Handling and Staging Radical Prostatectomy Specimens: Recommendations from the 2009 ISUP Consensus Conference

Lars Egevad
Dept of oncology-pathology, Karolinska Institutet, Stockholm, Sweden

The clinical importance of the pathology reports of radical prostatectomy (RP) specimens has increased in recent years. Patients with adverse histopathological findings may now be offered adjuvant therapies such as radiotherapy, chemotherapy or hormonal treatment. In the future we will most likely see more individualized therapy in these cases. Thus, it is increasingly important that the pathologist is able to make a correct assessment of stage and grade of RP specimens. With this in mind the International Society of Urological Pathology (ISUP) organized a consensus meeting on Handling and Staging Radical Prostatectomy Specimens, held in Boston, Massachusetts, USA at the 2009 USCAP meeting. All senior ISUP members were invited to the consensus process and 157 members from 26 countries participated. Prior to the meeting a web-based survey was completed by the delegates. The conference was conducted by 5 working groups and attended by 116 delegates. At least 65% agreement was required for consensus.

1. Handling of radical prostatectomy specimens

The prostate undergoes rapid autolysis because of the presence of proteolytic enzymes. Thus, RP specimens should be either immediately fixed in abundant formalin or promptly transported fresh on ice to the pathology laboratory. Upon arrival to the laboratory, the prostate should be weighed and measured in three dimensions (vertical, transverse and sagittal) to enable correlation with e.g. radiological exams. It was agreed that the weight of the prostate itself must be recorded independent of the seminal vesicles, i.e. after their removal. The size of the seminal vesicles varies and some surgeons may choose not to remove the entire seminal vesicles. Therefore, recording of only the total weight of the specimen can be misleading.

A variety of methods are used for harvesting of fresh tissue for research. Most pathologists take shave or punch biopsies from the cut surfaces of an incision into the prostate (68%) or very rarely fine needle aspirates or scrapings. The harvesting method was not standardized by the consensus panel.

Inking the prostate is mandatory. It was decided that a minimum of two colors should be used to distinguish between right and left side. Before final cutting for embedding the prostate should be fully fixed. Bread-loafing of the unfixed prostate is not recommended because of the difficulties to obtain slices of equal thickness and because of the risk that surgical margins do not get adequately examined. Techniques for enhanced fixation such as formalin injection and microwaving are useful and may shorten fixation time of RP specimens.
The surgical margins of the apex and base of the prostate need to be carefully examined. There was a consensus that the cone method with sagittal slicing should be used both at the apex and the base. The shave method where a thin shave slice from apex or base is embedded en face is discouraged. 8

Whether whole mounts or standard-size blocks should be used was not addressed by the meeting as this is up to the discretion of the individual pathologist. A contentious area is whether the prostate should be completely or partially embedded. In a previous survey study among pathologists from 217 laboratories in 15 west European countries as many as 71.6% of respondents always embedded the entire prostate and only 10.8% always practiced partial embedding. 9 There seems to be a geographic variation in terms of embedding routines. The delegates at the consensus meeting were almost equally split between total and partial embedding. There was an overwhelming consensus that if partial embedding is used, the specific sampling method should be documented. 10

A proposal was launched to assign a stage pT2a to cases with no cancer found in the RP specimen but with cancer in preoperative needle biopsy specimens. This proposal was however rejected and it was agreed that these cases should continue to be considered pT0.

2. T2 substaging and prostate cancer volume

A prostate cancer that is found to be organ-confined in the RP specimen is assigned stage pT2. In recent decades there has been a significant stage shift of prostate cancer and pT2 tumors have become more common. In TNM 2002 pT2 was substaged in pT2a (Tumor involves one half of one lobe or less), pT2b (Tumor involves more than half of one lobe, but not both lobes), and pT2c (Tumor involves both lobes). 11 This substaging has been heavily criticized. The pT2 substaging is a direct translation of the cT2 substaging, which is based on digital rectal exam findings, while the pT2 substaging is based on tumor involvement of histopathological slides taken throughout the prostate. The definition of pT2b and pT2c is problematic. An objection against pT2b is that it is very unlikely that a tumor would be large enough to fill out more than 50% of one half of the prostate and still be both organ-confined and restricted to one side of the midline. There is a large variation in the distribution of TNM 2002 pT2 substages among different prostate cancer series, with pT2b varying from 0% to 19.1% of cases. 12, 13 Furthermore, it is unclear whether the main tumor has to be bilateral for stage pT2c. Yet, 71% of the pre-meeting survey responders would assign a pT2c to a case with a separate minute contralateral tumor focus. In the TNM 2010 staging, the pathological substaging of pT2 prostate cancers has been retained, although the prognostic value of this has been questioned. 14

There was an agreement that the current pT2 substaging should not be used, but there was no consensus as to what sort of substaging it should be replaced with. Among proposals were reduction of the current 3-tier substaging to a 2-tier substaging (by omitting the current pT2b category) or to use a simple to measure and potentially clinically relevant tumor volume parameter as a cut-off between pT2a and pT2b. A 10 mm diameter cut-off was discussed (corresponding to a sphere volume of 0.5 ml) but no decision was taken as
to the exact definition of such a cut-off. There was also a proposal that there should be a minimum size for a second tumor to be considered for the whole case to be classified as pT2c. However, again the delegates failed to agree on a common definition.

