Prostate cancer reporting and staging: needle biopsy and radical prostatectomy specimens

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Prostatic adenocarcinoma remains the most common cancer affecting men. A substantial majority of patients have the diagnosis made on thin needle biopsies, most often in the absence of a palpable abnormality. Treatment choices ranging from surveillance to radical prostatectomy or radiation therapy are largely driven by the pathologic findings in the biopsy specimen. The first part of this review focuses on important morphologic parameters in needle biopsy specimens that are not covered in the accompanying articles. This includes tumor quantification as well as other parameters such as extraprostatic extension, seminal vesicle invasion, perineural invasion, and lymphovascular invasion. For those men who undergo radical prostatectomy, pathologic stage and other parameters are critical in prognostication and in determining the appropriateness of adjuvant therapy. Staging parameters, including extraprostatic extension, seminal vesicle invasion, and lymph node status are discussed here. Surgical margin status is also an important parameter and definitions and reporting of this feature are detailed. Throughout the article the current reporting guidelines published by the College of American Pathologists and the International Collaboration on Cancer Reporting are highlighted.

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The morphologic aspects of prostatic adenocarcinoma have a critical role in the management and prognostication of patients with prostatic adenocarcinoma. Today, most men diagnosed with prostatic adenocarcinoma have the diagnosis made on a needle biopsy, the majority of which are performed for an elevated serum PSA. Management recommendations for these patients are driven by a number of clinical and pathologic factors. In current practice, a significant percentage of patients judged to have low-risk disease are placed on surveillance protocols. Criteria for identification of patients suitable for surveillance are largely based on characterization of the tumor in the prostate needle biopsy specimen.^{1,2} Of note is the increasing interest in identifying patients of intermediate risk that also can be safely placed on surveillance protocols.³ For those patients that elect radical prostatectomy as the primary treatment, the pathologic findings in the resection specimen are critical for prognostication and for determining the appropriateness of adjuvant treatment such as radiation therapy or

hormonal therapy.^{4,5} For needle biopsy specimens the data described below are largely based on standard biopsy protocols ranging from the original sextant (6 cores) to more contemporary extended techniques (12–14 cores). How these features will relate to the targeted MRI-guided biopsy technique is not well understood.

In this article, the reporting of prostatic adenocarcinoma in needle biopsy and radical prostatectomy specimens is reviewed. The recommendations follow recent guidelines from the College of American Pathologists (Tables 1 and 2) and the International Collaboration on Cancer Reporting.^{6–9} For radical prostatectomy specimens the recommendations from the International Society of Urological Pathology are also referenced.^{10–14} Topics covered in accompanying articles in this journal issue, including histologic type (see Humphrey PA, Zhou M, and Osunkoya A), Gleason grading (see Epstein JJ), intraductal carcinoma (see Zhou M), and treatment effect (see Evans A) are not repeated here.

Needle biopsy specimens

Tumor Quantitation

The quantification of tumor in needle biopsy specimens is a powerful predictor of pathologic stage at radical prostatectomy and outcome after treatment of

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Table 1 College of American Pathologists Reporting Guidelines: Needle Biopsy (modified from College of American Pathologists Protocol for the Examination of Specimens from patients with Carcinoma of the Prostate Gland)⁶

Histologic type

Histologic grade

- Gleason primary (predominant) pattern
- Gleason worst remaining pattern
- Grade group
- Percentage pattern 4 (for Gleason score 3+4=7)
- *Percentage Gleason patterns 4 and 5 (for Gleason score ≥ 7)
- Intraductal carcinoma (document if identified)

Tumor quantitation

- Number cores positive/total number cores and percentage of prostatic tissue involved or
- Number cores positive/total number cores and total linear mm carcinoma/total linear mm tissue or
- Number cores positive/total number cores and percentage of prostatic tissue involved and total linear mm carcinoma/total linear mm tissue
- Periprostatic fat invasion (document if identified)
- Seminal vesicle/ejaculatory duct invasion (document if identified)
- *Lymphovascular invasion
- *Perineural invasion
- *Additional pathologic findings

*Data elements not required for accreditation purposes.

