Histopathology 2012, **60**, 87–117. DOI: 10.1111/j.1365-2559.2011.04025.x

REVIEW

Staging of prostate cancer

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(2012) *Histopathology* **60**, 87–117

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Prostatic carcinoma (PCa) is a significant cause of cancer morbidity and mortality worldwide. Accurate staging is critical for prognosis assessment and treatment planning for PCa. Despite the large volume of clinical activity and research, the challenge to define the most appropriate and clinically relevant staging system remains. The pathologically complex and uncertain clinical course of prostate cancer further complicates the design of staging classification and a substaging system suitable for individualized care. This review will focus on recent progress and controversial issues related to prostate cancer staging. The 2010 revision of the American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) tumour, node and metastasis (TNM) system is the most widely used staging system at this time. Despite general acceptance of the system as a whole, there is controversy and uncertainty about its application, particularly for T2 subclassification. The three-tiered T2 classification system for organ-confined prostate cancer is superfluous, considering the biology and anatomy of PCa. A tumour size-based substaging system may be considered in the future TNM subclassification of pT2 cancer. Lymph node status is one of the most important prognostic factors for prostate cancer. Nevertheless, clinical outcomes in patients with positive lymph nodes are variable. Identification of patients at the greatest risk of systemic progression helps in the selection of appropriate therapy. The data suggest that the inherent aggressiveness of metastatic prostate cancer is closely linked to the tumour volume of lymph node metastasis. We recommend that a future TNM staging system should consider subclassification of node-positive cancer on the basis of nodal cancer volume, using the diameter of the largest nodal metastasis and/or the number of positive nodes.

Keywords: metastasis, multifocality, neoplasia, nodal classification, prognosis, prostate, prostatic adenocarcinoma, specimen handling and reporting, tumour, node and metastasis/American Joint Committee on Cancer staging

Abbreviations: AJCC, American Joint Committee on Cancer; DRE, digital rectal examination; L3E, level 3 established; L3F, level 3 focal; PCa, prostatic carcinoma; PLND, pelvic lymph node dissection; PSA, prostate-specific antigen; RT-PCR, reverse-transcription polymerase chain reaction; TNM, tumour, node and metastasis; TRUS, transrectal ultrasonography; TURP, transurethral resection of the prostate; UICC, International Union Against Cancer

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Introduction

Prostatic carcinoma (PCa) is the most commonly diagnosed cancer in men. It is estimated that 240 890 new cases of PCa will be diagnosed in 2011, accounting for 33 720 cancer deaths in the USA.[1] Accurate and uniform staging is vital for prediction of tumour behaviour, treatment selection, evaluation of response to established and experimental treatment, and exchange of information and data among institutions. The tumour, node and metastasis (TNM) staging system for prostatic carcinoma was first introduced in 1992, when the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) adopted a unified TNM staging system for prostate cancer.[2] Repeated revisions have been undertaken in an effort to optimize prognostic accuracy (Tables 1 and 2). The 2010 AJCC made several changes in its staging of PCa from its 2002 version.[3] These changes included extraprostatic extension and microscopic bladder neck invasion, both being included in the T3a category, Gleason score being recognized as the preferred grading system, and the prognostic factors of Gleason score and preoperative prostate-specific antigen (PSA) being incorporated into stage grouping (Table 3).[3] We review the current status and applications of the TNM staging system, with a focus on controversial issues related to staging of PCa.

Clinical staging versus pathological staging

Both clinical and pathological staging of PCa provide methods with which to assess the extent of tumour spread and to predict patient prognosis. Clinical staging is based on data obtained prior to the first definite treatment. The extent of clinically evident tumour is determined by digital rectal examination (DRE), transrectal ultrasonography (TRUS), or other imaging techniques. Pathological staging requires histological identification of the extent of tumour within the prostate and in surrounding tissues. Although the criteria for assessment of the clinical staging of PCa are well defined, there is still ambiguity in translating these criteria into routine surgical pathology practice following radical prostatectomy. Anatomically distinct lobes are not grossly or histologically definable in the prostate, despite the use of this distinction in staging systems (Figure 1). In addition, PCa is often multifocal,[4] and clear methods for pathological staging of multifocal small tumours have not been defined. There is no pT1 category corresponding to clinical stage T1 tumours, whereas subclassification of clinical T1 stages (T1a versus T1b) depends on pathological quantification of tumour volume in the prostatic chips.

T1 carcinoma in the 2010 TNM staging system is defined as clinically inapparent tumour that is neither palpable nor visible by imaging. T1 prostate cancers are further divided into three categories (Table 1; Figure 2). T1a cancer is defined as incidental tumour identified in transurethral resection of the prostate (TURP), involving $\leq$ 5% of tissue resected. T1b cancer is defined as incidental prostate cancer involving >5% of tissue resected. T1c PCas are those non-palpable or visible tumours identified by needle biopsy owing to elevated serum PSA. Clinical T2 PCas(cT2) are organ-confined tumours, but are palpable by DRE or visible by various imaging techniques. TRUS-detected cT2 cancers were smaller than but similar in Gleason grade, extraprostatic extension and prognosis to palpable T2 cancers (detected by DRE).[5] Intraprostatic adipose tissue does not exist, so identification of fat invasion in needle biopsies constitutes T3a cancer (Figure 3). Similarly, T3b cancer can be identified by needle biopsy of seminal vesicles (Figure 4). Histopathological assessment of bone biopsy is rarely needed for the diagnosis of bone metastasis, because various imaging tools are available for the detection of distant metastasis (Figure 5).

