

REVIEW

Prognostic factors in prostate cancer. Key elements in structured histopathology reporting of radical prostatectomy specimens

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Summary

Prostate cancer is the most common visceral cancer and the second most common cause of cancer death in males. The number of radical prostatectomies performed each year is increasing and accurate data from the histopathological examination of these specimens aid clinicians in stratifying patients for surveillance and adjuvant therapies. This review focuses on the histopathological prognostic factors which should be routinely recorded in pathology reports and complements the Royal College of Pathologists of Australasia Structured Reporting Protocol for Prostate Cancer (Radical Prostatectomy). Such structured pathology reports have been shown to significantly enhance the completeness and quality of data provided to clinicians. The review also discusses the International Society for Urological Pathology Consensus Conference recommendations which were published recently.

Abbreviations: EPE, extraprostatic extension; LVI, lymphovascular invasion; PSM, positive surgical margin; SVI, seminal vesicle invasion.

Key words: Pathology, prognostic factors, prostate cancer, radical prostatectomy.

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INTRODUCTION

Prostate cancer is the most common visceral cancer in men with 16 329 new cases reported in Australia in 2005, representing 29.1% of new cancers in males. It is also the second most common cause of cancer death in males, accounting for almost 3000 deaths in Australia in 2005.¹ Both the number of new cases and the number of deaths from prostate cancer are increasing, partly driven by the ageing of the population.² There is a wide variation in the biological behaviour of prostate cancer: most tumours are relatively slow-growing, however, a significant minority have the propensity for aggressive behaviour, including metastatic spread, and such tumours

can be fatal.³ In the only randomised study of radical prostatectomy reported, 26% of the 348 men assigned to watchful waiting had distant metastases and almost 20% of this group had died after a median follow up of 10.8 years.⁴

The number of radical prostatectomies performed each year in Australia is increasing rapidly; in 2008 there were 5572 compared with 3830 in 2005.⁵ Accurate data from the histopathological examination of radical prostatectomy specimens are essential in predicting the risk of cancer recurrence after prostatectomy and to aid clinical decisions on surveillance or adjuvant therapy.^{6,7} Given the significant variation in the biological behaviour of prostate cancer, identification of those patients with aggressive cancers is essential so that they can be offered appropriate post-operative therapy. Conversely, patients with disease that is less aggressive and has been adequately resected should be identified, avoiding the potential complications of unnecessary adjuvant therapy. Pathological information, such as Gleason grade and pathological stage, is a major component of the most common nomograms used to guide clinical decision making and hence has a pivotal role in the rational planning of patient management.⁸

Structured pathology reports with standardised definitions for each component have been shown to significantly enhance the completeness and quality of data provided to clinicians, and have been recommended both in North America and the United Kingdom.^{9–12} A recent study in Ontario, Canada, demonstrated a much higher rate of completeness for the mandatory elements, based on the College of American Pathologists prostate cancer checklist, in synoptic reports (96.2% complete) versus traditional narrative reports (50.8%).¹¹

This article will review the key prognostic factors that are derived from pathological examination of radical prostatectomy specimens, with an emphasis on practical assessment and clear communication of essential data to clinicians. The specimen should be handled in a systematic and thorough fashion to facilitate the collection of accurate and complete pathological data, however, a detailed description of the handling of radical prostatectomy specimens is outside

the scope of this article as it has been comprehensively outlined in other reviews.^{13–16} This report is intended to complement the Royal College of Pathologists of Australasia Structured Reporting Protocol for Radical Prostatectomy Specimens which was published in 2010¹⁷ and incorporates the recommendations of the International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Reporting of Radical Prostatectomy specimens held in Boston in 2009.¹⁸

GLEASON GRADING

The Gleason grading system has been in use for over 40 years and is now the accepted grading system for prostate cancer throughout the world.¹⁹ Over time it has undergone a number of modifications, the most recent of which was developed at the 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma.²⁰ The Gleason score is an important, independent predictor of tumour behaviour and is a crucial parameter in the tables and nomograms, such as Partin tables and Kattan nomograms, which are typically used to guide clinical treatment decisions.^{6,7} Hence, a Gleason score should be given for all prostatic specimens containing adenocarcinoma except for those showing morphological changes consistent with androgen withdrawal.

The method for Gleason scoring is described in the 2005 ISUP Consensus Conference recommendations and is summarised in Tables 1 and 2.²⁰ Unlike many other tumour grading systems, Gleason grading is based solely on the architectural patterns of the tumour, best assessed at low power magnification (40–100×), and is not influenced by detailed nuclear features. In line with these recommendations, the Gleason score for radical prostatectomy specimens is assigned from assessment of the dominant nodule (i.e., the largest nodule). In contrast to needle biopsy specimens, for radical prostatectomy specimens the entire tumour nodule(s) is available for examination and the Gleason score is derived by adding the primary grade (or the primary pattern, i.e., that occupying the greatest area) to the secondary grade (i.e., the pattern occupying the second largest area). Usually the dominant nodule has the highest Gleason score; however, in the unusual situation where there is a smaller nodule (non-dominant nodule) that is composed of higher Gleason grade patterns, the Gleason score of that nodule is also reported. As agreed at the 2005 ISUP consensus conference, if there is a nodule of Gleason score 4 + 4 = 8 in the peripheral zone and a separate, larger nodule of 2 + 2 = 4 in the transition zone, it is not logical to expect that the presence of a discrete lower grade tumour could in some

way mitigate the poor prognosis associated with the higher grade tumour.²⁰ In such situations, the Gleason score of both nodules is recorded rather than assigning a misleading score of 2 + 4 = 6.

In radical prostatectomy specimens the dominant or highest grade nodule may show more than two Gleason patterns/grades. The grade that is the third most prevalent (i.e., occupies the third largest area in the tumour nodule) is referred to as the tertiary grade.²¹ In a radical prostatectomy specimen, where the tertiary grade is higher than the primary or secondary grades (usually grade 5 or 4) the tertiary grade is also recorded.²⁰ There is an increasing volume of evidence that small volumes of tertiary grade 5 patterns (and to a lesser extent tertiary grade 4) are associated with aggressive pathological features and a higher risk of biochemical recurrence.^{22–28} More problematic is the question of how extensive clusters of individual cells, strands or nests without lumina need to be to qualify as a tertiary grade 5. Of note, one survey of current grading practices amongst genitourinary pathologists, found the large majority required identification of such clusters at <40× magnification.²⁹

The 2005 ISUP Conference also reached consensus on expanding the spectrum of Gleason pattern 4 to include ill-defined glands with poorly formed lumina, provided that such ill-defined glands are present in a cluster excluding the possibility of tangential sectioning. Very small well-formed glands with smooth lumina are still regarded as belonging to Gleason pattern 3. A consequence of this expansion of pattern 4 is that there has been an increase in the proportion of high grade tumours.^{30–32} This may have a significant effect on patient treatment guidelines and nomograms that include Gleason score. Interestingly, a recently published comparison of the predictive performance of Gleason pattern 3 versus 4 in core biopsy specimens with post-radiation prostate specific antigen (PSA) as an endpoint, found that classical Gleason scoring outperformed the 2005 ISUP modified Gleason scoring.³² Further studies in radical prostatectomy specimens are required to determine the effect of the changes to Gleason scoring on its clinical utility.