essentially any type. It is also a factor in determining patient suitability for management on a surveillance protocol.² Quantification of tumor for surveillance protocols have variably used parameters such as the absolute number of cores involved (two or three), the percentage of cores involved ($< 20\%$ or $< 33\%$ or $< 50\%$), and the greatest percentage of any core involvement ($< 50\%$ of any core; $< 30\%$ or 6 mm of any core).² There are strong correlations between the absolute number of cores involved and the proportion of cores involved with tumor volume in the prostate gland and with pathologic stage.^{15–18} There is also a strong correlation with outcome in patients treated by radical prostatectomy or radiation therapy.^{18–20}

Reporting the number of cores received and the number of cores involved is a required element for prostate needle biopsy specimens.^{6,8} For cases submitted with one core per site in separate containers this is straightforward. For the most part, if the number of cores per container is limited to two (eg, left apex and left lateral apex) this can usually also be accomplished. When more than two cores are placed in a container and/or when the number of cores placed in each container is not specified this becomes problematic and often essentially impossible. In the example in Figure 1 there are numerous fragments of tissue, three of which are involved by cancer. From the specimen, it is impossible to know how many cores were actually placed in the container. If it is known that this represents, for example, three cores, it is impossible to know if the

Table 2 College of American Pathologists Reporting Guidelines: Radical Prostatectomy (modified from College of American Pathologists Protocol for the Examination of Specimens from patients with Carcinoma of the Prostate Gland)⁶

*Prostate size

Histologic type

Histologic grade

- Primary pattern
- Secondary pattern
- Tertiary pattern
- Gleason score
- Grade group
- *Percentage Gleason patterns 4 and 5 (for Gleason score ≥ 7)
- *Intraductal carcinoma

Tumor quantification

- Percentage of prostate involved by tumor and/or
- Greatest dimension (mm)
- *Additional dimensions (mm)

Extraprostatic extension

- Focal or nonfocal (if present)
- Urinary bladder neck invasion
- Seminal vesicle invasion

Margins

- Limited (< 3 mm) or non-limited (≥ 3 mm)
- *Linear length of positive margins
- *Focality (unifocal or multifocal)
- Location(s) of positive margin
- *Margin positivity at area of extraprostatic extension
- *Gleason pattern at positive margin
- Treatment effect on carcinoma (only required if applicable)
- *Lymphovascular invasion
- *Perineural invasion

Regional lymph nodes

- Number involved/number examined
- *Site of involved lymph nodes
- *Size of largest metastatic deposit (mm)
- *Size of largest lymph node involved (cm)
- *Extranodal extension
- Pathologic stage classification (see Table 3)

*Data elements not required for accreditation purposes.

Figure 1 Scan of a glass slide from a needle core biopsy specimen. The needle biopsy cores are extensively fragmented making it impossible to determine the actual number of cores submitted in the container. The blue lines mark the three tissue fragments that contain adenocarcinoma. Determining the number of cores involved by the carcinoma is similarly not possible in this case.

Figure 2 Scan of a glass slide from a needle core biopsy specimen. The pathologist counted the tissue fragments and reported that there were 21 cores present (numbers were on slide when received from referring institution). A more accurate way of reporting this specimen would be that there were 21 tissue fragments; the number of submitted cores is impossible to determine. It was also reported that there were 4 cores positive for cancer (green); the number of cores that had tumor is not known but it would be accurate to indicate that 4 of the tissue fragments contained tumor.

three involved fragments are from one, two, or three of the cores. Given the critical need to provide both the number of cores submitted and the number involved, this type of specimen argues very much for placement of a specified number (one or two) of cores in individually labeled containers. In another example (Figure 2), the pathologist dutifully counted each piece of tissue on the slide (the numbering on the slide is as received in our lab) and each piece with cancer and then in the synoptic report indicated 'number of cores: 21' and 'number of positive cores: 4.' This implies some level of ability to make this determination. The submitting urologist will know how many cores were in the container (undoubtedly not 21) but even with that knowledge would be unable to determine the absolute number involved or the proportion involved. Application of criteria for surveillance is impossible in both of these instances. In our practice, for both of these specimens, for the number of cores submitted we would report 'not applicable.' For the number of cores involved we would report three and four tissue fragments involved, respectively.