Prostate cancer is strikingly multifocal. At the 2005 ISUP consensus conference on Gleason grading, it was decided that a separate Gleason score should be assigned to each of the dominant tumor foci. It was now discussed whether the index tumor should be defined as a) the largest tumor b) the tumor with the highest Gleason score or c) the tumor with the highest stage, but no consensus was reached.

It has been debated whether transition zone tumors may have a better outcome than peripheral zone tumors of corresponding grade and stage. Clinically these tumors sometimes undergo multiple biopsies because of persistent PSA-elevation until they are diagnosed. It was agreed that the zonal / anterior localization of the index tumor in a prostatectomy specimen should therefore be mentioned in the pathology report.

Volume of prostate cancer correlates with other prognostic factors such as grade, stage and ploidy and also with prognosis after radical prostatectomy. Some authors have reported that tumor volume is not an independent predictor of prognosis when Gleason score, extra-prostatic extension, surgical margins and seminal vesicle invasion are included in the analysis, while others found tumor size to be an independent predictor of outcome. An overwhelming majority of delegates supported that a measure of the tumor size should be given (such as volume, diameter or percentage).

3. Extraprostatic extension, lymphovascular invasion and locally advanced disease

Extraprostatic extension (EPE) is the preferred designation for cancer growing beyond the confines of the prostate gland and the term capsular penetration is no longer recommended. The prostatic capsule is a rather poorly defined plane between the prostatic stroma and the extraprostatic loose connective tissue. The prostate is particularly poorly circumscribed anteriorly and at the apex and base. The definition of EPE is therefore contentious, particularly in these areas. Cancer growth into adipose tissue is helpful when diagnosing EPE although the pathologist must be aware that occasional intraprostatic fat cells may cause a false positive EPE diagnosis. The assessment of cancer growing into extraprostatic connective tissue is even more complicated and subject to interobserver variability. It was decided by the consensus meeting that even in the absence of fat involvement, EPE can be identified posteriorly and posterolaterally when there is tumor within fibrous tissue bulging beyond the contour of the gland. An example of this situation is when cancer is growing in connective tissue on the same level as adjacent extraprostatic adipose tissue. Similarly, EPE is difficult to determine anteriorly where the prostatic stroma merges with thick smooth muscle bundles. Yet, a majority of delegates thought it is possible to identify EPE anteriorly. Anterior EPE can be diagnosed either when cancer invades adipose tissue or when it grows beyond the general contour of the gland, as extrapolated from posterior and posterolateral regions.
Benign glands are frequently admixed with striated muscle in the apex and anteriorly. Thus, tumor growing around striated muscle cells is not by itself diagnostic of EPE.

It has been shown that the amount of EPE has prognostic importance and that patients with focal EPE have a more favorable outcome than those with extensive EPE. Several definitions of focal EPE have been proposed. Epstein et al defined focal EPE as a few glands immediately exterior to the prostate in 1 to 2 sections. Wheeler et al considered tumor outside the prostate to a depth of less than one high-power field in 1 to 2 sections as focal EPE. Sung et al recently advocated a quantitative assessment of the depth of EPE by measuring the radial diameter. They found that EPE reaching less than 0.75 mm outside the prostate was the best cut-off and claimed this measure to be superior to more subjective methods. There are certain limitations with all these methods. It is subjective what is meant by a few neoplastic glands. The definition using a high-power field depends of the size of the visual field of the microscope. A disadvantage with measuring the radial diameter is that it may be difficult to determine the level of the capsular plane which hampers an exact measurement. This method may also require measurement with an ocular micrometer which is time-consuming. Thus, the optimal method for quantitation of EPE remains to be determined. In line with this, the consensus meeting decided that EPE should be somehow quantitated but there was no consensus as to what method to use.

Bladder neck invasion was designated as pT4 in previous editions of TNM. However, it has been shown that patients with microscopic bladder neck invasion (neoplastic cells within thick smooth muscle bundles at the base of the prostate), have a prognosis similar to ordinary EPE and it was decided that these cases should be assigned a stage pT3a. This has been changed accordingly in TNM 2010. pT4 should be restricted to cases with grossly visible bladder neck invasion.

Lymphovascular invasion in RP specimens has been reported to be an independent predictor of lymph node metastases and biochemical recurrence and should be reported.

