Leaders

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Macroscopic examination of prostatic specimens

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Clinical context of prostatic disease

Benign hyperplasia and adenocarcinoma of the prostate are common diseases; this Broadsheet is published at an opportune time as awareness, investigation and treatment of both diseases are changing. Up to 25% of men past middle age may need assessment and treatment of clinically benign disease.¹ Open surgery, involving enucleation of hyperplastic nodules, has been largely replaced by transurethral prostatectomy (TURP) with its lower complication rate. These latter specimens may also decline as other forms of treatment for hyperplasia (for example, stents, drugs, lasers, microwave therapy) prove their efficacy.

In previous years finger guided transrectal or, more rarely, transperineal biopsies were performed on patients with symptoms of prostatism and in whom digital rectal examination (DRE) was suggestive of malignancy or in patients presenting with metastatic disease in whom a primary carcinoma was not clinically apparent. As up to 60% of patients with clinically apparent prostatic carcinoma are known to have metastatic disease at presentation, the value of a malignant diagnosis on biopsy was most commonly to permit palliation by hormonal therapy. Following the success in the USA in detecting prostate confined adenocarcinoma by annual DRE and the possibility of detecting impalpable carcinomas by elevated serum prostate specific antigen (PSA) and transrectal ultrasound (TRUS),² the frequency of prostatic biopsies has increased in Britain. Fine needle aspiration cytology is an alternative to biopsy, but is not widely practised in Britain and is beyond the scope of this Broadsheet.

In Britain controversy surrounds radical prostatectomy. Attention is drawn to the limited knowledge of the natural history of prostatic cancer, the absence of valid randomised studies on surveillance versus treatment (radical prostatectomy and radical radiotherapy) and the

inadequacy of current clinical staging systems to distinguish gland confined (usually equated with curable) and locally extensive disease (in which postoperative tumour recurrence is likely). Nevertheless, some surgeons see radical prostatectomy as the only potential cure and more acceptable, as innovation in techniques has reduced the postoperative incidence of incontinence and impotence. The number of centres in which radical surgery is practised is still relatively small, but is increasing.

The dissection of the prostate as a component of radical cystectomy has been described in a previous Broadsheet.³

Needle biopsy

Biopsy protocols vary. Some are confined to sampling a palpable or hypoechoic ultrasound lesion, whereas others (especially when an elevated serum PSA is the sole abnormality) extend to quadrant or sextant biopsies. These may include the gland apex and seminal vesicles and are sometimes referred to as "staging biopsies". Screening for prostatic cancer is controversial but pilot studies are being carried out in Britain and the USA.² The use of biopsy to monitor disease after radical radiotherapy has also become more frequent.

The size of the biopsy specimen is governed by the needle used. The 18 gauge needle provides less than half the amount of tissue as the traditional 14 gauge needle, but is becoming more widely used because of reduced rates of post-biopsy infection and haemorrhage.⁴ These finer biopsy specimens fragment easily but this can be minimised by transferring the specimen directly from the needle into a cassette. Formol saline is the fixative commonly used, but Bouin's solution gives superior nuclear definition which is valuable in the diagnosis of carcinoma and prostatic intraepithelial neoplasia (PIN). The length of the biopsy is measured (without handling) to ensure that the entire biopsy is

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represented in subsequent sections. Multiple sections are routinely requested as additional diagnostic confidence is derived from seeing levels of a lesion or, less commonly, a malignant focus may be restricted to a number of sections.

The report includes:

- site of the biopsy as supplied;
- number and dimension(s) of the biopsy specimen(s);
- presence of PIN;
- approximate length or proportion of the specimen invaded by adenocarcinoma and number of cores involved;
- tumour grade;
- extent of tumour, assessable/not—that is, invasion of adipose tissue, striated muscle, seminal vesicle;
- vascular invasion;
- perineural spread;
- any other pathology—for example, atrophy, inflammation.