The quantification of the linear extent of tumor in the cores has been approached using many methods.¹ These have included the use of both millimeter measurements and estimated surface area (percent involvement). Specifics have included length/percentage in each individual core, length/percentage for the core with the largest amount of tumor, and an overall length/percentage for the entire case. The observation that reporting guidelines do not designate a specific method to be used reflects data indicating no one method has been proven to be superior to others.^{6,7} Studies have generally found that the greater the amount of tumor by any of these

methods, the larger the volume of tumor in the gland and the more likely that the tumor is not organ confined at radical prostatectomy.^{15–18} Linear measurements in mm can be determined by ocular micrometer or by knowing the diameter of the field at various magnifications and using this to estimate length.

A substantial and unresolved issue in determining linear extent is how to account for 'skip' areas where there is benign tissue between foci of adenocarcinoma. This is a controversial area with little data to determine the optimal approach. One study with a small number of patients found that using an 'end-to-end' approach that included intervening benign tissue in the tumor measurement better predicted tumor volume in the radical prostatectomy.²¹ Another study tested the importance of the length of the intervening tissue in determining whether to include it or not in the tumor measurement and found that if consistently applied, including or excluding benign tissue did not make a significant difference.¹⁸ In a study comparing an in-house method (end-to-end approach) with percentages reported on the outside, the in-house approach was superior in predicting pathologic stage but the authors did not perform alternate methods themselves on the selected cases.²² Another report compared cases where the needle biopsy specimens had only one or two cores involved with the cores having at least 2 mm of intervening benign tissue with the corresponding radical prostatectomy specimens.²³ In this study, 78% of such cases had a solid tumor nodule while 22% contained only scattered small foci. The authors did not discuss if the length of the benign tissue predicted the likelihood of solid *versus* multifocal disease. Figure 3 illustrates an extreme example of this issue. Here the two small foci of adenocarcinoma are located at opposite ends of a needle core biopsy. In this case, the pathologist reported the prostatic adenocarcinoma to involve 90% of the core using an approach that measures tumor without excluding benign tissue. It has been recommended that in such cases the discontinuous nature of the tumor be specified.²² If this were the only positive core in this case, it would make the patient ineligible for surveillance. Because of this unresolved issue, a statement from multiple organizations recommended reporting such biopsies using a method that essentially describes what is on the slide. In this instance, the report might read that the core contains '2 discontinuous foci measuring 4 mm in aggregate, involving 15% of the core, and spanning 80% of the core.' Providing this detail on all cases with skip lesions would require considerable time and effort but for those infrequent cases where the reporting could alter management for the patient it may be a reasonable approach to take.⁸

Figure 3 This single needle core biopsy (red marks the opposite ends) contains two discrete foci of tumor (marked with black lines). There is a long segment of uninvolved prostatic tissue intervening. The biopsy was reported as having 90% involvement by tumor. This can be misleading in an extreme example of skip areas such as this biopsy illustrates. Recent recommendations for cases such as this would quantify the tumor as 'two discontinuous foci measuring 4 mm in aggregate, involving 15% of the core, and spanning 80% of the core.'¹

Periprostic Fat Invasion (Document if Identified)

Prostate needle biopsy specimens can contain periprostatic fat and when involved by tumor this is equated with there being extraprostatic extension and a pathological stage of at least pT3a. Ravery *et al.*²⁴ published a report where at the time of the sextant biopsy, cores were directed to include extraprostatic tissue. In 75% of cases where 'capsular penetration' was diagnosed on the core, extraprostatic extension was confirmed at radical prostatectomy. The current standard biopsy approach that includes lateral cores is similar to that used by Ravery *et al.*²⁴ In a series of 72 needle biopsies with extraprostatic extension, Miller *et al.*²⁵ reported that this finding is usually associated with high-stage and high-grade disease. The diagnosis of extraprostatic extension should be limited to only cases where there is unequivocal fat involvement (Figure 4). It is generally agreed that fat is only rarely present within the prostate parenchyma,^{26–28} although one report identified intraprostatic fat in 4% of totally embedded whole-mounted radical prostatectomy specimen.²⁹ These foci consisted of small collections of 5–20 adipocytes. Intraprostatic adipose tissue has also been described in a needle biopsy specimen.³⁰ Nonetheless, practically speaking, unequivocal fat involvement in a needle biopsy specimen remains a surrogate for extraprostatic extension and should be reported when present.^{6,8}