EXTRAPROSTATIC EXTENSION

Extraprostatic extension (EPE; Fig. 1) is defined as the presence of neoplastic glands outside the prostate in the periprostatic tissue. EPE became accepted terminology at a 1996 Consensus Conference, and replaces earlier terms such as extracapsular or extraglandular invasion, penetration, and perforation.³³ The assessment of EPE can be difficult, as the

Table 1 Summary of Gleason grades (post ISUP 2005 modifications)

| Gleason grade | Criteria | Comments |
|---------------|--|---|
| 1 | Closely packed small regular glands forming a circumscribed rounded nodule | Very rarely use in radical prostatectomy specimen reports. Do not use for needle biopsy specimens |
| 2 | Glands more loosely arranged; not quite as uniform; fairly circumscribed but may have minimal infiltration at margins | May be used in radical prostatectomy and TURP specimen reports. Do not use for needle biopsies |
| 3 | Discrete glandular units/acini with marked variation in size and shape; infiltrates in and amongst benign prostatic tissue. Very rarely cribriform (see below) | |
| 4 | Fused micro acinar glands; ill-defined glands with poorly formed lumina; large cribriform irregular glands; hypernephroid | |
| 5 | Minimal if any glandular differentiation – solid sheets, cords or single cells. Comedocarcinoma | |

Table 2 Schema for Gleason scoring of radical prostatectomy specimens according to ISUP 2005 Consensus Conference recommendations

| Number of grades | Proportion of grades present | Comments |
|-------------------------------------|---|--|
| 1 | One of 2, 3, 4 or 5 only | Double grade to get score (e.g., 4+4 = 8) Record for dominant nodule +/- non-dominant (smaller) nodule if of higher grade (if present) |
| 2 – Primary and secondary | Grades mixed | Report both grades, dominant pattern* first (2+3, 3+4, 4+3...) Record for dominant nodule +/- non-dominant (smaller) nodule if of higher grade (if present) |
| | Secondary grade is lower and of limited amount (<5%) | Ignore lower grade: 4+3 becomes 4+4 Record for dominant nodule +/- non-dominant (smaller) nodule if of higher grade (if present) |
| | Secondary grade is higher and of limited amount (<5%) | Include higher grade: 3+3 becomes 3+4 Record for dominant nodule +/- non-dominant (smaller) nodule if of higher grade (if present) |
| 3 – Primary, secondary and tertiary | Grades 2, 3, 4 or 5 | Report dominant grade (largest area) first, then secondary grade (second largest area), then tertiary grade (only if 4 or 5), e.g., 3+4 = 7 with tertiary grade 5, e.g., 2+3 = 5 with tertiary grade 4 Record for dominant nodule +/- non-dominant (smaller) nodule if of higher grade (if present) |

* Dominant (primary) grade is that which occupies the greatest area. For radical prostatectomy specimens secondary grade is defined as that which occupies the second greatest area. Tertiary grade is defined as that which occupies the third greatest area (provided that it is higher than the primary and secondary grades).

prostate is not surrounded by a discrete, well defined fibrous capsule.³⁴ Instead, the 'capsule' is made up of a band of concentrically placed fibromuscular tissue that is an inseparable component of the prostatic stroma.³⁵ Adding to the difficulty, there is often a fibrotic reaction in the vicinity of EPE and the neoplastic extraprostatic glands are often seen in fibrous tissue, not fat.³⁵ Therefore, EPE can be identified in several different situations and can be diagnosed in any of the following settings: (1) the presence of neoplastic glands abutting on or within periprostatic fat (most useful at the lateral, posterolateral and posterior aspects of the prostate); (2) neoplastic glands surrounding nerves in the neurovascular bundle (posterolaterally); (3) the presence of a nodular extension of tumour beyond the periphery of the prostate or beyond the compressed fibromuscular prostatic stroma at the outer edge of the gland (Fig. 1A,B,C,E).³⁶ This latter situation is best identified at low power magnification. In this assessment, the edge of the prostate is defined as the plane between fat and the condensed fibromuscular prostatic stroma which is best initially determined in a region without distortion by tumour. Tracking along the edge of the prostate at low power, EPE is present when there is bulging of the tumour beyond the normal rounded contour of the prostate gland. Higher power magnification should then be used to confirm that the neoplastic glands are in stroma that is fibrous and beyond the condensed smooth muscle of the prostate.^{36,37} Similarly, the presence of cancer within fibrous stroma that is in the same tissue plane as adipose tissue on either side is also a helpful indicator of EPE.

A 'capsule' cannot be readily identified at the base or apex and it can be particularly challenging for pathologists to identify the boundary of the prostate gland at the apex. At this site, benign glands are frequently admixed with skeletal muscle and the presence of neoplastic glands within skeletal muscle does not necessarily constitute EPE at the apex (Fig. 1F). A modest majority (62%) of survey respondents at the 2009 ISUP Consensus Meeting in Boston believe there is no reliable method to consistently diagnose EPE in sections from the prostatic apex,³⁶ although in occasional cases cancer may be seen in adipose tissue in the apical area. In this region it is more important to accurately assess the completeness of surgical resection. Similarly, the assessment of EPE at the

anterior aspect of the prostate may be difficult as the prostatic stroma blends in with extraprostatic fibromuscular tissue, but in this region EPE can be diagnosed when the carcinoma appears to extend beyond the boundary of the normal prostatic glandular tissue.^{14,36}

The degree of EPE can be assessed in semi-quantified manner as focal or extensive (also referred to as 'established' or 'non-focal'). Focal is defined as extraprostatic glands which occupy no more than one high power field on no more than two sections while extensive EPE represents anything more than this.³³ Other groups have advocated more rigorously quantifying the radial extent of EPE by measuring the maximum distance that the tumour bulges beyond the outer edge of the fibromuscular prostatic stroma.³⁸ However, the practical utility of such parameters is limited by the difficulty in precisely defining the outer limit of the prostate gland. The identification of any EPE is important, as both focal and extensive EPE are associated with a significantly higher risk of recurrence at both 5 and 10 years.^{37,39} In studies of the risk of progression following radical prostatectomy, the progression-free probability in node negative patients with uninvolved seminal vesicles at 10 years for organ confined disease is 85–89%, falling to 67–69% for focal EPE and to 36–58% for extensive EPE.^{37,39}

The only study addressing interobserver variability in the diagnosis of EPE amongst a group of expert urological pathologists found good overall agreement ($\kappa = 0.63$). However, the group were given a selection of slides that included an equal number of slides deemed positive, negative or equivocal and it is interesting to note that there was poor agreement with the equivocal slides ($\kappa = 0.29$). This was attributed to the prostate's lack of a true capsule and it was noted that the diagnosis of EPE at the apex was particularly subjective.⁴⁰ Another study found significant variation in the diagnosis of EPE between an experienced reviewer and pathologists without a subspecialty interest in prostate.⁴¹

SURGICAL MARGINS

The outer surface of the radical prostatectomy specimen should be carefully inked before macroscopic dissection to aid in the

