprostatic connective tissue can sometimes be disrupted, resulting in ink being put on a portion...
of the gland that does not represent the margin. This underscores the importance of careful handling of these specimens. In addition, as alluded to before, the handling of an apical prostatic segment using a shave or en face technique may result in spurious positive findings caused by excessive block trimming.

Capsular incision is another cause of margin positivity (Figure 16). In this situation, the ink is located on prostatic tissue that may be capsular or subcapsular. Such cases have been designated as stage pT2+ disease, indicating that the tumor is essentially organ confined elsewhere, but EPE in the region of the capsular incision cannot be assessed (Figure 17). Commonly, the capsular incision is located in the posterolateral aspect, where surgeons may cut into the prostate proper to preserve the neurovascular bundle. The apex is another common site where positive margins occur from the capsular incision. The apical tissues are often difficult to assess, and as already mentioned, evaluation of EPE at the apex is problematic. Some pathologists believe that margin positivity at the apex, at least in areas across which benign glands are not cut, should be considered EPE (ie, stage pT3a margin-positive disease and not stage pT2+).

There is significant variation in the incidence of stage pT2+ disease across institutions. This mostly relates to the vagaries of pathologic interpretation rather than to differences in surgical technique.

Another cause of margin positivity is the inability to excise tumor that demonstrates EPE (Figure 18). In the region of the neurovascular bundles, urologists will commonly avoid wide resection to maintain potency. In some situations, very little tissue can be excised because of proximity to important structures such as the rectum. It is uncommon to see widespread positive margins in the presence of extensive extraprostatic tumor, especially with the more refined selection of candidates for radical prostatectomy.

The incidence of margin positivity has decreased during the last 2 decades, in part because of clinical stage migration related to screening techniques such as serum PSA and to the use of other selection criteria such as clinical stage and preoperative biopsy Gleason score (Partin tables). Improvements in surgical technique may also play some role in the reduction in margin positivity. There do not appear to be any significant differences in overall margin positivity related to radical perineal, retropubic, or laparoscopic prostatectomy.

The most common site of margin positivity is the apex, followed by the posterior and posterolateral regions. The anterior and bladder neck margins are least commonly involved. In patients who undergo radical prostatectomy for stage T1a or stage T1b disease, anterior margin positivity is more often seen because of the transition zone and the anterior locations of these tumors. In stage T1c and stage T2 disease, posterior and posterolateral sites are often involved. In about 15% to 25% of patients with clinical stage T1c disease, an anterior tumor location is seen, sometimes associated with margin positivity (Figure 20).

The role of intraoperative frozen section analysis of margins in radical prostatectomy specimens has been studied to a limited extent. Because such analysis results in significant numbers of false-negative and false-positive observations, there is no compelling reason to assess margins using this technique.

Disease progression is seen significantly more often in patients with prostate cancer with positive margins compared with those with negative margins. In 2 studies, progression-free probability at 5 years following radical prostatectomy ranged from 81% to 83% for margin-negative disease and from 58% to 64% for margin-positive disease. There is some indication that the location of the tumor is important, because several studies have demonstrated that positive apical margins do not correlate independently with disease progression in multivariate analysis. In contrast, bladder neck margin positivity predicts an increased risk of recurrence. There is some indication that the degree of margin positivity is important. Extensive or multifocal positive margins demonstrate a higher risk of progression than solitary or focal positive margins.

TUMOR VOLUME (INTRAGLANDULAR EXTENT)

The assessment of tumor volume or intraglandular extent in radical prostatectomy specimens is somewhat controversial. Tumor volume correlates with Gleason score, pathologic stage, margin status, and disease progression following radical prostatectomy. Findings from several studies, however, suggest that tumor volume is not an independent prognostic factor once the other variables are known. In addition, there is no standard method for assessing tumor volume in routine specimens. The irregular distribution of prostate cancer, especially stage T1c disease, makes the determination of tumor volume difficult. This difficulty is compounded by partial sampling techniques that may limit the ability to accurately determine intraglandular extent. There are also problems when multiple distinct tumor nodules are identified. Disease progression based on the volume of the largest tumor nodule is comparable to that based on the total tumor volume; as such, only the index tumor volume needs to be measured.

Several different techniques for estimating tumor volume have been suggested. One method is a visual inspection of the percentage of specimen involved by cancer, which has been found to be an independent prognostic factor in stage pT2 disease. The visual percentage can be reported in categories such as less than 1%, less than 5%, 5% to 10%, 11% to 20%, and so on. Other authors suggest that measurement of the diameter of the largest tumor nodule is an independent prognostic factor. An other potential measure of intraglandular extent is the number of blocks of radical prostatectomy tissue involved by tumor, divided by the total number of blocks, expressed as a percentage. Such a parameter, however, can yield misleading results because a high proportion of blocks may contain tiny amounts of tumor and the overall intraglandular extent or volume is very small.