Seminal Vesicle/Ejaculatory Duct Invasion (Document if Identified)

Seminal vesicle invasion (pT3b) is defined by the 'tumor infiltration of the muscular wall of the seminal vesicle.' Because of difficulties with

Figure 4 A prostate needle biopsy specimen showing unequivocal involvement of fat (a). When this is present, it should be reported as indicating the presence of extraprostatic extension. The second image (b) shows carcinoma close to fat but not involving it. In cases like this, it is not possible to accurately diagnose extraprostatic extension and so need not be reported.

anatomic definitions for seminal vesicle and ejaculatory duct, it is recommended that this refer only to the extraprostatic part of the seminal vesicle.¹³ In some patients, the clinician will specifically target the seminal vesicles during the biopsy procedure and submit these as a separate specimen. In such cases, if tumor is recognized within the smooth muscle wall of seminal vesicle tissue it should be reported as such (Figure 5a). Biopsies designated as 'seminal vesicle' can however have tumor in prostatic tissue or in the peri-seminal vesicle soft tissue and when this is present the report must clearly indicate that the adenocarcinoma is present in the specimen but not in the seminal vesicle tissue (if present) (Figure 5b). Biopsies of the prostate gland, most often from the base, may contain tissue that could represent either seminal vesicle or ejaculatory duct. In such cases if the tissue is involved by the adenocarcinoma this should be commented on but a note should indicate that this may not represent seminal vesicle for staging purposes.⁸

Lymphovascular Invasion

Lymphovascular invasion as a prognostic feature has been studied in radical prostatectomy specimens

Figure 5 In a biopsy submitted as coming from the seminal vesicle (a), involvement of the seminal vesicle tissue is present. In a second seminal vesicle biopsy (b) there is perineural tumor (arrow) in the soft tissue adjacent to the muscular wall but not in the seminal vesicle wall. Reporting a case such as this needs to be clear to indicate that although the specimen contains adenocarcinoma and seminal vesicle tissue, the seminal vesicle tissue is not involved by the tumor.

(see below) but there is little data available for needle biopsies. Experience of most urologic pathologists has been that this is a quite unusual finding in needle biopsies, even with high-volume and high-grade disease. Because of the lack of data, this is included as a non-required or recommended element.⁶⁻⁸

Perineural Invasion

Reporting the presence or absence of perineural invasion is not a required element in either the College of American Pathologists or the International Collaboration on Cancer Reporting guidelines.^{6,7} The significance of perineural invasion in needle biopsy specimens has been extensively studied, with the general conclusion that although it is a significant predictor of pathologic stage and outcome after radical prostatectomy on univariate analysis, it is not an independent factor on multivariable analysis.^{31,32} A more recent report, based on the evaluation of 3226 patients, found perineural invasion to be present in the biopsies of 20% of those undergoing radical prostatectomy.³³ In that large series, it was independently associated with adverse pathologic findings (extraprostatic extension, seminal vesicle invasion, and positive surgical margins) in the radical prostatectomy specimen. It was also an independent predictor of biochemical disease-free survival, cancer-specific survival, and overall

survival. One recent report in MR/US fusion biopsies found perineural invasion to be an independent predictor of extraprostatic extension.³⁴ The significance of perineural invasion in men otherwise eligible for active surveillance has been studied. In an analysis of radical prostatectomy specimens from men eligible for active surveillance, Trpkov *et al.*³⁵ found no increase in adverse pathologic findings in patients with perineural invasion in the biopsy compared with those without. In another report, Moreira *et al.*³⁶ found a significantly higher clinical progression for men on active surveillance with perineural invasion *versus* those without. Should future studies support the latter finding it may be that perineural invasion will be included as a required element. In current guidelines it is a non-required or recommended element.^{6,8}

Additional Pathologic Findings

A wide range of other histopathologic abnormalities can be present in prostatic biopsies, including high-grade prostatic intraepithelial neoplasia, atrophy, and inflammatory processes. In the presence of adenocarcinoma, there is no data to indicate clinical significance to any of these.