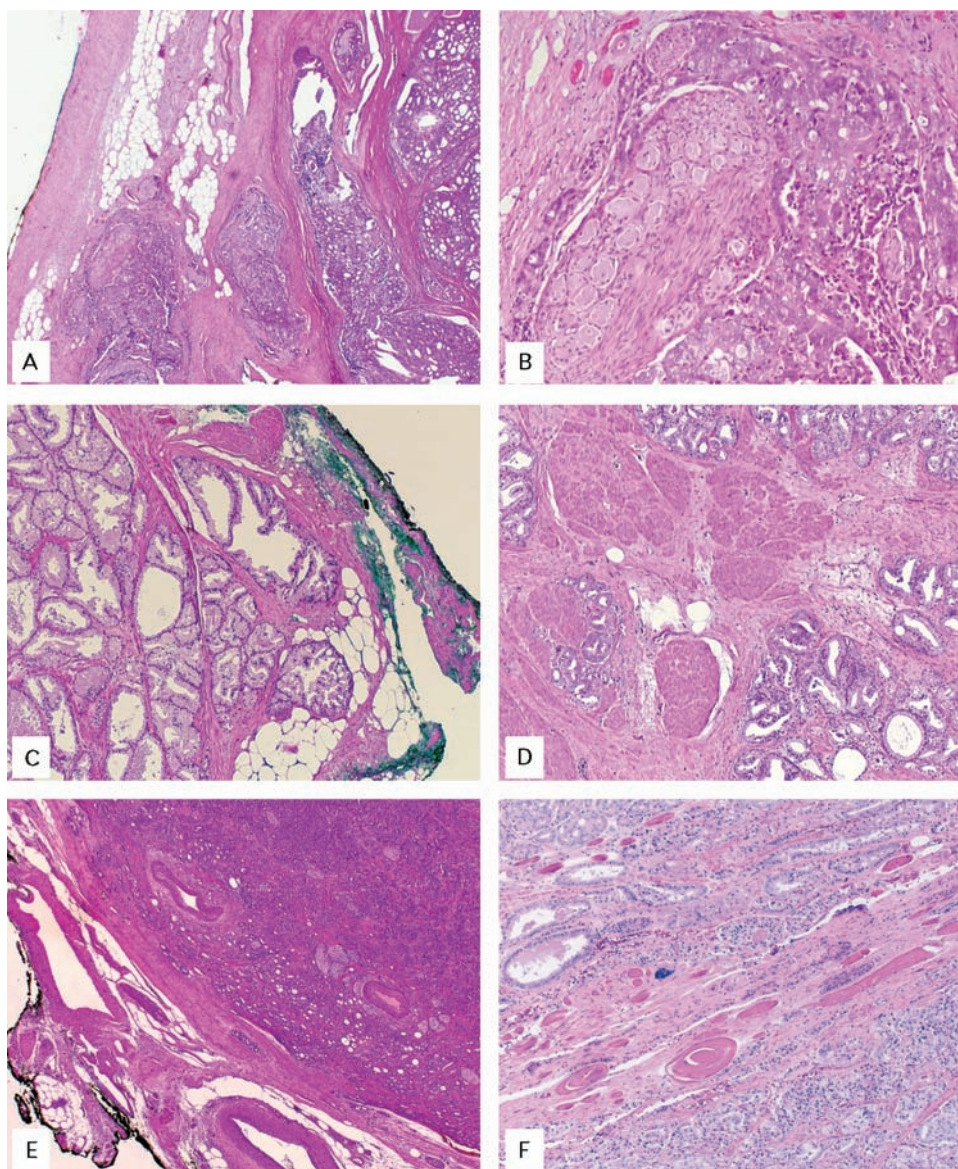


Fig. 1 (A) Extraprostatic extension with bulge beyond normal contour of the gland and involvement of the posterolateral neurovascular bundle. (B) Higher power view of (A) showing carcinoma around a nerve and ganglion. (C) Extraprostatic extension with neoplastic glands in direct contact with adipose tissue. (D) Microscopic involvement of urinary bladder base (pT3a): tumour infiltrating between thick smooth muscle bundles of bladder base. (E) Organ confined tumour (pT2): tumour is still within a layer of condensed fibromuscular tissue and does not bulge beyond the normal contour of the prostate. (F) Skeletal muscle is often present within prostate at the apex of the gland and does not necessarily constitute EPE.

determination of margin status (Fig. 2). A positive surgical margin (PSM) can then be defined as cancer extending to the inked surface of the specimen, representing a site where the urologist has cut through cancer (Fig. 2C,D).^{13,14} PSMs are reported in between 10% and 48% of patients treated by radical prostatectomy for both organ confined and non-organ confined prostate cancer, with the rates in the lower range generally occurring in the more contemporary cohorts.^{42–44} A PSM has a significant adverse impact on the likelihood of progression-free survival, including PSA recurrence-free survival, local recurrence-free survival and development of metastases after radical prostatectomy in multivariate analysis.^{14,45–48} The risk of PSA recurrence with a PSM has a reported hazard ratio of 1.5–2.6 compared to an uninvolved margin.^{43,45,46} However, most studies suggest only one-third of patients with a PSM will have a biochemical recurrence.^{43,45,46}

Somewhat counter-intuitively, in contrast to other organs such as rectum and pancreas where tumour close to the margin (<1 mm) has a prognosis similar to transected tumour at the margin,^{49,50} the presence of prostate carcinoma close to but not involving the margin should not be labelled as a positive surgical margin as this finding has been shown to have no prognostic significance.^{51,52} Specifically, prostate carcinoma that extends very close to a smooth inked margin, e.g., carcinoma separated from the ink by 1 or 2 strands of fibrous tissue or fibroblasts, should not be considered as a positive margin (Fig. 2A,B). This is most commonly seen posterolaterally in cases where neurovascular bundle preservation leaves virtually no extraprostatic tissue. Studies on such cases have shown that additional tissue removed from these sites did not contain any carcinoma and the prognosis was not worsened.^{52,53}