Agreement between clinical and pathological stages would facilitate assessment of patient prognosis and guide appropriate therapy. However, clinical staging is an inaccurate tool with which to predict final pathological stage (see further discussion below).[6] None of the current imaging modalities, including TRUS and magnetic resonance imaging, is reliable for predicting extraprostatic extension or seminal vesical invasion. Furthermore, over 80% of PCas are multifocal, which makes accurate clinical staging even more difficult and unreliable.[7] Clinical tumour understaging has consistently been shown to range from 40% to 60%.[8–11] This is clearly attributable to the multifocal, histologically heterogeneous nature of prostatic carcinoma. Bostwick *et al.* found that 59% of clinical stage T2, T3 and T4 PCas in men undergoing radical prostatectomy were understaged when compared with final pathological stage.[12] Five per cent of the tumours were clinically staged higher than the pathological stage.[12] Thus, the clinical and pathological stages corresponded in only 36% of the cases. The clear discordance between clinical staging and pathological staging with current classification systems often surprises the patient with an amended prognosis, and forces the urologist to adjust the treatment that is underway.

Table 1. American Joint Committee on Cancer (AJCC) clinical TNM classification of prostatic tumours

	2010	2002	1997	1992
Primary tumour (T) – clinical				
TX	Primary tumour cannot be assessed	Primary tumour cannot be assessed	Primary tumour cannot be assessed	Primary tumour cannot be assessed
T0	No evidence of primary tumour	No evidence of primary tumour	No evidence of primary tumour	No evidence of primary tumour
T1	Clinically inapparent tumour neither palpable nor visible by imaging	Clinically inapparent tumour neither palpable nor visible by imaging	Clinically inapparent tumour neither palpable nor visible by imaging	Clinically inapparent tumour neither palpable nor visible by imaging
T1a	Tumour incidental histological finding in ≤ 5% of tissue resected	Tumour incidental histological finding in ≤ 5% of tissue resected	Tumour incidental histological finding in ≤ 5% of tissue resected	Tumour incidental histological finding in ≤ 5% of tissue resected
T1b	Tumour incidental histological finding in >5% of tissue resected	Tumour incidental histological finding in >5% of tissue resected	Tumour incidental histological finding in >5% of tissue resected	Tumour incidental histological finding in >5% of tissue resected
T1c	Tumour identified by needle biopsy (e.g. because of elevated PSA)	Tumour identified by needle biopsy (e.g. because of elevated PSA)	Tumour identified by needle biopsy (e.g. because of elevated PSA)	Tumour identified by needle biopsy (e.g. because of elevated PSA)
T2	Tumour confined within prostate	Tumour confined within prostate	Tumour confined within prostate	Tumour confined within prostate
T2a	Tumour involves ≤ one-half of one lobe	Tumour involves ≤ one-half of one lobe	Tumour involves one lobe	Tumour involves ≤ one-half of one lobe
T2b	Tumour involves >one-half of one lobe but not both lobes	Tumour involves >one-half of one lobe but not both lobes	Tumour involves both lobes	Tumour involves >one-half of one lobe but not both lobes

Table 1. (*Continued*)

	2010	2002	1997	1992
T2c	Tumour involves both lobes	Tumour involves both lobes	–	Tumour involves both lobes
T3	Tumour extends through the prostate capsule	Tumour extends through the prostate capsule	Tumour extends through the prostate capsule	Tumour extends through the prostate capsule
T3a	Extracapsular extension (unilateral or bilateral)	Extracapsular extension (unilateral or bilateral)	Extracapsular extension (unilateral or bilateral)	Unilateral extracapsular extension
T3b	Tumour invades seminal vesicle(s)	Tumour invades seminal vesicle(s)	Tumour invades seminal vesicle(s)	Bilateral extracapsular extension
T3c	–	–	–	Tumour invades the seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall	Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall	Tumour is fixed or invades adjacent structures other than the seminal vesicles
T4a	–	–	–	Tumour invades any of: bladder neck, external sphincter, or rectum
T4b				Tumour invades levator muscles and/or is fixed to the pelvic wall
Regional lymph nodes (N) – clinical				
NX	Regional lymph nodes were not assessed	Regional lymph nodes were not assessed	Regional lymph nodes cannot not be assessed	Regional lymph nodes cannot be assessed

Table 1. (*Continued*)