Radical prostatectomy specimens

Prostate Size

The most recent College of American Pathologists guidelines no longer include prostate gland measurements as a required element in the synoptic summary.⁶ The International Collaboration on Cancer Reporting does include weight but not dimensions as a required element.⁹ This recognizes that measurements (dimensions and weight) are an essential part of the gross description and so it is not necessary to repeat them in this part of the report.

Tumor Quantitation

- Percentage of prostate involved by tumor
- And/or
- Greatest dimension (mm)
- *Additional dimensions (mm)

The significance of quantitation of tumor in the radical prostatectomy specimen has been an area of considerable debate among urological pathologists. Because of the nature of prostatic adenocarcinoma with tumor multifocality and frequent growth without formation of a distinct solid mass, determination of actual tumor volume has long been viewed as problematic. A number of approaches, including eyeball estimation, use of a grid system, image analysis, measuring the proportion of blocks with tumor, measuring the maximum tumor dimension, and others have been described.¹¹ There is substantial data indicating that

tumor volume predict pathologic stage, biochemical failure, and development of metastases.^{37–39} Studies evaluating the greatest dimension of the tumor as a surrogate for volume have also found it to be a significant predictor of pathologic stage and outcome.^{40,41} In the International Society of Urological Pathology review of this topic, the authors concluded that although cancer volume correlated with many important parameters, there were insufficient data to conclude it was an independent predictor of outcome in contemporary studies. It is however certain that our clinical colleagues have considerable interest in the information. This remains a required element in College of American Pathologists guidelines;⁶ it is not required but recommended in the International Collaboration on Cancer Reporting data set.^{7,9}

Extraprostatic Extension

Focal or nonfocal (if present). The presence of extraprostatic extension defines the pT3a category in the pathologic staging of prostatic adenocarcinoma.

The presence of extraprostatic extension is associated with an increased risk of biochemical recurrence, distant metastases and cancer-specific survival. It is therefore a required element in both the College of American Pathologists and the International Collaboration on Cancer Reporting guidelines.^{6,7,9} The assessment of extraprostatic extension is made challenging by the fact that the prostate gland for the most part does not have a well-defined capsule.⁴² The most straightforward criteria for extraprostatic extension is invasion into periprostatic fat (Figure 6a). The rare occurrence of fat within the prostate gland discussed above is not problematic in the radical prostatectomy specimen. Extraprostatic extension is also diagnosed when there is clear extension beyond the confines of the prostate. This includes extension along fibrous bands or nerves within the periprostatic tissue (Figure 6b).¹² In many prostate glands there is condensation of the muscular stroma at the gland periphery with a loose often non-muscle containing stroma beyond (Figure 6c). Involvement of this

Figure 6 These images illustrate foci of extraprostatic extension. In **a** the tumor is directly involving fat. In **b** there is a single malignant gland in fibrous connective tissue within the fat. The image in **c** shows tumor in loose fibrous connective tissue beyond the boundary where smooth muscle fiber (arrows) ends. In image **d** there is a focus of perineural tumor (arrow) adjacent to (at the level of) fat.

stroma, with or without associated desmoplasia, can also be used to support the presence of extraprostatic extension. In this situation, the presence of fat at the same level adjacent to the tumor will help support the diagnosis (Figure 6d).^{7,9} The apex and the anterior aspect of the prostate are particularly problematic. Involvement of the apex is not by definition extraprostatic extension, including cases where the tumor is present at the margin.¹² Anteriorly, there is a paucity of glands and the anterior fibromuscular stroma as described by McNeal⁴³ does not have a defined capsule. Using a 'guesstimated' contour joining benign glandular elements has been discussed, but given the anatomy of the anterior prostate gland, this would not be reliable. For these reasons, fat involvement is the most important criteria for extraprostatic extension at this location. Both the apex and anterior prostate contain skeletal muscle and this is not a useful indicator of extraprostatic extension. It has however been reported that the presence of tumor in skeletal muscle in apex biopsies is associated with an increased risk of a positive surgical margin at the apex.⁴⁴