Currently, the significance of reporting high grade PIN (that is, 2 or 3) on biopsy is its concomitant association with adenocarcinoma. Re-biopsy of these glands reveals adenocarcinoma in 30 to 60% of cases.⁵

The length of tumour involvement does not necessarily correlate with disease volume in radical prostatectomy specimens,⁶ but a malignant diagnosis based on a cluster of acini in the presence of marginal abnormalities in other investigations may prompt surveillance and re-biopsy rather than radical treatment.

Although no particular grading system is superior, the Gleason system⁷ is most frequently used at international meetings and for publication, hence it facilitates the comparison of results. In a study comparing 316 18 gauge needle biopsy specimens with matched prostatectomy specimens, there was complete concordance of Gleason sum scores in 53% of poorly differentiated tumours, which compares well with previous studies using the 14 gauge needle.⁴ Greater discrepancies were found in well differentiated carcinomas, the biopsy grade being frequently lower than that of the radical specimen.

Despite its limitations on biopsy material, Gleason grading, taken with other factors, can provide useful information. In a series of 157 patients, the presence of Gleason pattern 4 or 5, more than three core samples with tumour, or any core sample with more than 50% tumour involvement accurately predicted significant tumour in all cases.⁶ Tumour in an apical biopsy, especially if invading striated muscle, forewarns the surgeon of the difficulty in achieving complete excision in the dissection adjacent to the internal sphincter. In patients with seminal vesicle invasion only 25% were free of progression five years postoperatively⁸ and this would deter consideration of radical surgery. Perineural spread is a predictor of extraglandular tumour invasion, especially when related to the diameters and number of nerves involved.⁹

In the management of benign hyperplasia prostatic biopsy specimens are being examined

at a research but not at a routine diagnostic level. Morphometric assessment of glandular and stromal components is carried out to see if these predict response to 5- α -reductase inhibitors and α blockers, respectively.¹⁰

Transurethral prostatectomy specimens

TURP FOR CLINICALLY BENIGN DISEASE

A proportion of these specimens will contain unsuspected foci of adenocarcinoma, and controversy surrounds the sampling necessary to detect such tumours and their significance. In a study of 457 TURPs processed in their entirety carcinoma was diagnosed in 14.2%.¹¹ Three series, each including a minimum of 100 TURPs, compared the results of a variety of restricted and total sampling methods. Carcinoma was diagnosed in 7–8% of TURPs on restricted sampling and 14–19% of those in which all the tissue was processed.^{12–14} A further study¹⁵ expressed the results as the probability of detecting different proportions of carcinoma in TURPs according to the percentage processed.

In practice the proportion of TURP fragments invaded by carcinoma fall into two groups, reflecting the classification commonly used in the USA¹⁶: stage A1, carcinoma in up to 5% of the tissue; stage A2, carcinoma in over 5% of the tissue or of high grade (combined Gleason grades 7 to 10). The UICC system is used in Britain and the similar range of stages is T1a (A1) and T1b (A2).¹⁷ The percentage of involved chips provides similar prognostic information to more detailed and time consuming morphometric analyses of surface area.¹⁸

Thirty two per cent of patients with A2 disease will develop progressive disease in four years.¹⁶ Progression of A1 disease becomes apparent on longer follow up—27% at 10 years.¹⁹ Therefore, depending on the physiological age of the patient, some form of radical therapy may be offered in certain centres. Most restricted sampling systems will permit detection of the high volume A2 carcinoma (and the equivalent T1b disease), but may not detect the A1 group or the small subgroup of A2 disease defined as “5% of fragments or less but of high grade”.

From the above knowledge of disease course and sampling dependent detection, the following approach is suggested for processing TURPs. The entire specimen from men aged 60 years or less is processed and one section examined from each block, as these patients may expect to live for an average of a further 10 years and even A1 disease may progress in this time. As TURPs in this age group are not common, this approach will not add greatly to the laboratory workload. In patients aged over 60 years in centres where radical treatment for A1 disease is practised, the urologists must select an age beyond which they would not consider radical treatment. All TURP tissue from men below this age is processed and examined as above. In patients above the selected age, some form of sampling is applied. If the TURP weighs 12 g or less it is processed

in its entirety. In excess of this weight, the system used by the authors is to process a minimum of 12 g, plus 2 g for every 5 g in excess of 12 g. It is important that the urologists are aware that a sampling system is operated so that a degree of corporate responsibility is assumed. Exceptions are obviously made to this protocol if surgeons strongly suspect cancer and request examination of further tissue when a benign diagnosis has been made. Also if stage A1 carcinoma is found, examination of all the remaining tissue has been recommended to confirm the staging. This is not required in stage A2 disease as the percentage involved is unlikely to decrease with greater sampling.²⁰ The demonstration of high grade PIN should lead to further sampling because of its high association with concomitant carcinoma.⁵