	2010	2002	1997	1992
N0	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis
N1	Metastases in regional lymph node(s)	Metastases in regional lymph node(s)	Metastases in regional lymph node(s)	Metastasis in a single lymph node, ≤ 20 mm in greatest dimension
N2	–	–	–	Metastasis in a single lymph node, >20 mm but not >50 mm in greatest dimension; or multiple lymph node metastases, none >50 mm in greatest dimension
N3	–	–	–	Metastasis in a lymph node >50 mm in greatest dimension
Distant metastasis (M)				
MX	–	Distant metastasis cannot be assessed (not evaluated by any modality)	Distant metastasis cannot be assessed	Distant metastasis cannot be assessed
M0	No distant metastasis	No distant metastasis	No distant metastasis	No distant metastasis
M1	Distant metastasis	Distant metastasis	Distant metastasis	Distant metastasis
M1a	Non-regional lymph node(s)	Non-regional lymph node(s)	Non-regional lymph node(s)	Non-regional lymph node(s)
M1b	Bone(s)	Bone(s)	Bone(s)	Bone(s)
M1c	Other site(s) with or without bone disease	Other site(s) with or without bone disease	Other site(s)	Other site(s)

PSA, Prostate-specific antigen.

Table 2. American Joint Committee on Cancer (AJCC) pathological TNM classification of prostatic tumours

	2010	2002	1997	1992
Primary tumour (pT) – pathological				
pTX	–	–	–	Primary tumour cannot be assessed
pT0	–	–	–	No evidence of primary tumour
pT1	There is no pathological T1 classification	There is no pathological T1 classification	There is no pathological T1 classification	Clinically inapparent tumour neither palpable nor visible by imaging
pT1a	–	–	–	Tumour incidental histological finding in ≤ 5% of tissue resected
pT1b	–	–	–	Tumour incidental histological finding in >5% of tissue resected
pT1c	–	–	–	Tumour identified by needle biopsy (e.g. because of elevated PSA)
pT2	Organ confined	Organ confined	Organ confined	Tumour confined within prostate
pT2a	Unilateral, one-half of one side or less	Unilateral, one-half of one lobe or less	Unilateral	Tumour involves ≤ one-half of one lobe
pT2b	Unilateral, involving more than one-half of side but not both sides	Unilateral, involving more than one-half of lobe but not both lobes	Bilateral	Tumour involves >one-half of one lobe but not both lobes
pT2c	Bilateral disease	Bilateral disease	–	Tumour involves both lobes

Table 2. (*Continued*)

	2010	2002	1997	1992
pT3	Extraprostatic extension	Extraprostatic extension	Extraprostatic extension	Tumour extends through the prostate capsule
pT3a	Extraprostatic extension or microscopic invasion of bladder neck	Extraprostatic extension [positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease)]	Extraprostatic extension	Unilateral extracapsular extension
pT3b	Seminal vesicle invasion	Seminal vesical invasion	Seminal vesical invasion	Bilateral extracapsular extension
pT3c	–	–	–	Tumour invades the seminal vesicle(s)
pT4	Invasion of rectum, levator muscle, and/or pelvic wall	Invasion of bladder, rectum	Invasion of bladder, rectum	Tumour is fixed or invades adjacent structures other than the seminal vesicles
pT4a	–	–	–	Tumour invades any of: bladder neck, external sphincter, or rectum
pT4b	–	–	–	Tumour invades levator muscles and/or is fixed to the pelvic wall
Regional lymph nodes (pN) – pathological				
pNX	Regional nodes not sampled	Regional nodes not sampled	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
pN0	No positive regional nodes	No positive regional nodes	No regional lymph node metastasis	No regional lymph node metastasis

Table 2. (*Continued*)

	2010	2002	1997	1992
pN1	Metastases in regional node(s)	Metastases in regional node(s)	Metastases in regional lymph node(s)	Metastasis in a single lymph node, ≤ 20 mm in greatest dimension
pN2	–	–	–	Metastasis in a single lymph node, >20 mm but not >50 mm in greatest dimension; or multiple lymph node metastases, none >50 mm in greatest dimension
pN3	–	–	–	Metastasis in a lymph node >50 mm in greatest dimension
Distant metastasis (pM) – pathological				
pMX	–	Distant metastasis cannot be assessed (not evaluated by any modality)	Distant metastasis cannot be assessed	Distant metastasis cannot be assessed
pM0	No distant metastasis	No distant metastasis	No distant metastasis	No distant metastasis
pM1	Distant metastasis	Distant metastasis	Distant metastasis	Distant metastasis
pM1a	Non-regional lymph node(s)	Non-regional lymph node(s)	Non-regional lymph node(s)	Non-regional lymph node(s)
pM1b	Bone(s)	Bone(s)	Bone(s)	Bone(s)
pM1c	Other site(s) with or without bone disease. When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced	Other site(s) with or without bone disease. When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced	Other site(s). When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced	Other site(s). When more than one site of metastasis is present, the most advanced category (pM1c) is used

PSA, Prostate-specific antigen.