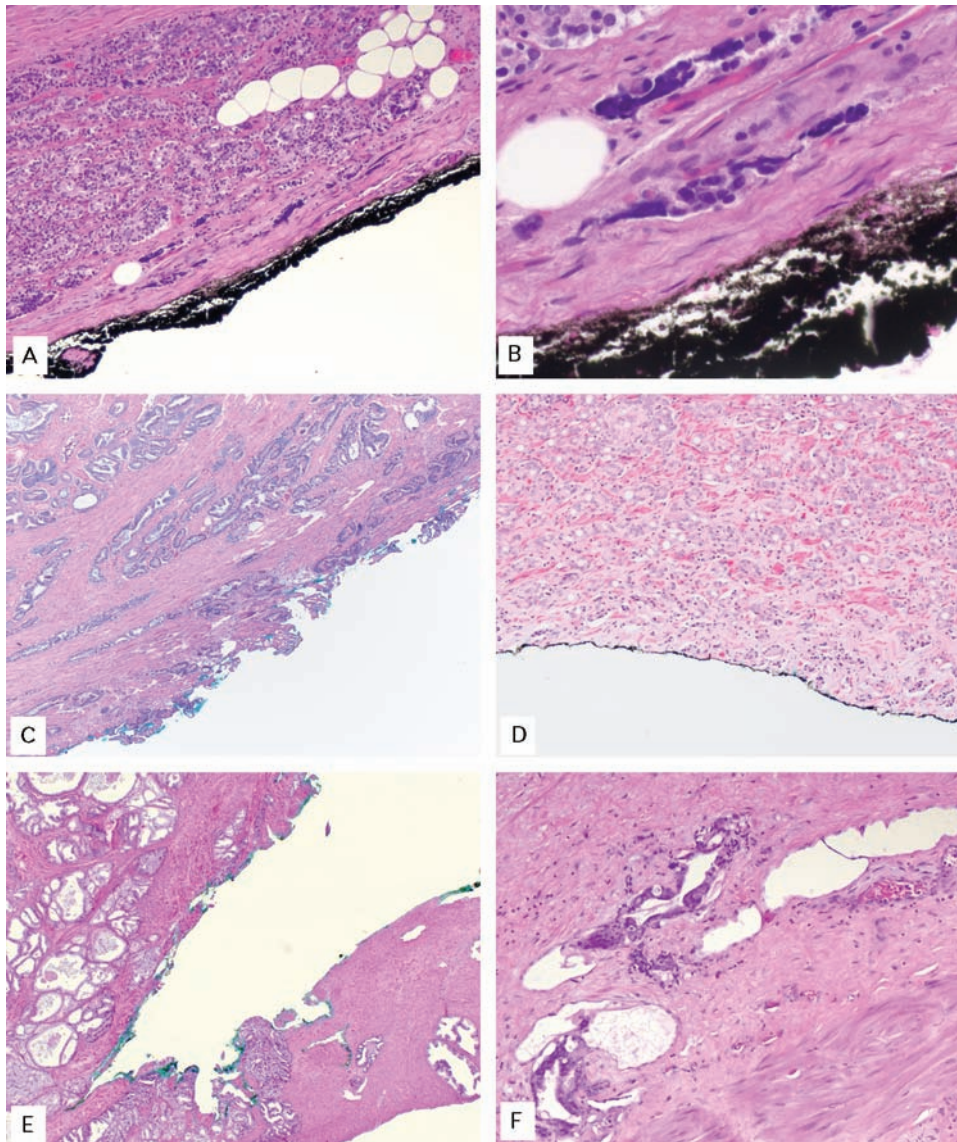


Fig. 2 (A) The surgical margin (black inked) is clear of tumour. (B) Higher power view of (A) showing that although carcinoma extends close to the inked surgical margin it is still separated from the margin by a few strands of fibrous tissue. This is a negative surgical margin. (C) Gleason grade 3 carcinoma involving the inked surgical margin (positive surgical margin). (D) Gleason grade 4 carcinoma involving the inked surgical margin (positive surgical margin). (E) Artefactual tear into the prostate with ink tracking into it mimicking a resection margin. (F) Lymphovascular invasion.

In rare cases, it can be impossible to ascertain whether the surgical margin is truly positive.⁴⁰ This can be due to marked crush or thermal artefact causing glandular distortion along the margin so that it cannot be histologically determined whether the crushed glands are malignant and whether the margin is actually positive rather than artificially retracted due to heat coagulation or tissue compression. On these rare occasions, the margins should be reported as equivocal. Another cause of difficulty is irregular tracking of ink in areas of tears or lacerations (Fig. 2E).^{40,54} This can occur during handling of the specimen in the operating theatre, transportation or processing in the laboratory. It is important not to over diagnose PSM, potentially exposing these patients to unnecessary postoperative adjuvant therapy with the attendant risk of significant complications.⁵⁵

The plane of the positive margin may also be significant, although the published data are inconsistent. Intraprostatic margin involvement or capsular incision (CI) occurs when

the urologist inadvertently develops the resection margin within the plane of the prostate rather than outside the 'capsule'. Capsular incision with a PSM is diagnosed when malignant glands are cut across adjacent to benign prostatic glands.³⁵ In these cases, the edge of the prostate in this region is left in the patient. Data on the prognostic significance of CI is contradictory.^{56–58} According to the largest series published (135 cases), a significantly lower 5 year biochemical progression free probability is found in patients with CI/intraprostatic margin involvement (71.3%) than in patients with organ confined disease with negative margins (96.7%), or focal EPE with negative margins (89.7%), although CI has a significantly better outcome than that associated with extensive/non-focal EPE and positive margins (58.5%).⁵⁹

Margin involvement associated with EPE is diagnosed when malignant glands in extraprostatic tissue are transected by the resection margin. This can be difficult to distinguish from capsular incision in some cases, particularly posteriorly and

posterolaterally, if there is a desmoplastic reaction. Cancer extending to a margin which is beyond the normal contour of the prostate gland, or beyond the compressed fibromuscular prostatic stroma at the outer edge of the prostate, can be diagnosed as a PSM with EPE, as can margin involvement when there is cancer in adipose tissue.⁵⁶ At the apex, the histological boundaries of the prostate gland can be difficult to define and again EPE with a positive margin can be difficult to differentiate from CI/intraprostatic margin involvement. Hence, if carcinoma extends to an inked margin at the apex where benign glands are not transected, this is considered a positive margin in an area of EPE by some authors.^{14,56} In contrast, other authors, and the majority of survey participants at the 2009 ISUP Consensus Conference, believe there is no reliable method to diagnose EPE in sections from the prostatic apex (see above).³⁶

Recent investigations have sought to more accurately define the risk of a PSM on recurrence rates in an attempt to better predict which patients would benefit from adjuvant therapy. However, despite the recent intense interest in surgical margins, these studies have yielded varying results. The sites of the PSM and the number of positive margins have been shown to influence biochemical recurrence and risk of progression in some publications.^{44,45,60} For instance, a margin involving the bladder neck or the posterolateral surface of the prostate has been reported as having a more significant adverse impact on prognosis than an involved apical or anterior margin.^{44,45,60} Moreover, the location of the PSM may be useful information for the urologist, or urology trainee, who could then modify their surgical technique in future operations to avoid iatrogenic margin positivity and increase the likelihood of curative surgery. In contrast, other investigators have found no association between location of PSM and recurrence rates.^{61–63} Measurement of the length of PSM is an indicator of the extent of margin involvement, which has been shown to be a significant prognostic factor correlating with the rate of postoperative disease recurrence in several publications.^{52,54,59,64–66} The 5 year PSA recurrence risk appears to be significantly greater when the length of involved margin is 3 mm or more, (53% versus 14%).^{59,65} However, Marks *et al.* found no significant association between extent and biochemical recurrence, possibly related to differences in the pathological interpretation of positive margins (see below) and the method of assessing the linear extent of margin involvement when multiple margins are involved.⁶⁷ A recent study found that the impact of a PSM after radical prostatectomy was greater in intermediate and high risk groups (based on Gleason score and prebiopsy PSA) than in low risk patients, while in another series the linear length of a positive margin was an independent prognostic factor for organ confined tumours only, i.e., pT2 not pT3.^{48,66}

The Gleason score of the tumour located at the PSM has also been suggested as a prognostic factor post-radical prostatectomy by two studies published in the latter half of 2010 and may need to be incorporated in future editions of structured reporting protocols. Cao *et al.* found that the Gleason score of the tumour at a PSM was a strong predictive factor for biochemical recurrence in both univariate and multivariate analysis.⁶⁸ Similarly, in a cohort of 107 patients with overall Gleason score 7 and extensive EPE, the Gleason score at the PSM influenced outcome.⁶⁹

Data on interobserver variation in the assessment of surgical margins are limited. In one study a group of 12 urological pathologists demonstrated good to excellent agreement

(kappa = 0.74).⁴⁰ In contrast, Bong *et al.* found major discrepancies in PSM rates between two different institutions in a single-surgeon series using the same criteria to evaluate the surgical margins.⁷⁰

SEMINAL VESICLE INVASION

The extraprostatic seminal vesicle may be involved by carcinoma through several mechanisms: (1) direct spread along the ejaculatory duct complex; (2) through the prostatic capsule into extraprostatic soft tissue then into the seminal vesicle; and (3) discontinuous metastasis.^{71–73} Villiers *et al.* found the majority invaded the seminal vesicle through the ejaculatory duct while the majority of Ohori and colleagues' cases showed invasion through capsule and soft tissue, i.e., via EPE.^{72,73}