The macroscopic report includes the total weight of the specimen, the weight processed and the number of cassettes. In those specimens being sampled, any white or yellow fragments (which may prove to be tumour) are included in the cassettes. The microscopic description includes the number of sections examined, and the presence of hyperplastic nodules and any other tissue—for example, seminal vesicle. As scattered foci of chronic inflammatory cells are common and not associated with clinical or bacteriological evidence of prostatitis, inflammation is only noted if extensive, acute or granulomatous. If adenocarcinoma is seen, a fraction and percentage of tissue pieces involved is given with the tumour grade. The presence of tumour in striated muscle, adipose tissue or seminal vesicle is recorded. The malignant foci are marked for ease of demonstration.

TURP FOR ADENOCARCINOMA

In patients with an established malignant diagnosis when a channel TURP becomes necessary for recurrent obstruction, only a small sample of the tissue is processed (6 g). This enables the grade to be compared with that in the initial specimen.

Retropubic prostatectomy specimens

The specimens consist of a series of enucleated periurethral nodules or a bilobed tissue mass, sometimes with a prominent middle “lobe”. Following retropubic prostatectomy (RPP), the periphery of the gland (equivalent to McNeal’s peripheral zone), in which 60% of carcinomas arise, remains in situ²¹ (fig 1).

The number of tissue masses, their size range and total weight are noted. Each specimen is incised at 5 mm intervals, whilst retaining tissue continuity, so that adjacent blocks can be selected if subsequently necessary. Homogeneous white or yellow areas are noted and sampled as they may prove to be carcinoma. Foci of haemorrhage are not uncommon and usually represent areas of infarction.

Blocks are selected from all the abnormal areas seen and one block per 5 g of tissue has been recommended.²² It must be acknowledged that sampling of RPP specimens is inconsistent with that of TURP specimens. Both operations remove identical tissue from men of similar age range and although numerous papers have been written relating diagnosis of carcinoma in TURP for clinically benign disease with sampling, its value and cost, similar information is not available for RPP specimens. If car-

Figure 1 Zonal anatomy of the prostate (reproduced with permission from Greene et al. *Br J Urol* 1991;68:499–509).

cinoma is identified microscopically, further blocks adjacent to the tumour containing tissue should be taken in an attempt to assess its extent.

Radical prostatectomy

The approach to radical prostatectomy specimens is largely based on knowledge gained from studies carried out in the USA.

PELVIC LYMPHADENECTOMY

Imaging techniques have a low sensitivity for detecting lymph node invasion. Consequently, before proceeding to a radical resection which would not be curative in a patient with positive nodes, most surgeons will submit bilateral pelvic lymph nodes to exclude metastatic disease, usually as intraoperative frozen sections. Nodal dissection can also be performed laparoscopically before radical surgery is planned, permitting a detailed examination of fixed specimens. However, the surgical time involved and reactive changes in the pelvis which may complicate subsequent surgery limit the use of this technique.

The nodes are commonly received closely adherent to each other and surrounded by adipose tissue, making individual dissection of nodes impossible. The macroscopic description for fixed or fresh nodes includes their size and a note of any palpable or visual abnormality on bisection. Blocks for frozen section include any abnormal areas and samples of each node. Between four and six sections are commonly examined from each side. These blocks prove technically difficult because of their fat content. The ex-cryostat and all residual tissue or the entire fixed specimen from laparoscopic dissection is processed. This complete examination follows reports and experience of finding isolated extranodal metastatic tumour.