Studies evaluating the reproducibility of the diagnosis of extraprostatic extension have highlighted the difficulties pathologists face.^{45–47} The major difficulty these studies have highlighted is handling cases where the extraprostatic extension is equivocal (Figure 7).⁴⁷ The AJCC Cancer Staging manual provides guidance for these cases. The general staging rules state that 'If uncertainty exists regarding how to assign a category, subcategory, or stage group, the lower of the two possible categories, subcategories, or groups is assigned for T, N, or M.'⁴⁸ On the basis of this principle, if a focus is equivocal

Figure 7 This photomicrograph shows perineural adenocarcinoma in dense fibrous tissue at the apparent edge of the prostate gland. There is not a well-defined condensation of smooth muscle in the area and there is no stromal response to the tumor. If uncertain as to whether this should be considered extraprostatic extension or not, the AJCC rules for staging would indicate that as it is not unequivocally extraprostatic extension it should be considered organ confined (pT2).

for extraprostatic extension, the tumor should be assigned to the pT2 category (all other things being equal).

Quantification of extraprostatic extension has been demonstrated to have prognostic significance.^{49–54} Two basic approaches have been used. The first defines focal using quantification of the tumor beyond the gland^{49,50,54} while the second uses measuring the radial extension beyond the gland.^{51–54} Either approach has demonstrated the significance of quantifying extraprostatic extension. The current College of American Pathologists and the International Collaboration on Cancer Reporting recommend using only a few neoplastic glands being outside the prostate or a tumor involving less than one high-power field ($\times 40$) in one or two sections to define focal extraprostatic extension with nonfocal being more than this.^{6,7,9}

Urinary bladder neck invasion. Before the seventh edition of the AJCC Cancer Staging Manual,⁵⁵ the staging of tumors with microscopic involvement of the bladder neck in the radical prostatectomy specimen was controversial. Some considered this to be pT4 (bladder invasion) while others considered it to be 'specimen confined' and not to affect assignment of T. In the seventh edition this was resolved with microscopic involvement of the bladder neck included in the definition of extraprostatic extension (pT3a).⁵⁵ This definition is retained in the eighth edition.⁴⁸ The change was based on data indicating that biochemical recurrence for cases with microscopic involvement of the bladder neck was similar to cases with extraprostatic extension.^{56–61} These studies are however confounded by the inclusion of cases with a positive bladder neck margin in the bladder neck invasion definition.^{56,62}

The definition of bladder neck invasion as described in the AJCC manual is 'tumor detected in bladder neck/proximal margin sections.'⁴⁸ This is problematic as depending on how the prostate gland is dissected, these 'sections' frequently contain prostatic glandular tissue. A more practical approach is to define bladder neck invasion as the presence of prostatic adenocarcinoma in thick smooth muscle bundles in the absence of benign prostatic glands (Figure 8a).^{7,9} If benign prostatic glands are present, then this should not be considered bladder neck invasion, even if the block comes from the bladder neck region (Figure 8b).^{12,63}

Seminal vesicle invasion. The presence of seminal vesicle invasion defines the pT3b category in the pathologic staging of prostatic adenocarcinoma.⁴⁸ Invasion of the seminal vesicle(s) indicates a worse prognosis than extraprostatic extension.^{64,65} By definition, seminal vesicle invasion requires demonstration of invasion of the muscular wall and is limited to the extraprostatic portion of the seminal vesicle (Figure 9a).^{13,48} Tumor present in the periseminal vesicle soft tissue should be reported as

Figure 8 In this section from the bladder neck (a) tumor is invading smooth muscle fibers without associated benign prostatic glands. This is considered to be pT3a disease in the current AJCC TNM staging system. In contrast, the bladder neck section in (b) also has tumor but in this case there are intermingled benign glands (b) and so it should not be assigned to the pT3a category.