Different definitions of seminal vesicle invasion have been used over the years complicating comparison of the published studies.⁷¹ At the 2009 ISUP Meeting, the proposal that seminal vesicle invasion (SVI) should be defined as carcinomatous invasion of the muscular wall of the seminal vesicle exterior to the prostate reached consensus (70% respondents).⁷⁴ Only extraprostatic seminal vesicle is included in this definition of SVI, as it is difficult differentiating between intraprostatic seminal vesicle and ejaculatory duct invasion since these structures merge without a clear histological cut-off.⁷² Hence, when tissue from the seminal vesicles is sampled for microscopic examination it is important to ensure that the portion of seminal vesicle sampled is not surrounded by prostatic tissue. No consensus was reached on whether the seminal vesicles should be completely submitted,⁷⁴ although a more recent study has concluded that sampling of the proximal one third of the gland was sufficient in the absence of lymphovascular infiltration by tumour.⁷⁵ In addition, it was concluded that older definitions that include invasion of the adipose tissue around the seminal vesicle are imprecise and should be discarded.⁷¹

SVI is a well established independent adverse prognostic factor^{14,76,77} and is an integral component of the commonly used nomograms that predict risk of post-prostatectomy cancer recurrence.^{6,7} The finding of SVI at the time of radical prostatectomy is an adverse finding that confers an increased risk of PSA recurrence exceeded only in magnitude by the presence of lymph node metastasis.^{76–78} Bilaterality and extent of extraprostatic SVI are not independently predictive of prognosis.⁶⁵ The presence of SVI and a PSM may also influence the response to adjuvant radiotherapy.^{71,79}

LYMPH NODE METASTASIS

Lymph node involvement is a well established independent adverse prognostic factor^{13,14} and is an integral component of the commonly used nomograms that predict the risk of post-prostatectomy disease recurrence.^{6,7} Attempts to stratify patients with lymph node metastases into prognostic subgroups based on additional factors have yielded conflicting results. The diameter of the largest metastatic deposit correlated with distant metastasis and cancer-specific survival in two studies but not in others.^{80–82} The number of positive nodes and the presence of extranodal extension are not independent predictors of distant metastasis or cancer-specific survival.^{80–83} The use of ancillary techniques to enhance detection of pelvic lymph node metastases has also been proposed. However, there is insufficient evidence at present to support the routine use of immunohistochemistry in the pathological assessment of

lymph node involvement as there is little published data on the prognostic significance of micrometastases.¹⁴

The use of frozen sections in the intra-operative diagnosis of pelvic lymph node metastasis depends on which institution the surgery is performed in. Its role has been called into question in the last decade due to high false negative rates, of 33–70%, and low cost:benefit ratio.^{84,85} However, it has been argued that intra-operative frozen section diagnosis is still useful in high risk patients (biopsy Gleason score 8–10, PSA >10 ng/mL) in the detection of lymph node metastases and prevention of unnecessary radical surgery.¹⁴

OTHER FACTORS

Lymphovascular invasion (LVI) has been reported in a few studies as an independent predictor of disease recurrence in multivariate analysis.^{86–88} LVI has been defined as the unequivocal presence of tumour cells within endothelial-lined spaces with no underlying muscular walls (Fig. 2F).^{86,88} Lymphatic and venous invasion are usually considered together due to the difficulties in distinguishing between the two by routine light microscopy. It is important that retraction and other artefacts should be excluded.

Microscopically detected invasion of the urinary bladder neck can be defined as the presence of neoplastic glands within the thick smooth muscle bundles of the bladder neck in coned sections from the base of the prostate in the absence of associated benign prostatic glandular tissue (Fig. 1D).⁸⁹ Specifically, neoplastic glands intermixed with benign prostatic glands at the bladder neck is equivalent to capsular incision rather than true bladder neck invasion.^{90–92} Microscopic bladder neck involvement is a significant predictor of PSA recurrence in univariate analysis but not in multivariate modelling in most, but not all, studies.^{92–94} In the recently published seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, microscopic bladder neck invasion is classified as stage pT3 disease since it has a similar biochemical recurrence free survival and cancer specific survival to patients with SVI or EPE.^{89,95}

The significance of tumour volume in radical prostatectomy specimens has been somewhat controversial.¹³ Tumour volume is a prognostic factor in univariate analysis, but in most studies is not an independent prognostic factor in multivariate analysis^{37,39,96} correlating with Gleason score, pathological stage and margin status.⁹⁷ Moreover, the irregular distribution and commonly multifocal nature of prostate cancers renders calculations of tumour volume problematic, while partial sampling methods also may have an adverse impact on the accuracy of such estimates. Standard research methods, such as computerised planimetry or image analysis are time and labour intensive and are not feasible for determination of tumour volume in the routine pathology practice setting. Hence, qualitative descriptors of disease extent (e.g., insignificant/minimal) have often been used, with an insignificant/minimal tumour usually being defined as having a volume of <0.5 cm³ negative margins, Gleason score ≤6, and no EPE (i.e., organ confined, pT2).^{98,99} Patients with such tumours have close to 100% biochemical recurrence free survival.¹⁰⁰ Recently, a working group at the 2009 ISUP Consensus Conference in Boston proposed simplifying this definition of clinically insignificant cancer by using an easily measured cut-off point of <10 mm greatest diameter for the dominant nodule instead of tumour volume <0.5 cm³.¹⁰¹ However, the proposal to adopt

the measurement of maximum diameter of the dominant tumour nodule as a standard for reporting tumour size did not achieve consensus. Ultimately, although there was strong support for reporting some quantitative measure of volume of tumour in radical prostatectomy specimens, no specific methodology was agreed upon.¹⁰¹

In some series transition zone cancers are associated with favourable pathological features,^{102,103} but others have demonstrated that the zonal location of prostate cancer, i.e., peripheral, central or transition, is not an independent prognostic indicator on multivariate analysis.^{104,105} Moreover, the zonal location of the cancer can be difficult to determine with tumours commonly overlapping the peripheral and transition zones. Likewise, perineural invasion is not an independent prognostic factor in multivariate analysis as it is found in nearly all radical prostatectomy specimens on thorough examination.⁸⁷

CONCLUSION

Thorough and systematic examination of radical prostatectomy specimens is essential for patient management and rational use of adjuvant therapy. On the basis of the published evidence it is clear that there are a number of robust, independently significant histopathological prognostic factors, including Gleason score, EPE, seminal vesicle margin, lymph node status and lymphovascular invasion, which should be routinely included in pathology reports for radical prostatectomy specimens. Compelling evidence for other factors is lacking, although future investigations may clarify some of the current areas of uncertainty. In contrast to other cancers, e.g., breast and colorectal carcinoma, there are at present no prognostic molecular biomarkers, other than PSA, suitable for routine use in the pathology laboratory.¹⁰⁶ Structured or synoptic pathology reports have been shown to significantly enhance the completeness of pathology data provided to clinicians and use of well formulated examples, such as the College of American Pathologists checklists or the Royal College of Pathologists of Australasia (RCPA) Structured Reporting Protocols, should be strongly encouraged.

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References

1. AIHW (Australian Institute of Health and Welfare) and AACR (Australasian Association of Cancer Registries). *Cancer in Australia: An Overview, 2008*. Canberra: AIHW, 2008; Cancer Series No. 46 (AIHW cat. no. CAN 42).
2. AIHW (Australian Institute of Health and Welfare) and AACR (Australasian Association of Cancer Registries). *Cancer in Australia: An Overview, 2006*. Canberra: AIHW, 2007; Cancer Series No. 37 (AIHW cat. no. CAN 32).
3. Bill-Axelsson A, Holmberg L, Ruutu M, *et al.* Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005; 352: 1977–84.