In a series of 310 patients, 12.9% were found to have positive lymph nodes on paraffin sections: frozen sections identified approximately two thirds of these.²³ The surgeon must be made aware of the false negative rate of this technique.

The major practical problem encountered in frozen sections is the time involved for the anaesthetised patients, theatre team and pathology staff. Various means of minimising the time involved have been considered. Unfortunately, simply sectioning the suspicious nodes is not accurate.²³ Lymph node imprints are performed in some centres but the false negative results compared with frozen section are not published. The management of patients with clinically localised disease but with pelvic nodal metastases is controversial, but survival advantages have been documented for radical prostatectomy versus hormonal or radiation therapy (75% *v* 39–54% 10 year survival).²⁴

RADICAL PROSTATECTOMY SPECIMEN

Apart from providing prognostic information, sampling and reporting of radical prostatectomies are important for two reasons.

Firstly, if tumour is present at the resection limit the patient may receive adjuvant radiotherapy. Secondly, there is a marked discrepancy between clinical (DRE and TRUS) and pathological disease staging: although most surgeons will only offer radical surgery to those with clinically gland confined disease, on pathological examination of the specimen resection limits are positive in 40–60% of cases. Thus pathological staging is essential as a basis for analysis and comparison of results.

Sampling must demonstrate the morphological features predictive of disease progression: Gleason sum score²⁵; volume²⁶; resection limit status²⁵; and seminal vesicle invasion.⁸ In multivariate analysis, the results from Johns Hopkins indicate that the Gleason score is the most significant, followed by positive margins,²⁵ whereas in Stanford the volume and the percentage of carcinoma of Gleason grades 4 and 5 were found to be the most significant.²⁷

MACROSCOPY

Prostatectomy specimens vary widely in shape and size, but hardly ever conform to the diagrammatic inverted cone seen in textbooks with the base at the bladder neck tapering to the apex adjacent to the external sphincter. The gland is best orientated by the knowledge that the seminal vesicles are posterior and superior (sometimes partially embedded in the gland), the posterior surface is flat and the anterior convex. A sound passed through the urethra will frequently show that the anterior aspect of the gland is shorter than the posterior.

The prostate is fixed in formol saline for 24 hours and its weight and dimensions recorded. The entire surface of the specimen is inked, two colours being used to indicate laterality. A third colour is used to paint a line down the centre of the anterior surface to facilitate subsequent orientation and minimise errors. At this stage, the limits are sampled including the vas deferens, bladder neck and urethra. The vasa deferens are identified as short stumps medial to the seminal vesicles. The complete circumference of the bladder neck and urethra are taken as "shave" limits. The distal orifice often seems to retract into the anterior wall of the specimen but is demonstrated by a sound passed through the urethra. Sampling the urethra frequently excavates the prostate. If the specimen is simply held vertically and a slice taken across the distal tissue, this may not include the urethral limit. The entire specimen held vertically is then divided into blocks 5 mm thick in the coronal plane. This can be achieved by cutting parallel to 5 mm glass rods attached to a board with plasticine or to 5 mm thick flat strips of Perspex glued to a board. The blocks are then laid down in order, apex to base and seminal vesicles, taking care to maintain superior/inferior surface relations. The cut surface is examined for evidence of asymmetry. Adenocarcinoma may appear as white or yellow areas with a more homogeneous texture than the fibrocystic gland. Pitfalls in macroscopic diagnosis include scarring round a transurethral resection cavity and any biopsy tracks.

The blocks are labelled consecutively in ink from the apex to the base and seminal vesicles. Numbers are written at a consistent site and help to indicate to the MLSO both the surface to be cut and the orientation on the slide (fig 2A). These blocks are then fixed for a further 24 hours in formol saline. A thinner block can then be taken from each numbered surface for routine processing, giving the residual slice the original number of the corresponding processed block so that adjacent tissue can be examined if necessary. Alternatively, the full thickness blocks can be processed providing the processing schedule is modified to take into account the size and texture of the block.

MICROSCOPY

The site and the area occupied by the tumour may be given for each level for clinicians wishing to compare the morphological and ultrasound findings, or the location may be summarised. Some form of mapping of the

adenocarcinoma is essential for clinicians to assess the role of preoperative investigations both within their own units and in comparison with others. Microanatomy may be described in terms of anterior/posterior/lateral or McNeal's zones may be applied (fig 1).

