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EDITORIAL

MORPHOLOGICAL ANALYSIS OF RADICAL PROSTATECTOMY SPECIMENS: RECENT TOPICS RELEVANT TO PROGNOSIS

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The pathology report should include clinically relevant information as well as provide clinically useful information derived from the macroscopic examination and microscopic evaluation of the radical prostatectomy (RP) specimens. The reporting pathologist should pay particular attention to the evaluation of the prognostic factors proven to be of prognostic importance and useful in clinical patient management, including histological type, grade and volume of cancer, the extent of local invasion and stage of cancer as well as the surgical margins status.

Handling of radical prostatectomy specimens is a challenging task for the pathologist. The prostate undergoes faster autolysis than most other organs, prostate cancer is notoriously difficult to identify with the naked eye, the tumors are smaller but yet more multifocal than most other clinically diagnosed cancers and prostate cancer is very heterogeneous, both morphologically and genetically. Thus, these specimens need to be handled with great care and according to standardized protocols to enable accurate assessment of grade and stage (1).

The aim of this contribution is to review recent topics relevant to the morphological evaluation of radical prostatectomy specimens with prostate cancer. Special reference is made to the International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens (2).

HANDLING OF RADICAL PROSTATECOMY SPECIMENS

A problem when handling radical prostatectomy specimens is that cancer is often not visible at general examination, and the tumor extent is always underestimated by the naked eye. The challenge is

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increased further by the fact that prostate cancer is a notoriously multifocal and heterogeneous tumor. For the pathologist, the safest method to avoid undersampling of cancer is evidently that the entire prostate be submitted (1, 2). Even though whole mounts of sections from RPs appear not to be superior to sections from standard blocks in detecting adverse pathological features, their use has the great advantage of displaying the architecture of the prostate and the identification and location of tumour nodules more clearly, with particular reference to the index tumour (Fig. 1); furthermore, it is easier to compare the pathological findings with those obtained from digital rectal examination, transrectal ultrasound and prostate biopsies.

PROGNOSTIC FACTORS IN RADICAL PROSTATECTOMY SPECIMENS

The pathology report should include clinically relevant information as well as provide clinically useful information derived from the macroscopic examination and microscopic evaluation of the radical prostatectomy specimens (3, 4).

Histological type of cancer

In recent years, a number of new and unusual histological variants or subtypes have been identified. These variants represent the spectrum of changes which can occur in adenocarcinoma (Table I). The biological behaviour of many of these variants may differ from typical adenocarcinoma and proper clinical management depends on accurate diagnosis and separation from tumours arising in other sites. It is recommended that subtypes, such as small cell, ductal and mucinous, should be reported if they are noted histologically. Mixtures of different histological types should be indicated (5).

Histological grade of cancer

Histological grading is the clinically most useful tissue-based predictor of prognosis of prostate cancer. Over the years there has been a gradual shift of how the Gleason grading is applied in practice with a general trend towards upgrading. A consensus conference was organized in 2005 by the International Society of Urological Pathology with the purpose to standardize both the perception of histological patterns and how the grade information is compiled and reported. Here is a summary of the ISUP modified Gleason grading system (6-8).

- The Gleason score is the sum of the primary (most predominant) Gleason grade and the secondary (second most predominant) Gleason grade. In needle biopsies, this definition is modified to include any component of higher grade (see below).
- A Gleason score of 1 + 1 = 2 is a grade that should not be diagnosed regardless of the type of specimen, with extremely rare exception.
- The diagnosis of Gleason score 2-4 on needle biopsies should be reported rarely, if ever.
- Individual cells would not be allowed within Gleason pattern 3.
- The vast majority of cribriform patterns are diagnosed as Gleason pattern 4 with only rare cribriform lesions satisfying diagnostic criteria for cribriform pattern 3 (See below).
- *Grading variations of acinar adenocarcinoma.* One should grade the tumour solely based on the underlying architecture. For instance, pseudohyperplastic cancer should be assigned a Gleason score of 3 + 3 = 6.
- *Grading variants of adenocarcinoma.* Ductal adenocarcinomas should be graded as Gleason score 4 + 4 = 8, whereas PIN-like ductal adenocarcinoma as Gleason pattern 3 and ductal adenocarcinoma with comedonecrosis as Gleason pattern 5, while retaining the diagnostic term of ductal adenocarcinoma to denote their unique clinical and pathological findings. There is no consensus on the way mucinous (colloid) carcinoma should be scored. Some authors think that all mucinous carcinomas should be assigned a Gleason score of 8, while others say that one should ignore the extracellular mucin and grade the tumour based on the underlying architectural pattern. The grading of glomeruloid glands is another controversial area in the modified Gleason system. Small cell carcinoma should not be assigned a Gleason grade. The appropriateness of assigning a Gleason score to sarcomatoid carcinoma is uncertain. In general, a Gleason grade is not assigned to the sarcomatoid component, whereas the glandular component is graded in the usual fashion.
- *Reporting secondary patterns of lower grade when present to a limited extent.* In the setting of high-grade cancer one should ignore lower grade