Table 3. American Joint Committee on Cancer (AJCC) stage grouping (2010 edition)

Stage	T	N	M	PSA (ng/ml)	Gleason score
I	T1a–c	N0	M0	<10	≤ 6
	T2a	N0	M0	<10	≤ 6
	T1–2a	N0	M0	X	X
IIA	T1a–c	N0	M0	<20	7
	T1a–c	N0	M0	≥10 and <20	≤ 6
	T2a	N0	M0	<20	7
	T2b	N0	M0	<20	≤ 7
	T2b	N0	M0	X	X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	≥20	Any Gleason
	T1–2	N0	M0	Any PSA	≥8
III	T3a–b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

M, Metastasis; N, node; PSA, prostate-specific antigen; T, tumour; X, unknown.

T1 prostatic carcinoma

STAGE T1A CARCINOMA

It is estimated that 6% of men scheduled for TURP will have incidental cancer in 5% or less of the resected prostatic chips (stage T1a).[13–17] The diagnosis of stage T1a cancer in patients with a relatively long life-expectancy presents urologists and oncologists with challenging management problems. The biological behaviour of stage T1a cancer is variable and unpredictable. A substantial number (10–26%) of patients with stage T1a cancer have clinical progression at 7–10 years. Thus, a critical issue in the management of patients with stage T1a cancer is to predict patient outcome. Information enabling the stratification of patients into different prognostic groups would be valuable for selection of treatment. In a study of 102 patients with stage T1a cancer, the authors found that a significant proportion (14%) of untreated patients with stage T1a cancer had cancer progression on long-term follow-up (mean follow-up, 9.5 years).[15] The amount of resected prostatic tissue (TURP weight) significantly influenced patient outcome. Those with TURP weight ≥30 g had 100% progression-free survival at 10 years, as compared with 73% progression-free survival for those with TURP weight <12 g ($P = 0.04$) (Figure 6). There was a trend towards a worse prognosis with increasing number of chips involved by the cancer. Patients with one or two chips involved by cancer had 88% 10-year progression-free survival, whereas only 73% 10-year progression-free survival was seen among patients with three or more chips involved by cancer. These findings suggest that patients with cancer involving fewer than three chips and TURP weight ≥30 g have an excellent prognosis and can be conservatively managed. The high rate of progression in patients with a small volume of prostatic tissue removed is more likely to be subject to sampling variation (i.e. less cancer detected), leading to stage bias with erroneous designation as T1a rather than T1b.[15]

In a more recent study of 144 consecutively diagnosed T1a cancers, Descazeaud *et al.*[13] found that 30 patients (21%) had cancer progression during a mean follow-up of 5.1 years. The authors identified five adverse parameters that were significantly associated with cancer progression: preoperative PSA ≥ 10 ng/ml, postopera-

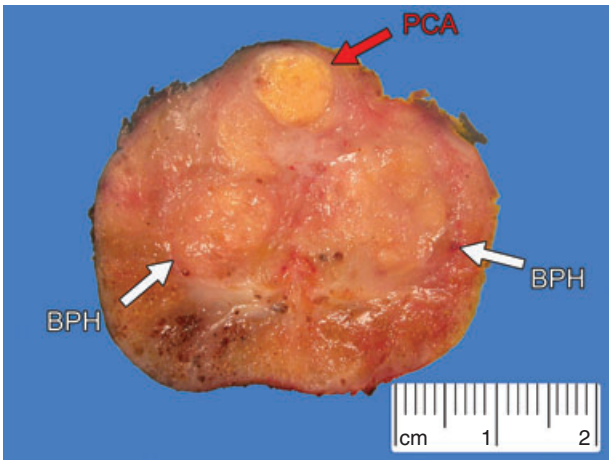

Figure 1. Cross-section of the prostate. Anatomically distinct lobes are not grossly definable. Note the yellow nodule in the anterior prostate, which represents prostatic adenocarcinoma (PCa). Benign prostatic hyperplasia (BPH) is seen in the transition zone of the prostate.

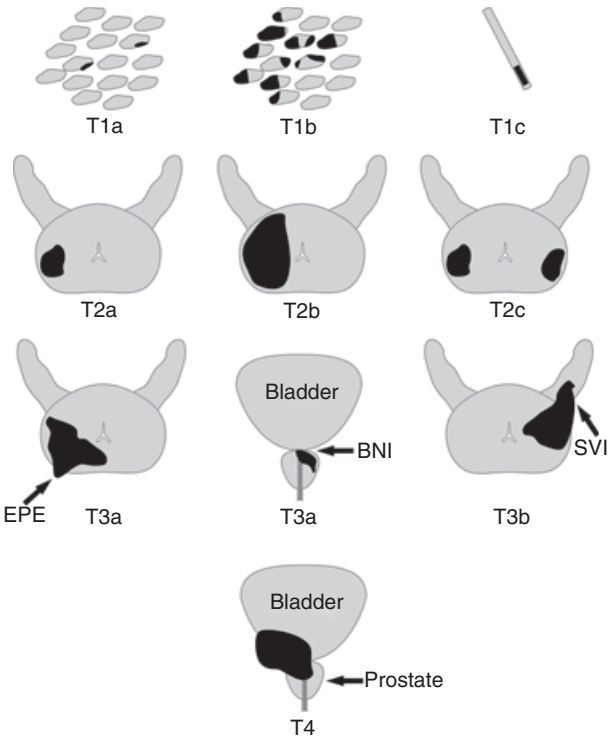

Figure 2. Schematic drawings of the 2010 TNM staging classification. EPE, extraprostatic extension; BNI, bladder neck invasion; SVI, seminal vesical invasion.