4. Bill-Axelsson A, Holmberg L, Filén F, *et al.* Radical prostatectomy versus watchful waiting on localized prostate cancer: the Scandinavian prostate cancer group-4 randomized trial. *J Natl Cancer Inst* 2008; 100: 1144–54.
5. Medicare Australia. *Medicare Australia Claims Data, MBS Item numbers 37210 and 37211*. Canberra: Medicare Australia, 2010. <https://www.medicareaustralia.gov.au>
6. Partin AW, Piantadosi S, Sanda MG, *et al.* Selection of men at high risk for disease recurrence for experimental adjuvant therapy following radical prostatectomy. *Urology* 1995; 45: 831–8.
7. Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol* 1999; 17: 1499–507.
8. Kattan MW, Eastham JA, Stapleton AM, Wheeler TM, Scardino PT. A preoperative nomogram for disease recurrence following radical prostatectomy for prostate cancer. *J Natl Cancer Inst* 1998; 90: 766–71.
9. Cross SS, Feeley KM, Angel CA. The effect of four interventions on the informational content of histopathology reports of resected colorectal carcinomas. *J Clin Pathol* 1998; 51: 481–2.
10. Mathers M, Shrimankar J, Scott D, *et al.* The use of a standard proforma in breast cancer reporting. *J Clin Pathol* 2001; 54: 809–11.
11. Srigley JR, McGowan T, MacLean A, *et al.* Standardized synoptic cancer pathology reporting: A population-based approach. *J Surg Oncol* 2009; 99: 517–24.
12. Gill AJ, Johns AL, Eckstein R, *et al.* Synoptic reporting improves histopathological assessment of pancreatic resection specimens. *Pathology* 2009; 41: 161–7.
13. Srigley JR. Key issues in handling and reporting radical prostatectomy specimens. *Arch Pathol Lab Med* 2006; 130: 303–17.
14. Epstein JI, Amin M, Boccon-Gibod L, *et al.* Prognostic factors and reporting of prostate carcinoma in radical prostatectomy and pelvic lymphadenectomy specimens. *Scand J Urol Nephrol Suppl* 2005; 216: 34–63.
15. Sehdev AE, Pan CC, Epstein JI. Comparative analysis of sampling methods for grossing radical prostatectomy specimens performed for nonpalpable (stage T1c) prostatic adenocarcinoma. *Hum Pathol* 2001; 32: 494–9.
16. Samaratunga H, Montironi R, True L, *et al.* International Society of Urological Pathology (ISUP) Consensus Conference on handling and staging of radical prostatectomy specimens. Working group 1: specimen handling. *Mod Pathol* 2011; 24: 6–15.
17. Kench J, Clouston D, Delahunt B, *et al.* *Royal College of Pathologists of Australasia Prostate Cancer (Radical Prostatectomy) Structured Reporting Protocol*. Sydney: Royal College of Pathologists of Australasia, 2010. <http://www.rcpa.edu.au/Publications/StructuredReporting/CancerProtocols.htm>.
18. Egevad L, Srigley JR, Delahunt B. International Society of Urological Pathology (ISUP) Consensus Conference on handling and staging of radical prostatectomy specimens: rationale and organization. *Mod Pathol* 2011; 24: 1–5.
19. Gleason DF. Classification of prostatic carcinomas. *Cancer Chemother Rep* 1966; 50: 125–8.
20. Epstein JI, Allsbrook WCJ, Amin MB, Egevad LL. The 2005 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma. *Am J Surg Pathol* 2005; 29: 1228–42.
21. Pan CC, Potter SR, Partin AW, Epstein JI. The prognostic significance of tertiary Gleason patterns of higher grade in radical prostatectomy specimens: a proposal to modify the Gleason grading system. *Am J Surg Pathol* 2000; 24: 563–9.
22. Egevad L, Granfors T, Karlberg L, Bergh A, Stattin P. Percent Gleason grade 4/5 as prognostic factor in prostate cancer diagnosed at transurethral resection. *J Urol* 2002; 168: 509–13.
23. Rasiyah KK, Stricker PD, Haynes AM, *et al.* Prognostic significance of Gleason pattern in patients with Gleason score 7 prostate carcinoma. *Cancer* 2003; 98: 2560–5.
24. Mosse CA, Magi-Galluzzi C, Tsuzuki T. The prognostic significance of tertiary Gleason pattern 5 in radical prostatectomy specimens. *Am J Surg Pathol* 2004; 28: 394–8.
25. Hattab EM, Koch MO, Eble JN, Lin H, Cheng L. Tertiary Gleason pattern 5 is a powerful predictor of biochemical relapse in patients with Gleason score 7 prostatic adenocarcinoma. *J Urol* 2006; 175: 1695–9.
26. Harnden P, Shelley MD, Coles B, Staffurth J, Mason MD. Should the Gleason grading system for prostate cancer be modified to account for high-grade tertiary components? A systematic review and meta-analysis. *Lancet Oncol* 2007; 8: 411–9.
27. Sim HG, Telesca D, Culp SH, *et al.* Tertiary Gleason pattern 5 in Gleason 7 prostate cancer predicts pathological stage and biochemical recurrence. *J Urol* 2008; 179: 1775–9.
28. Whittemore DE, Hick EJ, Carter MR, *et al.* Significance of tertiary Gleason pattern 5 in Gleason score 7 radical prostatectomy specimens. *J Urol* 2008; 179: 516–22.
29. Egevad L, Allsbrook WC, Epstein JI. Current practice of Gleason grading among genitourinary pathologists. *Hum Pathol* 2005; 36: 5–9.
30. Delahunt B, Srigley JR, Lamb DS. Gleason grading: consensus and controversy. *Pathology* 2009; 41: 613–4.
31. Uemura H, Hoshino K, Sasaki T, *et al.* Usefulness of the 2005 International Society of Urologic Pathology Gleason grading system in prostate biopsy and radical prostatectomy specimens. *BJU Int* 2008; 103: 1190–4.
32. Delahunt B, Lamb DS, Srigley JR, *et al.* Gleason scoring: a comparison of classical and modified (International Society of Urological Pathology) criteria using nadir PSA as a clinical end point. *Pathology* 2010; 42: 339–43.
33. Sakr WA, Wheeler TM, Blute M, *et al.* Staging and reporting of prostate cancer—sampling of the radical prostatectomy specimen. *Cancer* 1996; 78: 366–8.
34. Ayala AG, Ro JY, Babaian R, *et al.* The prostatic capsule: does it exist? Its importance in the staging and treatment of prostatic carcinoma. *Am J Surg Pathol* 1989; 13: 21–7.
35. Chuang AY, Epstein JI. Positive surgical margins in areas of capsular incision in otherwise organ-confined disease at radical prostatectomy: histologic features and pitfalls. *Am J Surg Pathol* 2008; 32: 1201–6.
36. Magi-Galluzzi C, Evans AJ, Delahunt B, *et al.* International Society of Urological Pathology (ISUP) Consensus Conference on handling and staging of radical prostatectomy specimens. Working group 3: extraprostatic extension, lymphovascular invasion and locally advanced disease. *Mod Pathol* 2011; 24: 26–38.
37. Wheeler TM, Dilliogluligil O, Kattan MW, *et al.* Clinical and pathological significance of the level and extent of capsular invasion in clinical stage T1-2 prostate cancer. *Hum Pathol* 1998; 29: 856–62.
38. Sung MT, Lin H, Koch MO, *et al.* Radial distance of extraprostatic extension measured by ocular micrometer is an independent predictor of prostate specific antigen recurrence: a new protocol for the substaging of pT3a prostate cancer. *Am J Surg Pathol* 2007; 31: 311–8.
39. Epstein JI, Partin AW, Sauvageot J, Walsh PC. Prediction of progression following radical prostatectomy. A multivariate analysis of 721 men with long-term follow-up. *Am J Surg Pathol* 1996; 20: 286–92.
40. Evans AJ, Henry PC, Van der Kwast TH, *et al.* Interobserver variability between expert urologic pathologists for extraprostatic extension and surgical margin status in radical prostatectomy specimens. *Am J Surg Pathol* 2008; 32: 1503–12.
41. Van der Kwast TH, Collette L, Van Poppel H, *et al.* Impact of pathology review of stage and margin status of radical prostatectomy specimens (EORTC trial 22911). *Virch Arch* 2006; 449: 428–34.
42. Eastham JA, Kattan MW, Riedel E, *et al.* Variation among individual surgeons in the rate of positive surgical margins in radical prostatectomy specimens. *J Urol* 2003; 170: 2292–5.
43. Simon MA, Kim S, Soloway MS. Prostate specific antigen recurrence rates are low after radical retropubic prostatectomy and positive margins. *J Urol* 2006; 175: 140–5.
44. Eastham JA, Kuroiwa K, Ohori M, *et al.* Prognostic significance of location of positive margins in radical prostatectomy specimens. *Urology* 2007; 70: 965–9.
45. Blute ML, Bostwick DG, Bergstralh EJ, *et al.* Anatomic site-specific positive margins in organ-confined prostate cancer and its impact on outcome after radical prostatectomy. *Urology* 1997; 50: 733–9.
46. Swindle P, Eastham JA, Ohori M, *et al.* Do margins matter? The prognostic significance of positive surgical margins in radical prostatectomy specimens. *J Urology* 2005; 174: 903–7.
47. Pfitzenmaier J, Pahernik S, Tremmel T, *et al.* Positive surgical margins after radical prostatectomy: do they have an impact on biochemical or clinical progression? *BJU Int* 2008; 102: 1413–8.
48. Alkhateeb S, Alibhai S, Fleshner N, *et al.* Impact of a positive surgical margin after radical prostatectomy differs by disease risk group. *J Urol* 2010; 183: 145–50.
49. Chang DK, Johns AL, Merrett ND, *et al.* Margin clearance and outcome in resected pancreatic cancer. *J Clin Oncol* 2009; 27: 2855–62.
50. Nagtegaal ID, Marijnen CAM, Kranenbarg EK, *et al.* Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002; 26: 350–7.
51. Emerson RE, Koch MO, Daggy JK, Cheng L. Closest distance between tumor and resection margin in radical prostatectomy specimens: lack of prognostic significance. *Am J Surg Pathol* 2005; 29: 225–9.
52. Epstein JI, Sauvageot J. Do close but negative margins in radical prostatectomy specimens increase the risk of postoperative progression? *J Urol* 1997; 157: 241–3.
53. Epstein JI. Evaluation of radical prostatectomy capsular margins of resection. The significance of margins designated as negative, closely approaching, and positive. *Am J Surg Pathol* 1990; 14: 626–32.
54. Watson RB, Civantos F, Soloway MS. Positive surgical margins with radical prostatectomy: detailed pathological analysis and prognosis. *Urology* 1996; 48: 80–90.