patterns if they occupy less than 5% of the tumour area.

- *Reporting secondary patterns of higher grade when present to a limited extent.* High-grade tumour of any quantity on needle biopsy should be included within the Gleason score.
- *Tertiary Gleason patterns.* The typical situation with tertiary patterns on biopsy includes tumours with patterns 3, 4, and 5 in various proportions. Such tumours should be classified overall as high grade (Gleason score 8-10) given the presence of high-grade tumour (patterns 4 and 5) on needle biopsy. On needle biopsies with patterns 3, 4, and 5, both the primary pattern and the highest grade should be recorded. For a radical prostatectomy specimen one assigns the Gleason score based on the primary and secondary patterns with a comment as to the tertiary pattern.
- *Percent pattern 4-5.* Whether or not the actual percentage of 4-5 pattern tumour should be included in the report is not clear based on published data to date and, if this emerges as an important parameter, meaningful discriminatory cut-off points for percentage of pattern 4-5 will need to be defined. It remains an option if one wants to include this information in addition to the routine Gleason score.
- It has recently been recommended that all cribriform patterns are diagnosed as Gleason pattern 4 rather than pattern 3 (9-11). Glomerulations most likely represent an early stage of cribriform pattern 4 cancer and should likely be graded as pattern 4.

The most immediate result of limiting the definition of Gleason pattern 3 and expanding the definition of pattern 4 is Gleason grade migration or up-grading, both in needle biopsies and radical prostatectomy specimens. There are clinical consequences with the up-grading in the Gleason score, for instance, in the type of therapy offered to an individual patient with PCa (8). As an example, patients with high grade tumours in the biopsy could be discouraged from undergoing active surveillance.

Staging

The protocol recommends the use of the TNM Staging System for carcinoma of the prostate of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) (12, 13). The most recent revision was published in 2009. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible. The prefix symbol "p" refers to the pathologic classification of the TNM (pTNM), as opposed to the clinical classification. Pathologic classification is based on gross and microscopic examination. By AJCC/UICC convention, the designation "T" of the TNM classification refers exclusively to the first resection of a primary tumour. Therefore, pT entails a resection of the primary tumour or biopsy adequate to evaluate the highest pT category; pN entails removal of nodes adequate to validate lymph node metastasis; and pM implies microscopic examination of distant lesions.

Tumour remaining in a resection specimen following previous (neoadjuvant) treatment of any type (radiation therapy alone, chemotherapy

Table I. *Histological classification of carcinoma of the prostate.*

1. Adenocarcinoma (acinar, conventional, not otherwise specified)
2. Variants of adenocarcinoma and other carcinomas
   - Pseudohyperplastic adenocarcinoma
   - Foamy gland adenocarcinoma
   - Atrophic adenocarcinoma
   - Adenocarcinoma with glomeruloid features
   - Mucinous (colloid) adenocarcinoma
   - Signet ring cell carcinoma
   - Oncocytic adenocarcinoma
   - Lymphoepithelioma-like carcinoma
   - Undifferentiated carcinoma, not otherwise specified
   - Prostatic duct adenocarcinoma
   - Small cell carcinoma and other neuroendocrine tumours
   - Sarcomatoid carcinoma
   - Basal cell carcinoma
   - Urothelial carcinoma
   - Adenosquamous carcinoma
   - Squamous cell carcinoma