extraprostatic extension, not seminal vesicle invasion (Figure 9b). Prostatic adenocarcinoma has been shown to involve the seminal vesicles by different routes, including direct invasion at the prostatic stroma/seminal vesicle junction, extension along the ejaculatory ducts, by invasion from extraprostatic tumor and finally indirectly, presumably by metastases.⁶⁶ This has implications for sampling of the seminal vesicles; it is generally agreed that a section taken at the junction of the seminal vesicle and the prostatic gland is the one most likely to detect seminal vesicle invasion.¹³ Additional random sections or sections grossly suspicious for tumor may also be submitted. Total submission of the seminal vesicles is not considered necessary.¹³

Margins

- Limited (< 3 mm) or non-limited (≥ 3 mm)
- *Linear length of positive margins
- *Focality (unifocal or multifocal)

Figure 9 In image (a) the tumor is extensively infiltrating the muscular wall of the seminal vesicle meeting the criteria for pT3b disease. In the second image (b) there is tumor present between the muscular walls of the seminal vesicle (arrows) that is largely within lymphovascular spaces. This should not be diagnosed as seminal vesicle invasion.

- Location(s) of positive margin
- *Margin positivity at area of extraprostatic extension
- *Gleason pattern at positive margin.

The presence of carcinoma at the surgical margin is well documented to have independent prognostic significance following radical prostatectomy.¹⁴ A positive surgical margin is defined by the presence of tumor touching the inked surface of the specimen (Figure 10a).^{7,14} The presence of even one or two collagen fibers between the tumor and the ink is enough to consider the margin negative (Figure 10b).⁷ It is generally accepted that the closeness of the tumor to the margin does not have prognostic significance based on most reports in the literature though this has not been uniformly found.^{67,68} In some cases the degree of cautery at the margin can make interpretation difficult; if tumor is extending into the cauterized tissue it should be considered to represent a positive margin (Figure 10c).

Figure 10 In the first image (a) there is tumor extending directly to the inked surface meeting the definition of a positive surgical margin. In image b the tumor is very close but does not actually touch the ink and this would be reported as a negative surgical margin. In c obvious tumor is extending into the inked cauterized surface; this is considered a positive surgical margin. Image d illustrates an example of tumor involving the inked cauterized margin at a site of extraprostatic extension.

In cases with positive surgical margins several additional parameters have been evaluated in the literature, including the location of the positive margin, quantification of the positive margin (linear length in mm), whether it is unifocal or multifocal, whether it is at a site of extraprostatic extension or not, and the Gleason score of the tumor at the margin. Some reports have found that specific locations are associated with a higher failure rate but other studies have found different (conflicting) locations while others have found location to not matter.^{69–74} Nonetheless, both the College of American Pathologists and the International Collaboration on Cancer Reporting list the location of positive margin(s) as a required element.^{6,9}

The data regarding quantification of the extent of surgical margin positivity have been more consistent.^{69,75–82} In several reports, a total length of 3 mm was found to be a useful cut point,^{74,76,78,80,82} and this has been adopted by the College of American Pathologists to define ‘limited’

and ‘non-limited’ involvement.⁶ The International Collaboration on Cancer Reporting has also adopted the 3 mm cut point but includes this as a recommended but not required element.⁹

It has also been reported that the presence of tumor at the inked margin at the site of extraprostatic extension confers a particularly higher risk of subsequent failure although data here are very limited (Figure 10d).⁸³ A detailed study of the distance of the extraprostatic tumor to the adjacent margin did not find this to impact outcome.⁸⁴ A special situation arises when tumor is at the margin in combination with benign glands. Published data indicates that positive margins at a site of ‘intraprostatic incision’ or ‘capsular incision’ is associated with a higher risk of failure than positive surgical margins in a pT2 tumor.^{78,85,86}

Finally, several reports have looked at the Gleason score of the tumor at the site of the positive surgical margin(s).^{75,79,82,87} These have found the tumor grade at the positive margin to be an independent

predictor of biochemical recurrence. Given the limited data, reporting this feature is at present not a required element in either the College of American Pathologists or International Collaboration on Cancer Reporting guidelines.^{6,7,9}