Other more quantitative methods include the use of grid-square analysis as proposed by Humphrey and Vollmer. This method and detailed volumetric analysis us-
ing computer-assisted devices are applicable in the research setting but are not practical for routine analysis of radical prostatectomy specimens.303–307

Because the findings from several studies suggest that tumor volume is not an independent prognostic factor, detailed tumor volume measurements in radical prostatectomy specimens need not be reported.33 However, many urologic pathologists provide at least some indication of the tumor volume using visual inspection of the percentage of tissue involved by cancer or other qualitative descriptors such as the presence of minimal, moderate, or extensive disease.23,43 In the situation in which only a very tiny tumor is present, as is occurring more commonly in the screened population with stage T1c disease, the presence of a miniscule tumor may allow the urologist to counsel the patient that he is likely cured of his disease.

The location of the tumor should be considered an optional description in the pathology report. Although a transition zone location is generally associated with a decreased risk of progression, study findings suggest that, given the Gleason score, pathologic stage, and lymph node status, the location of the tumor is not an independent prognostic variable.10 discards such a diagnosis.

Tumor Subtype

More than 99% of prostatic adenocarcinomas have conventional or so-called acinar morphology. Nevertheless, there are several other variants of adenocarcinoma and other carcinomas that rarely affect the gland and that can be seen in radical prostatectomy specimens.109,110 The histologic variants of prostatic carcinoma are listed in Table 6. Certain types of carcinomas such as transitional cell carcinoma or small cell carcinoma should not be primarily treated with radical prostatectomy. However, some variants of adenocarcinoma, including ductal adenocarcinoma, mucinous carcinoma, and signet ring carcinoma, may occasionally be encountered (Figure 21). There are few reported series of these types of tumors handled in radical prostatectomy but are not practical for routine analysis of radical prostatectomy specimens.103–107

Figure 13. Low-power photomicrograph showing seminal vesicle extensively infiltrated by adenocarcinoma (hematoxylin-eosin, original magnification ×150).

Figure 14. Invasion of bladder neck musculature at the prostatic base. In the TNM system, this finding would indicate stage pT4 disease. However, follow-up outcomes indicate that such a finding is better considered an indicator of stage pT3 disease (hematoxylin-eosin, original magnification ×150).

Figure 15. Low-power photomicrograph showing infiltrating carcinoma extending through periprostatic fat to involve the inked margin of a radical prostatectomy specimen (hematoxylin-eosin, original magnification ×150).

Figure 16. Diagram showing the concept of capsular incision (stage pT2+). A pT2+ stage can be derived from a tumor that is confined to the gland (stage pT2) or from a tumor that shows extraprostatic extension (stage pT3). (Reprinted with permission from Humphrey PA. Prostate Pathology. Chicago, Ill: ASCP Press; 2003. Copyright 2003, American Society for Clinical Pathology.)

Figure 17. Photomicrograph showing area of capsular incision. Note the tumor involving green ink, with no periprostatic tissue beyond this plane (hematoxylin-eosin, original magnification ×600).

Figure 18. Low-power photomicrograph showing bulging tumor beyond the contour of the gland (extraprostatic extension). Note the presence of tumor on the inked surface, indicating margin positivity (hematoxylin-eosin, original magnification ×150).

Figure 19. Low-power photomicrograph showing infiltrating acinar carcinoma involving the inked margin in an anterior location (hematoxylin-eosin, original magnification ×300).

Vascular Invasion

The literature on vascular invasion as a prognostic factor in radical prostatectomy specimens is scant.33 At the time of the CAP conference in 1999, vascular invasion was considered a category 3 prognostic factor.11 In most cases, vascular invasion is seen in advanced-stage and large-volume tumors.112,113 Vascular and lymphatic space involvement is rarely encountered in low-grade or small-volume tumors.23 Because recent studies indicate that vascular invasion is an independent predictor of disease progression, this may eventually be reclassified as a category 2 prognostic factor.12,111 The CAP recommendation is to report the presence of vascular space invasion in radical prostatectomy specimens.32

In most instances of vascular invasion, tumor is seen in thin-walled lymphatic or sinusoidal vessels (Figure 22). However, infiltration of periprostatic venous structures is occasionally identified in advanced disease.