55. Thompson IMJ, Tangen CM, Paradelo J, *et al.* Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomised clinical trial. *JAMA* 2006; 296: 2329–35.
56. Barocas DA, Han M, Epstein JI, *et al.* Does capsular incision at radical retropubic prostatectomy affect disease-free survival in otherwise organ-confined prostate cancer? *Urology* 2001; 58: 746–51.
57. Kumano M, Miyake H, Muramaki M, *et al.* Adverse prognostic impact of capsular incision at radical prostatectomy for Japanese men with clinically localized prostate cancer. *Int Urol Nephrol* 2009; 41: 581–6.
58. Shuford MD, Cookson MS, Chang SS, *et al.* Adverse prognostic significance of capsular incision with radical retropubic prostatectomy. *J Urol* 2004; 172: 119–23.
59. Chuang AY, Nielsen ME, Hernandez DJ, Walsh PC, Epstein JI. The significance of positive surgical margin in areas of capsular incision in otherwise organ confined disease at radical prostatectomy. *J Urol* 2007; 178: 1306–10.
60. Obek C, Sadek S, Lai S, Civantos F, Rubinowicz D, Soloway MS. Positive surgical margins with radical retropubic prostatectomy: anatomic site-specific pathologic analysis and impact on prognosis. *Urology* 1999; 54: 682–8.
61. Sofer M, Hamilton-Nelson KL, Civantos F, Soloway MS. Positive surgical margins after radical retropubic prostatectomy: the influence of site and number on progression. *J Urol* 2002; 167: 2453–6.
62. Stephenson AJ, Wood DP, Kattan MW, *et al.* Location, extent and number of positive surgical margins do not improve accuracy of predicting prostate cancer recurrence after radical prostatectomy. *J Urol* 2009; 182: 1357–63.
63. Resnick MJ, Canter DJ, Guzzo TJ, *et al.* Defining pathologic variables to predict biochemical failure in patients with positive surgical margins at radical prostatectomy: implications for adjuvant therapy. *BJU Int* 2010; 105: 1377–80.
64. Epstein JI. Evaluation of radical prostatectomy capsular margins of resection. The significance of margins designated as negative, closely approaching, and positive. *Am J Surg Pathol* 1990; 14: 626–32.
65. Babaiaab RJ, Troncso P, Bhadkamkar VA, Johnston DA. Analysis of clinicopathologic factors predicting outcome after radical prostatectomy. *Cancer* 2001; 91: 1414–22.
66. Cao D, Humphrey PA, Gao F, Tao Y, Kibel AS. Ability of length of positive margin in radical prostatectomy specimens to predict biochemical recurrence. *Urology* 2011; Jan 20: (Epub ahead of print).
67. Marks RA, Koch MO, Lopez-Beltran A, *et al.* The relationship between the extent of the surgical margin positivity and prostate specific antigen recurrence in radical prostatectomy specimens. *Hum Pathol* 2007; 38: 1207–11.
68. Cao D, Kibel AS, Gao F, Tao Y, Humphrey PA. The Gleason score of tumor at the margin in radical prostatectomy is predictive of biochemical recurrence. *Am J Surg Pathol* 2010; 34: 994–1001.
69. Brimo F, Partin AW, Epstein JI. Tumor grade at margins of resection in radical prostatectomy specimens is an independent predictor of prognosis. *Urology* 2010; 76: 1206–9.
70. Bong GW, Ritenour CWM, Osunkoya AO, Smith MT, Keane TE. Evaluation of modern pathological criteria for positive margins in radical prostatectomy specimens and their use for predicting biochemical recurrence. *BJU Int* 2008; 103: 327–31.
71. Potter SR, Epstein JI, Partin AW. Seminal vesicle invasion by prostate cancer: prognostic significance and therapeutic implications. *Rev Urol* 2000; 2: 190–5.
72. Ohori M, Scardino PT, Lapin SL, *et al.* The mechanisms and prognostic significance of seminal vesicle involvement by prostate cancer. *Am J Surg Pathol* 1993; 17: 1252–61.
73. Villers AA, McNeal JE, Redwine EA, Freiha FS, Stamey TA. Pathogenesis and biological significance of seminal vesicle invasion in prostatic adenocarcinoma. *J Urol* 1990; 143: 1183–7.
74. Berney DM, Wheeler TM, Grignon DJ, *et al.* International Society of Urological Pathology (ISUP) Consensus Conference on handling and staging of radical prostatectomy specimens. Working group 4: seminal vesicles and lymph nodes. *Mod Pathol* 2011; 24: 39–47.
75. Samaratunga H, Samaratunga D, Perry-Keene J, Yaxley J, Delahunt B. Distal seminal vesicle invasion by prostate adenocarcinoma does not occur in isolation of proximal seminal vesicle invasion or lymphovascular infiltration. *Pathology* 2010; 42: 330–3.
76. Debras B, Guillonneau B, Bougaran J, Chambon E, Vallancien G. Prognostic significance of seminal vesicle invasion on the radical prostatectomy specimen. Rationale for seminal vesicle biopsies. *Eur Urol* 1998; 33: 271–7.
77. Tefilli MV, Gheiler EL, Tiguert R, *et al.* Prognostic indicators in patients with seminal vesicle involvement following radical prostatectomy for clinically localized prostate cancer. *J Urol* 1998; 160: 802–6.
78. Epstein JI, Partin AW, Potter SR, Walsh PC. Adenocarcinoma of the prostate invading the seminal vesicle: prognostic stratification based on pathologic parameters. *Urology* 2000; 56: 283–8.
79. Swanson GP, Goldman B, Tangen CM, *et al.* The prognostic impact of seminal vesicle involvement found at prostatectomy and the effects of adjuvant radiation: data from Southwest Oncology Group 8794. *J Urol* 2008; 180: 2453–7.