tive PSA ≥ 2 ng/ml, prostate weight ≥60 g, weight of resected tissue ≥40 g, and Gleason score ≥6. The 5-year progression rate was 12% if only one of these parameters

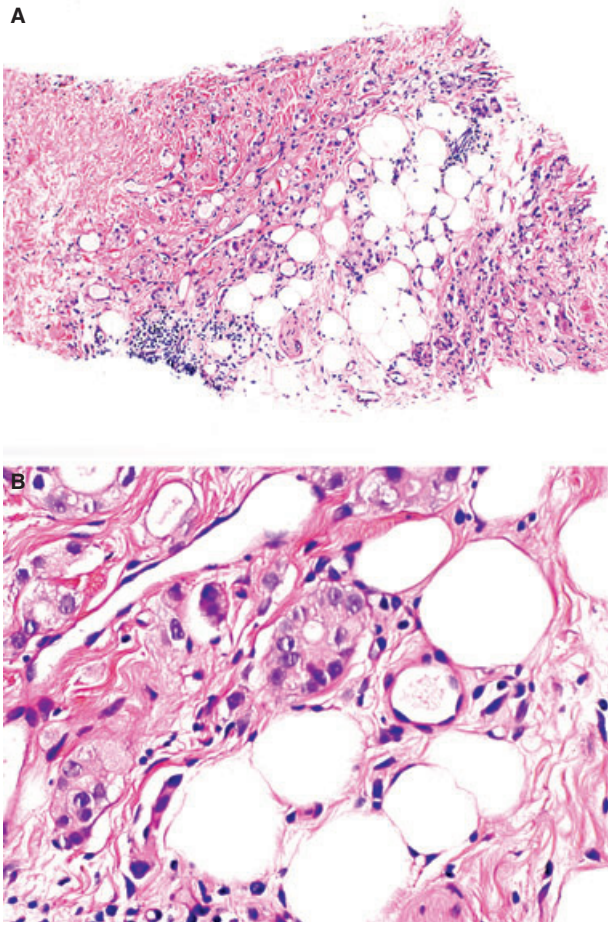

Figure 3. (**A** and **B**) The presence of fat invasion in needle biopsy indicates cT3a prostate cancer.

was present, whereas it was 47% if two or more parameters were present.[13]

STAGE PT1A VERSUS PT1B CARCINOMA

The current TNM pathological staging of prostate cancer on TURP chips stratifies patients into stage T1a or T1b on the basis of the percentage area of tumour (≤ 5% versus >5% or greater) in the TURP specimen. Decisions on patient treatment are often made according to this cutoff. This approach is based on a study dated prior to the PSA era.[18] In 1980, Cantrell *et al.*[18] further refined the staging of clinically inapparent PCa. The authors showed that tumour extent and histological grade in TURP specimens could accurately predict cancer progression. However, there were only 117 patients in this study, and there was progression in only 14 patients after 4 years. Despite these limitations, it was found that subdividing disease extent into two groups, ≤ 5% and >5%, was a

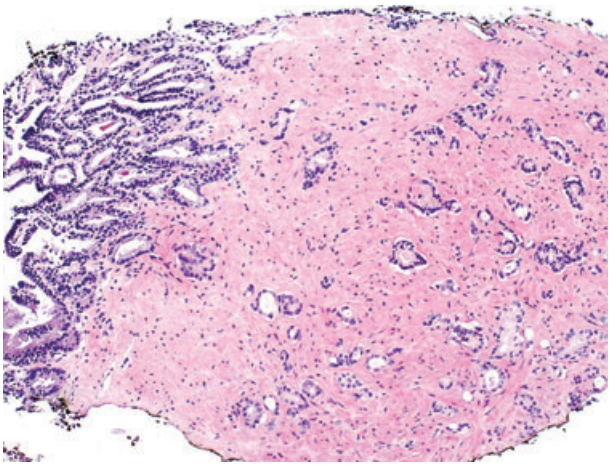

Figure 4. Seminal vesical invasion in needle biopsy (cT3b cancer). The seminal vesicle is essentially indistinguishable from the ejaculatory duct on needle biopsy. The diagnosis of seminal vesical invasion relies on correct identification and labelling of the specimen by the urologist.