Grading

The Gleason grading system is based on the microarchitecture of the tumour.⁷ Each tumour is assigned two grades, according to the predominant patterns by area, which are summed to give the Gleason score—for example, 2 + 3. When the morphology is uniform, the grades are identical—for example, Gleason 4 + 4. If areas of grade 4 or 5 are present, the sum of the percentage of these patterns is given.

Tumour volume

Measurement of tumour volume is approximate. The shrinkage factor should be established within each laboratory. The tumour is outlined microscopically at each level (fig 2B), and the areas measured using squared paper or by computer aided techniques. The summated areas are multiplied by the interval between the sections (5 mm).

The predictive value is greatest when quantitative Gleason grade and volume are combined. In a study of 209 carcinomas 58% of cases with more than 3.2 ml of grades 4 to 5 had nodal metastases, whereas below this volume the frequency was 0.58%.²⁷

Resection margins

Resection margin positivity is most common posteriorly, posterior-laterally and at the urethral limit. The frequency with which tumour is present at these sites relates to its natural distribution in the peripheral zone and at the apex of the gland, unfortunately close to the nerves and striated muscle that the surgeon is trying to preserve to enable the patient to retain potency and continence.

The problems encountered in the interpretation of the relation between tumour and limits of excision are clearly discussed by Epstein.²⁸ Carcinoma in the shave urethral limit is reported as positive by the authors, but in other departments, apical limits are only recorded as positive if carcinoma is seen in striated muscle or, if tumour is seen in prostate but not in striated muscle, it is of high grade or part of the major tumour. Interpretation of the peripheral limits is confused by the term "capsule" which is variable in structure and distribution and is frequently absent. Identification of the "capsule" is made more difficult by the desmoplastic response commonly seen around tumours which invade adipose tissue. Therefore, a terminology independent of "capsule" and widely used in America is being adopted. It depends on defining three limits:

- 1 Contour of the gland at low power which is dictated by muscle outline. Benign acini are virtually always within this limit and

Figure 2 Section of radical prostatectomy specimen. (A) Macroscopy. (B) Microscopy of same section with tumour outlined.

- beyond it is adipose tissue. However, rare exceptions can occur.
- 2 The tissue external to the muscle outline, which may be up to 1 cm in width consisting of adipose/fibrous tissue, blood vessels and nerves but may simply be strands of fibrous tissue.
  - 3 The inked resection edge.

Rarely, when the gland has been incised during removal, limits 1 and 2 will be absent.

These definitions allow the tumour to be classified as:

- 1 Gland confined: within the muscle outline.
- 2 Specimen confined but outside the gland: invading beyond the muscle outline but not present at the inked surgical limit.
- 3 Limit positive disease: tumour present at the inked margin.

In limit positive disease the important feature is the extent of invasion. The demonstration of rare acini in occasional sections within adipose tissue is not associated with an increased risk of progression (less than 20% at five years irrespective of margin status). In limit positive disease with more extensive invasion, however, 40% of patients will progress at five years.²⁸

Seminal vesicles

Invasion of the seminal vesicles is usually a clear-cut diagnosis. In cases where small foci of tumour are difficult to distinguish from cross-cuts of seminal vesical epithelium, a prostatic origin is indicated by the immunocytochemical detection of PSA. Seminal vesicle invasion carries a poor prognosis: 75% of patients will relapse by five years.

Vascular invasion

Vascular channel infiltration by tumour is recorded, although it is not an independent prognostic factor.

LIMITED EXAMINATION

Various protocols have been described, tested and shown by their designers to give similar prognostic information to the more detailed sampling outlined above.²⁹ In addition to blocks from the resection limits, junction with seminal vesicles and apex (adjacent to the resection limit), they include a block of the major tumour with the nearest peripheral limit. However, the macroscopic location of tumours within the gland is difficult and unreliable. Therefore, sampling throughout the gland is recommended.