Perineural Invasion

Perineural invasion is an almost ubiquitous finding in radical prostatectomy specimens, especially in peripheral zone adenocarcinomas (Figure 23). Perineural infiltration often represents a pathway of EPE. In the posterior or lateral aspects in the regions of the neurovascular bundles, tumor commonly spreads along nerve bundles and twigs to reach the extraprostatic compartment. Studies have shown a positive correlation between perineural invasion and disease progression.114,115

Findings from other studies, however, suggest that perineural invasion in radical prostatectomy specimens is not an independent predictor of progression.92,112 Results of another study suggest that involvement of larger-caliber nerves is an independent predictor of progression.116 Perineural invasion in radical prostatectomy specimens is not considered a mandatory parameter to be reported.

CLINICAL SIGNIFICANCE OF PROGNOSTIC PARAMETERS

The relationship among the pathologic prognostic factors garnered from radical prostatectomy specimens is
Figure 20. Whole-mount section of prostate showing multifocal irregular distribution of tumor as outlined by ink dots (hematoxylin-eosin).

Figure 21. A, Mucinous adenocarcinoma, which is an uncommon variant of prostatic adenocarcinoma. B, Small cell carcinoma involving a radical prostatectomy specimen (hematoxylin-eosin, original magnification ×600).

Figure 22. Low-power photomicrograph showing lymphovascular space invasion. Note the dilated sinusoidal-type space containing high-grade adenocarcinoma (hematoxylin-eosin, original magnification ×150).

Figure 23. Perineural invasion. In radical prostatectomy specimens, this finding is almost ubiquitous in tumors involving the peripheral zone (hematoxylin-eosin, original magnification ×600).
complex and has been subject to multivariate modeling.\textsuperscript{6,4,65,76,117} The critical parameters to record in a pathology report are the Gleason score, including the primary and secondary grades, and the pathologic stage, including the presence of EPE (stage pT3a), seminal vesicle invasion (stage pT3b), and lymph node positivity (stage pN1). Margin status is also an important prognostic factor. These major prognostic factors in the pathology report are often used to make decisions regarding the use of adjuvant treatments, including radiotherapy and hormone therapy. In addition, the prognostic variables can be used in mathematical models such as the Kattan nomograms to predict the likelihood of PSA recurrence in an individual.\textsuperscript{4,6}

**Table 6. Histologic Variants of Prostatic Carcinoma**

- Prostatic duct adenocarcinoma
- Mucinous (colloidal) adenocarcinoma
- Signet ring cell carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma
- Basaloid and adenoid cystic carcinoma
- Transitional cell carcinoma
- Small cell carcinoma
- Sarcomatoid carcinoma
- Lymphoepithelioma-like carcinoma
- Undifferentiated carcinoma, not otherwise specified

**STANDARDIZED REPORTING OF RADICAL PROSTATECTOMY SPECIMEN FINDINGS**

The pathology report of a radical prostatectomy specimen is primarily used for decision making regarding the necessity of adjuvant therapies and for prognostication in the individual patient. The report may also be used for education, research, quality monitoring, system planning, and cancer registry purposes. A synoptic presentation of the data is easier to analyze than the traditional narrative or paragraphic approach.\textsuperscript{118–120} A checklist-based synoptic report is rapidly becoming an accepted standard of practice for cancer pathology reporting, and this has been advocated by the American College of Surgeons Commission on Cancer.\textsuperscript{21} In radical prostatectomy pathology reports, it is important to clearly present the relevant prognostic factors, including Gleason score, pathologic stage, margin status, and others, in a clear and unambiguous fashion.

Checklists developed by organizations such as the CAP and the Association of Directors of Anatomic and Surgical Pathology provide templates for synoptic reporting of radical prostatectomy specimen findings.\textsuperscript{82,122} The CAP checklists are reviewed and, if necessary, updated on a yearly basis and include all relevant information related to the sixth edition of the TNM staging system.\textsuperscript{48} In addition, the essential prognostic elements for patient management and the optional (nonessential) elements are indicated on the CAP checklists. These templates are useful for accurately reporting radical prostatectomy specimen findings and help to ensure the completeness of the pathology report for patient management purposes.

In summary, this review has concentrated on the salient analytic aspects of assessing radical prostatectomy specimens, with emphasis on the morphologic-based prognostic and predictive factors. Preanalytic aspects related to specimen handling and postanalytic aspects of pathology reporting have also been discussed. The proper microscopic analysis of radical prostatectomy specimens mandates meticulous macroscopic specimen handling. Most important, the clinical translation of the analysis is dependent on a crystal-clear radical prostatectomy pathology report in which the relevant diagnostic and prognostic descriptors of prostate cancer can be easily discerned.

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