80. Sgrignoli AR, Walsh PC, Steinberg GD, Steiner MS, Epstein JI. Prognostic factors in men with stage D1 prostate cancer: identification of patients less likely to have prolonged survival after radical prostatectomy. *J Urol* 1994; 152: 1077–81.
81. Cheng L, Bergstrahl EJ, Chevillie JC, *et al.* Cancer volume of lymph node metastasis predicts progression in prostate cancer. *Am J Surg Pathol* 1998; 22: 1491–500.
82. Boormans JL, Wildhagen MF, Bangma CH, Verhagen PC, van Leenders GJ. Histopathological characteristics of lymph node metastases predict cancer-specific survival in node-positive prostate cancer. *BJU Int* 2008; 102: 1589–93.
83. Cheng L, Pisansky TM, Ramnani DM, *et al.* Extranodal extension in lymph node-positive prostate cancer. *Mod Pathol* 2000; 13: 113–8.
84. Young MPA, Kirby RS, O'Donoghue EPN, Parkinson MC. Accuracy and cost of intraoperative lymph node frozen sections at radical prostatectomy. *J Clin Pathol* 1999; 52: 925–7.
85. Beissner RS, Stricker JB, Speights VO, *et al.* Frozen section diagnosis of metastatic prostate adenocarcinoma in pelvic lymphadenectomy compared with nomogram prediction of metastasis. *Urology* 2002; 59: 721–5.
86. Cheng L, Jones TD, Lin H, *et al.* Lymphovascular invasion is an independent prognostic factor in prostatic adenocarcinoma. *J Urol* 2005; 174: 2181–5.
87. Van Den Ouden D, Hop WCJ, Kranse R, Schroder FH. Tumour control according to pathological variables in patients treated by radical prostatectomy for clinically localized carcinoma of the prostate. *Br J Urol* 1997; 79: 203–11.
88. Herman CM, Wilcox GE, Kattan MW, Scardino PT, Wheeler TM. Lymphovascular invasion as a predictor of disease progression in prostate cancer. *Am J Surg Pathol* 2000; 24: 859–63.
89. Pierorazio PM, Epstein JI, Humphreys E, *et al.* The significance of a positive bladder neck margin after radical prostatectomy: the American Joint Committee on Cancer Pathological Stage T4 designation is not warranted. *J Urol* 2010; 183: 151–7.
90. Poulos CK, Koch MO, Eble JN, Daggy JK, Cheng L. Bladder neck invasion is an independent predictor of prostate-specific antigen recurrence. *Cancer* 2004; 101: 1563–8.
91. Rodriguez-Covarrubias F, Larre S, Dahan M, *et al.* Prognostic significance of microscopic bladder neck invasion in prostate cancer. *BJU Int* 2009; 103: 758–61.
92. Zhou M, Reuther AM, Levin HS, *et al.* Microscopic bladder neck involvement by prostate carcinoma in radical prostatectomy specimens is not a significant independent prognostic factor. *Mod Pathol* 2009; 22: 385–92.
93. Dash A, Sanda MG, Yu M, *et al.* Prostate cancer involving the bladder neck: recurrence-free survival and implications for AJCC staging modification. American Joint Committee on Cancer. *Urology* 2002; 60: 276–80.
94. Yossepowitch O, Engelstein D, Konichezky M, *et al.* Bladder neck involvement at radical prostatectomy: positive margins or advanced T4 disease? *Urology* 2000; 56: 448–52.
95. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, editors. *AJCC Staging Manual*. 7th ed. New York: Springer, 2010; 457–468.
96. Epstein JI, Carmichael M, Partin AW, Walsh PC. Is tumor volume an independent predictor of progression following radical prostatectomy? A multivariate analysis of 185 clinical stage B adenocarcinomas of the prostate with 5 years of followup. *J Urol* 1993; 149: 1478–81.
97. McNeal JE. Cancer volume and site of origin of adenocarcinoma in the prostate: relationship to local and distant spread. *Hum Pathol* 1992; 23: 258–66.
98. Stamey TA, Freiha FS, McNeal JE, *et al.* Localized prostate cancer. Relationship of tumor volume to clinical significance for treatment of prostate cancer. *Cancer* 1993; 71 (Suppl 3): 933–8.
99. Epstein JI, Walsh PC, Carmichael M, Brendler CBJ. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. *JAMA* 1994; 271: 365–74.
100. Postma R, de Vries SH, Roobol MJ, *et al.* Incidence and follow-up of patients with focal prostate carcinoma in 2 screening rounds after an interval of 4 years. *Cancer* 2005; 103: 708–16.
101. Van der Kwast TH, Amin MB, Billis A, *et al.* International Society of Urological Pathology (ISUP) Consensus Conference on handling and staging of radical prostatectomy specimens. Working group 2: T2 sub-staging and prostate cancer volume. *Mod Pathol* 2011; 24: 16–25.
102. Noguchi M, Stamey TA, McNeal JE, *et al.* An analysis of 148 transition zone cancers: clinical and histological characteristics. *J Urol* 2000; 163: 1751–5.

103. Shannon BA, McNeal JE, Cohen RJ. Transition zone carcinoma of the prostate gland: a common indolent tumour type that occasionally manifests aggressive behaviour. *Pathology* 2003; 35: 467–71.
104. Augustin H, Hammerer PG, Blonski J, *et al.* Zonal location of prostate cancer: significance for disease-free survival after radical prostatectomy? *Urology* 2003; 62: 79–85.
105. Chun FK, Briganti A, Jeldres C, *et al.* Zonal origin of localized prostate cancer does not affect the rate of biochemical recurrence after radical prostatectomy. *Eur Urol* 2007; 51: 949–55.
106. Schlomm T, Erbersdobler A, Mirlacher M, Sauter G. Molecular staging of prostate cancer in the year 2007. *World J Urol* 2007; 25: 19–30.