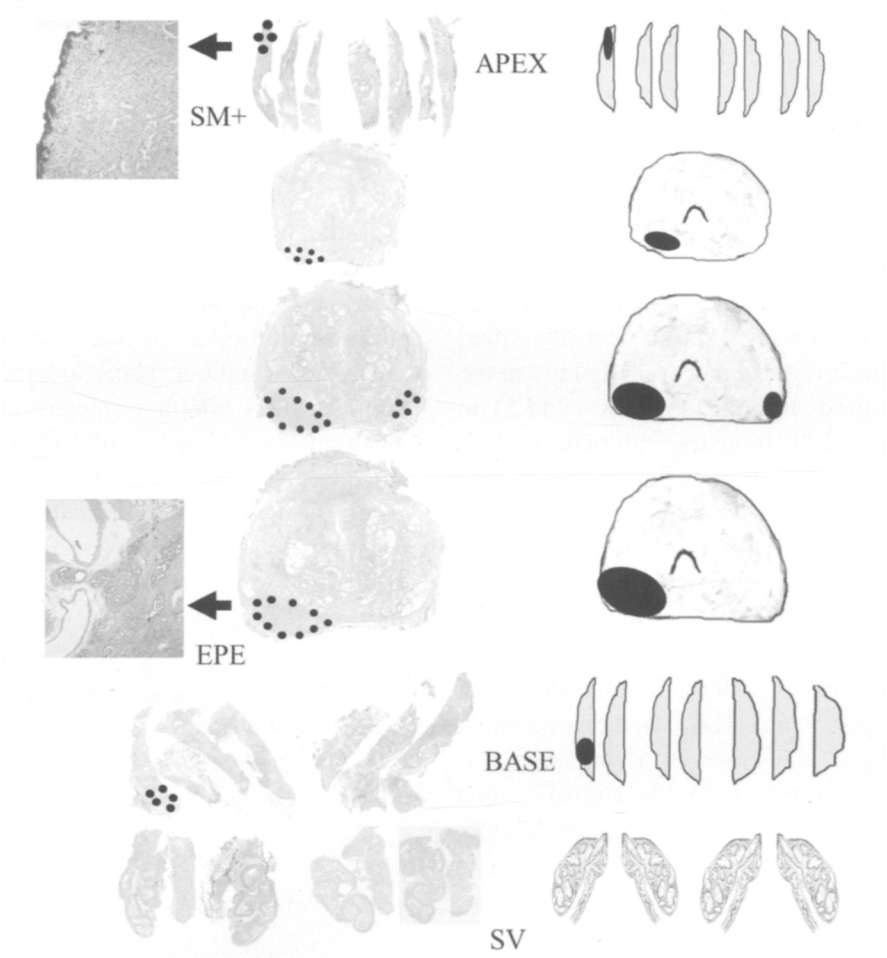

Fig. 1. *Complete sampling with the whole mount technique of a prostate specimen. Hematoxylin and eosin-stained sections of prostate specimen are shown on the left and the corresponding mapping on the right. The dotted areas on the slides and the black areas of the map represent two prostatic cancer foci, the index tumour being present on the left of the slides. Extraprostatic extension (EPE) and positive surgical margin (SM+) are present in the postero-lateral aspect of the body of the prostate and in one of the slides of the apex (see details in the separate images) (SV: seminal vesicles).*

therapy alone, or any combined modality treatment) is codified by the TNM using a prescript "y" to indicate the post-treatment status of the tumour (e.g., ypT1). The classification of residual disease may be a predictor of postoperative outcome. In addition, the ypTNM classification provides a standardized framework for the collection of data needed to accurately evaluate new neoadjuvant therapies.

Tumor multifocality

Prostate cancer is multifocal in up to 80% of cases. The dominant or index tumor is usually the largest, paramount importance in prognosis (and therapy, such as focal therapy) (Fig. 1). The other foci are usually small. Noguchi M et al. found that only index tumor volume, and not total tumor volume, was an independent predictor of progression (14). The concept of an index tumor was discussed at the ISUP consensus conference, however there was no agreement as to an appropriate definition for this. In particular, no consensus was reached as to which parameter should have priority for defining the index tumor when there is a conflict between highest grade, stage or volume between separate tumor foci.

T2 substaging

Staging category pT2 includes tumors that are confined within the prostate gland and among

controversies relating to tumors that present in this staging category are issues relating to the value of substaging, the reporting of multifocal tumors and the relevance of tumor size as a prognostic parameter (3, 15).