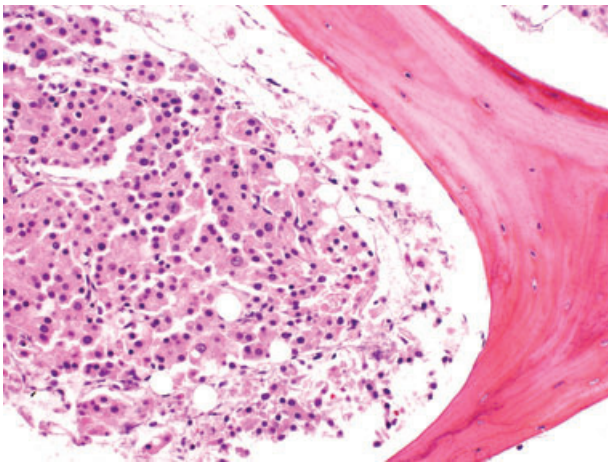

Figure 5. Bone metastasis from prostate cancer (M1b).

clinically useful determinant. This single important study is the basis for the TNM subclassification of localized (T1a/b) PCa, from the initial proposal by the UICC and AJCC in 1992 to the current staging manual (7th edition) in use today.

With the advent of nomograms, risk of progression can be given on a variable scale rather than with the dichotomic TNM system. With narrow TNM classification bins, valuable information may be lost and patients may receive inappropriate therapy from among the many treatment options now available.[19–22] In an analysis of 914 patients diagnosed by TURP between 1990 and 1996 (all of whom were managed

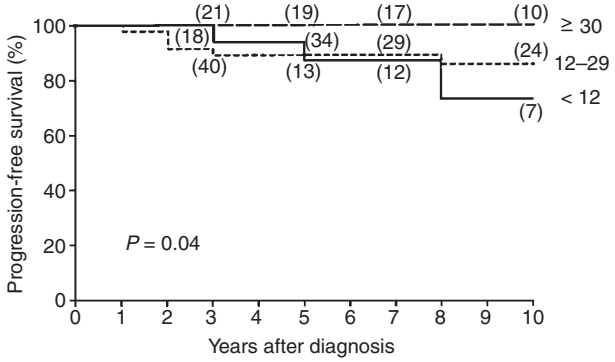

Figure 6. Kaplan–Meier curves (progression-free survival) for 102 untreated patients with T1a prostate cancer according to the amount of prostatic tissue removed (transurethral resection specimen weight in grams). The numbers in parentheses represent the numbers of patients under observation at 3, 5, 7 and 10 years. Prostate weight was analysed as a continuous factor (modified from Cheng *et al.*,[15] with permission).

conservatively),[16] the investigators from the Transatlantic Prostate Group found that the percentage of positive chips was highly predictive of prostate cancer death when assessed as a continuous variable or as a categorical variable grouped into quintile, quartile, tertile and median groups.[16] In the univariate model, the most informative grouping was into four unequal categories (i.e. ≤ 10%, >10–25%, >25–75%, and >75%). The percentages of prostate cancer death at 10 years were 8%, 21%, 38%, and 56%, respectively, for those with ≤ 10%, >10–25%, >25–75% and >75% chip involvement by cancer. After controlling for preoperative PSA and Gleason score, the extent of TURP chip involvement by cancer remained significant. The authors concluded that the current T1a/b TNM subdivision could be greatly improved by adopting a four-group subdivision. This would improve the prognosis for patients diagnosed by TURP, allow for the construction of better nomograms, and further refine management decisions for patients with low-risk to intermediate-risk disease who would qualify for active surveillance.[16]

T1C CARCINOMA VERSUS CLINICAL STAGE T2 CARCINOMA (CT2)

The current clinical staging system categorizes men with tumours detected by needle biopsies secondary to elevated PSA as cT1c, and men with palpable but localized PCa as cT2. The current TNM staging system implies that patients with prostate cancer detected by PSA screening have a better prognosis than those with palpable prostatic tumours. The data suggest, however,