4. **Seminal vesicles and lymph nodes**

Seminal vesicle invasion (SVI) by prostate cancer has been shown to be a predictor of poor prognosis after RP. However, there have been no uniform recommendations on to how to handle and report the seminal vesicles. Only 38% of pre-meeting survey responders practiced total embedding and it was decided at the consensus conference that it should not be mandatory to totally embed the seminal vesicles in all specimens. In a classical study by Ohori et al (1993), three different routes of SVI were described. The most common variant was invasion through the base of the seminal vesicle. Thus, if partial embedding is used, it should include a block from the base.

The base of the seminal vesicle is inserted into the prostate and surrounded by prostatic tissue. It has been suggested that cancer invasion into the intraprostatic portion of the seminal vesicles has better prognosis than extraprostatic SVI. It was decided that invasion
of the intraprostatic seminal vesicle should not be considered as SVI, and hence be reported as pT3a rather than pT3b.\textsuperscript{32} There was no consensus whether tumor present only within endothelial lined spaces in the muscular wall of the seminal vesicles should be consider pT3b.

A positive vas deferens margin is exceptionally rare and basically only occurs in advanced cases with positive margins elsewhere. Yet, some pathologists routinely sample the vas deferens margins, while others find it unnecessary. It was decided that sampling of the vas deferens margins should not be mandatory.

There was no consensus on how to sample lymph nodes. Some of the conference delegates sample all tissue from lymph node dissections while a majority would only sample grossly visible lymph nodes. The number of lymph nodes seen on microscopy was reported by most respondents of the pre-meeting survey. However, counting pelvic lymph nodes is more difficult than in other lymph node specimens, because of the pronounced fat infiltration. The diameter of the largest lymph node metastasis is the most predictive parameter for these specimens and should therefore be reported.\textsuperscript{33}

5. Surgical Margins

The purpose of radical prostatectomy is to remove the entire tumor. It has been shown that margin status is a predictor of biochemical recurrence.\textsuperscript{34-37} The definition of a positive margin is cancer reaching ink. It has been shown that patients with cancer coming close to the margin have the same outcome as margin negative patients.\textsuperscript{38, 39} It was therefore decided that tumor extending close to the "capsular" margin yet not to it should be reported as a negative margin.

There is some evidence that the location of margin positivity may correlate with prognosis\textsuperscript{40} although results are conflicting\textsuperscript{41}. A positive bladder neck margin may have worse prognosis although it is unclear if bladder neck location is an independent predictor of outcome.\textsuperscript{40, 42} Furthermore, it has some importance for the surgeon to know where the surgical margin is positive as this feedback enables them to modify their surgical technique when necessary. Locations of positive margins should be reported as Posterior, posterolateral, lateral, anterior at either the apex, mid, base.

Extent of margin positivity correlated with prognosis in most studies.\textsuperscript{34, 35, 43, 44} Several efforts have been made to define focal margin positivity. Epstein defined focal margin positivity as limited involvement with only 1 or 2 areas showing tumor extending to margins.\textsuperscript{34} Babaian et al and Weldon et al used 3 mm as a cutoff.\textsuperscript{35, 44} Vis et al diagnosed a focally positive margin when only a few tumor cells touched ink.\textsuperscript{37} Watson et al allowed only one single gland to touch ink to call it focally positive.\textsuperscript{36} No consensus could be reached as to what definition to use for focal margin positivity. The conference recommended that until we can reach such a consensus, we should report the extent of a positive margin as millimeters of linear involvement.
It has been suggested that the grade of a cancer at a positive margin may have prognostic importance but it was decided that this should be left up to the pathologist’s discretion.\footnote{45}

The significance and reporting of intraprostatic (“capsular”) incision has been debated. A recent study showed that isolated intraprostatic incision into tumor entails a higher rate of biochemical recurrence than organ confined or focal extraprostatic extension with negative margins.\footnote{45} Another study found that intraprostatic incision into tumor has a prognosis comparable to pT3a disease with positive margins.\footnote{46} Conflicting results may be explained by controversial diagnostic criteria for intraprostatic incision, particularly at the apex. A majority (72\%) of the pre-meeting survey respondents would report intraprostatic incision into cancer when present. However, no consensus could be reached whether intraprostatic incision should be reported in cases with tumor at ink without benign glands cut across at the apical perpendicular margin section. There was no consensus either whether intraprostatic incision should be reported when benign glands are at the ink in the absence of cancer at ink. It was agreed that tumor in skeletal muscle without benign glands at the apical perpendicular margin section should be reported as organ-confined.

It was recommended that the proximal and distal margins should be reported as bladder neck and apical margins, respectively. The terms proximal and distal urethral margins should be avoided as the urethra is often retracted and the true surgical margin mainly consists of prostatic tissue or extraprostatic connective tissue.

6. Concluding remarks

The ISUP 2009 consensus conference on Handling and Staging Radical Prostatectomy Specimens was the third in a series of consensus meetings organized by ISUP. The aim was to provide guidelines for practicing pathologists on how to handle these specimens. As far as possible we attempted to seek evidence-based consensus although in some areas with scant data in the literature, majority decisions were taken based on common sense and wide-spread practice. Several areas were identified where there is a need of further studies.

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