The pathological substaging of pT2 prostate cancers currently mirrors clinical T2 substaging. A pT2a tumor is defined as a unilateral tumor, occupying less than half of one lobe, a pT2b tumor is unilateral, occupying more than half of one lobe, while a pT2c tumor is bilateral. There are several problems with this classification. Stage pT2b is a very rare finding, as most tumors that are larger than one lobe of the prostate gland grow across the midline and are rarely organ-confined. Tumors classified as pT2b are thus large and have less favorable outcome than pT2c tumors. The definition of pT2c is unclear and in particular it is uncertain whether the presence of separate but minute foci of tumor in the contralateral lobe is sufficient to classify a tumor as pT2c, or if the main tumor focus must cross the midline before being considered pT2. There is also debate as to why extension across the midline of the gland should be considered an important prognostic feature. In line with this, a majority of the delegates present at the ISUP consensus meeting voted to abandon the current pT2 substaging category. Given the favorable prognosis of organ-confined disease it can also be questioned whether substaging is at all justified (3).

Extraprostatic extension (pT3a)

The prostatic capsule is a poorly defined structure and not a true capsule, but is rather a transition between condensed prostatic stroma and more loosely arranged extra-prostatic connective tissue. This structure is particularly poorly defined around the apex, the anterior prostate and at the base of the gland. For these reasons, extra-prostatic extension (EPE) is considered a more appropriate terminology than capsule penetration. Extra-prostatic extension is most frequently encountered in the posterolateral region at the neurovascular bundle. Tumor adjacent to or invading into adipose tissue is diagnostic of extra-prostatic extension (Fig. 1). However, contrary to the situation with core biopsies, it was also agreed that prostatectomy specimens may be diagnosed with extra-prostatic extension even when extra-prostatic cancer is surrounded by desmoplastic connective tissue. Thus, tumor within a fibrous band, beyond the prostatic parenchyma or beyond condensed smooth muscle, is sufficient to diagnose extra-prostatic disease.

In areas where the so-called capsule is particularly poorly defined such as at the anterior, the apex and at the bladder neck, growth into or at the level of adipose tissue is not required for the diagnosis of extra-prostatic extension. At the apex and anteriorly, there is a continuous transition between prostatic tissue and the striated muscle tissue of the pelvic floor.

Extra-prostatic extension can be stratified as focal or established (or extensive or non-focal). Patients with focal extra-prostatic extension have a more favorable outcome after radical prostatectomy than those with established/extensive extraprostatic extension and it was agreed that the extent of extraprostatic extension should therefore be specified in the report. There is, however, no uniform definition of these categories and measures such as "a few glands outside the prostate" or "less than one high-power field" have been used to define focal extra-prostatic extension (3, 16). Recently, Sung et al. proposed that the radial distance of extra-prostatic extension should be used, with a cut-off at 0.75 mm having prognostic significance (17). This method has some disadvantages: It is labour intensive and because the prostatic capsule is so poorly defined, it is very difficult to know from where this distance should be measured. It was recommended at the consensus conference that extra-prostatic extension be stratified as focal or established, but no consensus was reached as to the definitions of these categories (3, 16).

Seminal vesicle invasion (pT3b)

Seminal vesicle invasion (SVI) is defined as cancer invading into the muscular coat of the seminal vesicle. SVI has been shown in numerous studies to be a significant prognostic indicator (18, 19).

Three mechanisms by which prostate cancer invades the seminal vesicles were described by Ohori et al (20) as:

1. by extension up the ejaculatory duct complex;
2. by spread across the base of the prostate without other evidence of EPE or involvement from tumour invading the seminal vesicles from the periprostatic and periseminal vesicle adipose tissue;

and

3. as an isolated tumour deposit without continuity with the primary prostate cancer tumour focus.

While in most cases, seminal vesicle invasion occurs in glands with EPE, the latter cannot be documented in a minority of these cases. Many of these patients had only minimal involvement of the seminal vesicles, or involve only the portion of the seminal vesicles that is at least partially intraprostatic. Patients in this category were reported to have a favourable prognosis, similar to otherwise similar patients without SVI. Despite this, the prognostic value of these categories has not been confirmed by others (21).

Locally advanced disease (pT4)

In previous editions of the TNM classification, bladder neck invasion was classified as pT4 disease, even when invasion was microscopic rather than macroscopic. It has, however, been shown that these patients have an outcome similar to those with ordinary extra-prostatic extension and it was agreed that the TNM classification should be revised accordingly. Indeed, in the latest edition, microscopic bladder neck invasion is now considered pT3a disease, while macroscopic bladder neck invasion is categorized as pT4 (3, 12).