that PCa detected by PSA screening (cT1c) and tumour detected on DRE (cT2) may have the same prognosis after treatment.[23] Armatys *et al.*[24] compared the clinicopathological characteristics of patients who underwent radical prostatectomy and whole mount specimen processing for cT1c (n = 223) and cT2 (n = 65) PCa. The authors found that patients with cT2 tumours were more likely to have a higher Gleason score and higher final pathological stage than those with cT1c tumours. There was no significant difference in age, preoperative PSA, prostate weight, tumour volume, surgical margin status, multifocality, presence of perineural invasion or high-grade prostatic intraepithelial neoplasia between patients with clinical stage cT1c tumours and those with cT2 tumours. No difference in PSA recurrence was observed between patients with clinical stage T1c tumours and those with cT2 tumours. Other studies have shown that the pathological characteristics are nearly identical in cT1c and cT2 tumours.[25–28] Stamey *et al.* reviewed 791 radical retropubic prostatectomy specimens for final pathology, comparing cT1c and cT2a disease with regard to cancer volume (2.4 cm^3 versus 1.8 cm^3), presence of Gleason pattern 4 or 5 (10% versus 10%), capsular penetration (30% versus 30%), and biochemical cure rates (70% versus 72%). They concluded that cT1c and cT2a tumours were similar.[29] Ramos *et al.* reviewed 1620 patients who had undergone radical prostatectomy for cT1c and cT2a disease. Positive surgical margins (20% versus 23%), seminal vesical invasion (5% versus 5%), lymph node metastasis (0.8% versus 0.3%) and 5-year recurrence rate (85% versus 83%) were similar for cT1c and cT2a disease.[30] Many studies have shown that the clinical behaviour of cT1c tumours is also similar to that of cT2 tumours following radical prostatectomy. The Shared Equal Access Regional Cancer Hospital (SEARCH) Database Study Group retrospectively reviewed Gleason grade, age, preoperative PSA, PSA-free survival and biopsy laterality in 992 patients after radical prostatectomy for cT1c and cT2 disease, and found similar rates of PSA recurrence.[31] Lerner *et al.*[32] found there was no significant disease-free survival advantage in the cT1c group versus the cT2a group (84% versus 75%). In series of 4453 patients at the Mayo Clinic, a comparison was made between cT1c to cT2a, cT2b and cT2c prostate cancer. Overall, 5-year PSA progression-free survival was 82.2% versus 82.5% for cT1c and cT2a cancer, respectively, and 7-year PSA progression-free survival was 72.9% versus 74.7%.[33]

The continued separation of cT1c from cT2 tumours could be problematic for other reasons as well. DRE has low sensitivity in assessing the presence and extent of PCa. This calls into question the current category of cT2 in the TNM staging system, which relies heavily on subjective detection of cancer by DRE.

The utility and practical application of substaging of cT2 cancer is problematic. In the 2010 TNM staging system, cT2 disease is defined as a palpable prostate-confined tumour. These tumours have been subdivided into three categories: T2a (unilateral tumour involving one-half of a lobe or less), T2b (unilateral tumour involving more than one-half of a lobe), and T2c (bilateral disease). Obek *et al.*[34] reviewed 89 patients with clinically palpable tumours (cT2) to assess whether clinicians' characterization of the disease as unilateral or bilateral by DRE correlated with final microscopic examination. In tumours characterized preoperatively as unilateral PCa, 69% were pathologically bilateral and 4% had no cancer in the lobe with palpable abnormality.[34] Clinically benign DRE missed 36% tumours with extraprostatic extension.[34] The current TNM staging of separate T2 categories may not hold true, as tumour laterality has not been shown to correlate significantly with biochemical failure independent of PSA, Gleason score, and palpation T stage.[35] A true T2b cancer (i.e. cancer occupying more than one-half of one lobe only) probably does not exist (see further discussion below).[36] Further refinement of the T1 and T2 clinical staging categories is needed for reliable stratification of patients into different prognostic groups.

Stage T2 prostatic carcinoma

The AJCC TNM staging system has undergone recent revisions for stage T2 tumours. T2 tumours are now subclassified as T2a (less than one-half of one lobe involved), T2b (more than one-half of one lobe involved), and T2c (bilateral involvement) (Figure 7).

The most controversial aspect of the 2010 TNM staging system is the subclassification of pT2 cancer. The TNM staging system for prostate cancer was initially adopted for worldwide use in 1992, with subsequent revisions being published in 1997, 2002, and 2010. The 1997 revision merged tumours occupying less than one-half of a lobe with larger tumours confined to a single lobe (formerly 1992 T2a and T2b) into a single category (T2a), and changed the T2b category to designate tumours involving both lobes (formerly 1992 T2c) (Tables 1 and 2). In 2002, the sixth edition of the TNM staging system refuted the two-tiered classification, and reverted back to the three-tiered system for T2 cancers. The subclassification of pT2 cancer remains the same in the seventh edition (2010). T2 disease was defined as organ-confined PCa,