Special techniques

Preservation of frozen tissue from prostatic specimens is not routinely required as the techniques that have established value can be applied to formalin fixed material. (Those laboratories involved in research are referred to Bova *et al.*³⁰)

ESTABLISHED TECHNIQUES

Both intraluminal acid mucin³¹ and crystalloids³² are associated more frequently, but not exclusively, with carcinoma. While the eosinophilic crystalloids can be identified on haematoxylin and eosin sections, they stain intensely dark blue with phosphotungstic acid haematoxylin (PTAH) and are not birefringent, whereas corpora amylacea are pink or brown with PTAH and demonstrate partial apple green fluorescence on polarisation.

Immunohistochemical demonstration of prostate specific acid phosphatase (PSAP) and PSA can be useful, even on decalcified tissues, for confirming the prostatic origin of a poorly differentiated tumour in the primary or a secondary site. Less than 2% of high grade prostatic carcinomas fail to express at least one marker,³³ although sensitivities and specificities should be confirmed in individual laboratories. In needle biopsy specimens there is a greater danger of false negative results because of sampling error as the proportion of positive cells can be small, particularly if only PSA is used (20% of high grade tumours have only 1–5% PSA positive cells).³³ These markers have also been used to identify crushed cells around nerves, thereby establishing the diagnosis of adenocarcinoma, but extreme caution is advised.

Cytokeratin immunoreactivity can be useful for the detection of basal prostatic cells³⁴ as they are positive with antibodies to cytokeratins 13, 14 and 16 in particular. Their demonstration may be useful for distinguishing between benign and malignant disease, although a negative result may be uninformative as some benign conditions may fail to exhibit consistent or continuous positive staining.³⁵

EXPERIMENTAL TECHNIQUES

Diagnosis of malignancy

No consistent or specific genetic abnormalities have been associated with prostatic carcinoma, although allelic losses affecting chromosomes 8p, 10p and q, 13, 16q, 17p, and 18q have been demonstrated.³⁶ Relations between such losses and the biology and prognosis of prostatic cancer have not been established as yet.

Expression of the A chain and α receptor of platelet derived growth factor has been observed in both epithelial and stromal cells in adenocarcinomas but not in benign conditions.³⁷ If confirmed, this may be useful in differential diagnosis, as antibodies are effective on fixed tissues.

Prognosis

The presence of an aneuploid tumour population has been associated with an increased risk of tumour recurrence and higher mortality, although the demonstration of such a population within generally heterogeneous tumours depends on the sampling method and analysis technique.³⁸ This may explain why some patients with an apparently diploid tumour have aggressive disease. The best results appear to be obtained by fine needle aspiration sam-

pling, which requires fresh tissue, followed by image analysis.³⁹ While pretreatment DNA ploidy determination has been recommended to offer more aggressive therapy to patients with aneuploid tumours, prospective studies are required to confirm the clinical usefulness of this technique in individual patients. Proliferation rates have been measured by a variety of techniques but their value relative to grade as independent prognostic factors have not been established.⁴⁰ Neuroendocrine differentiation, as demonstrated by chromogranin A, has been linked to poor prognosis in most studies.⁴¹ Overexpression of p53 has also been associated with poor prognosis although whether it has value independent from grade is unclear.⁴²

There is a correlation between decreased expression of E-cadherin, loss of tumour differentiation and risk of progression.⁴³ The E-cadherin gene locus has been mapped to chromosome 16q, a frequent site of allelic loss in prostate cancer. Microvessel density in prostatic carcinoma is an independent predictor of pathological stage,⁴⁴ which may be useful for determining treatment strategies.

Response to therapy

The determination of the androgen receptor status of carcinoma cells may be valuable for determining the response to androgen ablation therapy, independent of grade and stage: poor responders have greater heterogeneity in receptor concentration per cell.⁴⁵ The percentage of positive nuclei appears not to be a sufficient criterion. Antibodies effective on formalin fixed material are now available.⁴⁶

Increased expression of bcl-2 has been correlated with the progression of prostatic cancer from androgen responsive to androgen independent.⁴⁷ This has also been the case for p53 overexpression.⁴⁸

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