Lymphovascular invasion. The prognostic significance of lymphovascular invasion as a finding in radical prostatectomy specimens has been recognized for many years.^{88,89} This has been confirmed in several large (number of cases ranging from 742 to 6678) contemporary series based on examination of the hematoxylin-and-eosin-stained slides.^{76,90–94} In these series lymphovascular invasion was identified in 2.8–21.5% of specimens (median, 7.4%). In all six large contemporary series, the presence of lymphovascular invasion was an independent predictor of biochemical recurrence on multivariable analysis. In general the presence of lymphovascular invasion is considered to be relatively uncommon, with the exception of the one series.⁹² Problems with histologic criteria for lymphovascular invasion in prostatectomy specimens have been reported on and strict criteria need to be applied in these specimens.^{12,95} Interestingly, in one series unequivocal and equivocal lymphovascular invasion were analyzed separately and both were independent predictors of biochemical recurrence.⁹¹ Despite the strong data in the literature, this element is not required in the College of American Pathologists or the International Collaboration on Cancer Reporting protocols.^{6,7,9}

Perineural invasion. The clinical significance of perineural invasion in the radical prostatectomy specimen has been evaluated in multiple studies.^{76,90} Perineural invasion is present in the majority of radical prostatectomy specimens. It has generally been accepted that perineural invasion in the radical prostatectomy specimen is not an independent predictor of outcome after surgery,⁶ and therefore it has not been a required element for reporting guidelines. There have been some studies to indicate otherwise but to date these have been in the minority.⁹⁰

Regional lymph nodes. A regional lymph node dissection may or may not be performed at the time of radical prostatectomy depending on surgeon preference and some assessment of likelihood of lymph node metastases being detected. When a lymph node dissection is submitted, quantification of the number of lymph nodes present is considered a required element in the report.^{6,7,9,13} In the current AJCC staging system there are only two N categories that apply: N0, no positive regional nodes; and N1, metastases in regional node(s).⁴⁸ The number of positive lymph nodes and the size of metastases are not part of the nodal category. Involvement of nonregional lymph nodes is reported as pM1a.⁴⁸

Although not part of the N category, determination of the number of nodes with metastases is a required

element. The number of positive lymph nodes is an independent predictor of survival in these patients.⁹⁶ Other features such as the size (mm) of the largest metastasis, the size of the largest involved lymph node (cm), and the presence or absence of extranodal extension are not required elements.^{6,7,9} The size of metastatic deposits has been reported to be a significant predictor of biochemical recurrence-free survival, distant metastasis, and cancer-specific survival in some but not all reports (Figure 11a).^{96–99} The International Society of Urological Pathology did however recommend reporting the size of the largest deposit.¹³

There are limited numbers of reports on the significance of extranodal extension in patients with lymph node metastases (Figure 11b). One series of 484 patients with lymph node metastases found extranodal extension in 58% of cases; this correlated significantly with biochemical recurrence-free survival in a univariate but not a multivariate analysis.⁹⁶ A recent meta-analysis of six publications considered suitable for inclusion, reported extranodal extension to correlate significantly with a higher risk of biochemical recurrence and distant metastases.¹⁰⁰ Interestingly, a survey of members of the International Society of Urological Pathology

Figure 11 The first photomicrograph (a) illustrates a lymph node with a microscopic metastases consisting of only a few malignant glands. In contrast image b shows a large lymph node metastasis that also has extranodal extension of the tumor.

Table 3 Pathologic stage classification (pTNM AJCC eighth edition)⁴⁸*Pathological T category (pT)*

pT2	Organ confined
pT3a	Extraprostatic extension (unilateral or bilateral) or microscopic invasion of bladder neck
pT3b	Tumor invades seminal vesicle(s)
pT4	Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall

Regional lymph nodes (N)

NX	Regional nodes were not assessed
N0	No positive regional nodes
N1	Metastasis in regional node(s)

Distant metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node(s)
M1b	Bone metastasis
M1c	Other site(s) with or without bone disease

found that 88% of respondents did report extranodal extension.¹³

Disclosure/conflict of interest

The author declares no conflict of interest.

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