Surgical margins and residual tumour (R)

In general, a prostatectomy specimen is surrounded by a thin layer of connective tissue and a wide surgical margin cannot be expected. Cancer must be seen extending to an inked margin for that margin to be considered positive (Fig. 1) (4, 22). A margin is reported as negative if cancer is separated from the inked surface by as little as a few collagen fibres. Tumor close to, but not extending to a margin, should be reported as a margin negative as this does not influence prognosis. Positive margins are most commonly seen at the apex of the gland but may occur anywhere. Similar to extra-prostatic extension, stratification of margin positivity into focal and more than focal may be useful, but the consensus conference failed to agree on methods for defining this. Among proposed definitions of focal margin positivity were; i) only a few tumor cells in contact with the inked margin, ii) margin positivity involving one gland in one section, iii) 3 mm or less of positive margin in one section and iv) limited margin positivity in only 1-2 areas. Until a clinically relevant cut-off is decided upon, it was recommended that the linear extent of margin positivity be reported. Similar to the case of extraprostatic extension, it was agreed that the location of any tumor positive margin should be reported, as this gives important feedback to the clinician.

Tumour remaining in a patient after therapy with curative intent (e.g., surgical resection) is categorized by a system known as R classification. This classification may be used by the surgeon to indicate the known or assumed status of the completeness of the surgical resection. For the pathologist, the R classification is relevant only to the margins of surgical resection specimens; patients with tumour involving the resection margins on pathologic examination may be assumed to have residual tumour. Such patients may be classified as to whether the involvement is macroscopic or microscopic (4, 22).

Lymphovascular invasion (LVI)

The TNM system uses the category LVI to indicate the presence of lymphatic or venous invasion. Most of the time when vascular invasion is noted it is in tumours with fairly advanced pathology such that it is unclear as to its independent prognostic significance. It has been shown that LVI correlates with risk of recurrence after radical prostatectomy, both in univariate and multivariate analysis (23).

Perineural invasion

Perineural invasion is almost ubiquitously present in radical prostatectomy specimens such that it is not useful as a prognostic parameter and we do not record it within radical prostatectomy pathology reports. As with all of the other parameters, the key question is whether the presence of (intra-prostatic) perineural invasion in the prostatectomy specimen is an independent prognosticator. At this time it is not entirely clear whether there are differences in terms of prognosis between intra-prostatic and extra-prostatic perineural invasion (24).

Volume of cancer

There are several methods for estimation of

tumor volume, including planimetry, the grid method, assessment of the percentage of the specimen involved by cancer and measurement maximum tumor diameter (3, 15, 23). Volume of prostate cancer correlates with other prognostic factors such as grade, stage and ploidy and also with prognosis in patients who have undergone radical prostatectomy. Some authors have reported that tumor volume is not an independent predictor of prognosis when Gleason score, the presence of extra-prostatic extension, surgical margin positivity and seminal vesicle invasion are included in the analysis. Other studies, based on series with larger tumors, have found that tumor volume is an independent prognostic factor. Because of these conflicting data, it was recommended that measurement and reporting of tumor volume should not be mandatory but that it was reasonable to give an objective measure of tumor size, such as greatest diameter of the largest tumor focus.

Quality indicators

The quality of surgical specimens are influenced by numerous factors: surgeon's experience, surgical technique, patients' characteristics (obesity, previous BPH surgery, gland volume), tumor features, selection criteria and hospital volume. Also the use of pre-operative androgen deprivation therapy may influence the surgery and the pathology features. The definition of quality indicators of prostatectomy surgical specimens are important to assess a high level of qualified assistance and management (25).

CONCLUSIONS

Substantial effort has been expended in the recent years in describing the available factors and determining their predictive value for staging, cancer recurrence, and patient survival. The pathologists derive many clinically important predictive factors in prostate cancer from light microscopic examination of RP specimens. The goal is to tailor the therapeutic approach to the clinical, morphological and molecular features of each patient. While in the future conventional histology will not be replaced in the evaluation of prostate cancer at radical prostatectomy and its correlation with outcome, it will undoubtedly be augmented by new markers and modern techniques.

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