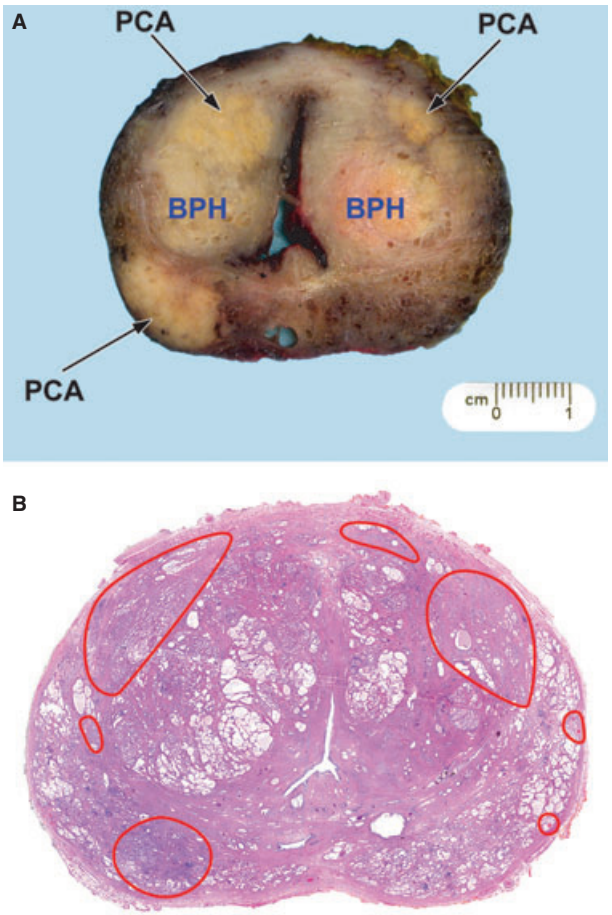

Figure 7. Gross and whole mount view of multifocal bilateral prostate cancer (pT2c). **A**, Gross pathology of a prostate with multifocal prostate cancer. PCa, prostate cancer; BPH, benign prostatic hyperplasia. **B**, Topographical distribution of different-sized tumour foci within a whole mount prostate specimen. Tumour foci are circled (modified from Andreoiu and Cheng,[7] with permission).

with pT2a representing involvement of <50% of one lobe, pT2b involvement of >50% of one lobe, and pT2c involvement of both lobes.

A group from Johns Hopkins analysed 1314 cases of T2 disease in patients who underwent prostatectomy, and calculated the biochemical progression-free survival.[37] Using the 1992 three-tiered classification grouping, they found a significant difference in outcome between men with pT2a and men with T2b disease, but not between the pT2b and pT2c groups. When the revised 1997 two-tiered system was used for progression-free survival analysis, there was an inferior predictive ability and underestimation of definitive therapy's ability to cure men with pT2a disease. Iyer *et al.*[38] also analysed biochemical recurrence-free probability in a large cohort of patients, and found that the 1992 classification of pT2 tumours could more accurately predict remission in patients following external beam radiation therapy. They found no difference in recurrence-free rates between 1992-classified pT2b and pT2c groups at 5 years after radiation therapy.[38] Cagiannos *et al.*[39] also noted significant difference in biochemical recurrence-free survival between the 1992 T2a and T2b subclassifications, but not between the T2b and T2c subclassifications. In a cohort of 1370 consecutive cases with pT2 cancer, Kordan *et al.*[40] found that current pT2 substaging had no prognostic significance, and suggested that future staging systems should collapse pT2 substages into a single category. Similar findings were reported in a large cohort of 1726 patients with pT2 cancer. No benefit was gained from inclusion of pT2 substaging in a nomogram design using the multivariate bootstrap-corrected prediction model.[41]

Questions have even arisen regarding the true validity of stage pT2b tumours. In the first study to investigate the pathological prevalence of pT2b tumours through examination of 369 totally embedded and serially sectioned whole mount radical prostatectomy specimens, not a single unilateral tumour occupying more than one-half of a single lobe (pT2b) could be identified in the large whole mount prostate cohort from Indiana University.[36] PCas were multifocal in 312 cases (85%). The majority of the specimens were pathological stage T2 (276, 75%). With the 2002 staging criteria, 54 (15%) of the tumours were stage pT2a, 222 (60%) were pT2c, 75 (20%) were pT3a, and 18 (5%) were pT3b. As the authors speculated, a palpable tumour involving >25% of the prostate would be most unlikely to be confined to a single lobe, particularly given the multifocal distribution of most PCas. As currently classified, a cT2b tumour probably represents pathologically bilateral disease, either through contiguous involvement by the primary tumours, *de novo* lesions of independent origin, or satellite lesions derived from intraglandular dissemination. Hence, pretreatment discussion with patients should reflect the similar outcome rates of T2b and T2c tumours, and it should be pointed out that this stage of prostate cancer behaves as a unified entity – that of bilateral multifocal disease.

The tendency for PCa to develop multifocally in a majority of cases has been demonstrated by many studies. The rate of detection of two or more separate deposits of carcinoma may range from 60% to 90%.[7,42,43] In a large series of whole mount prostatectomies, Cheng *et al.*[42] analysed the anatomical distribution of small-volume PCa (<0.5 cm^3). Tumour multifocality and bilaterality were identified in 69% and 37% of

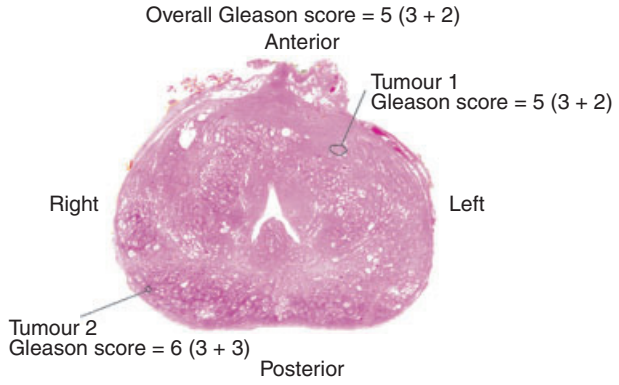

Figure 8. Whole mount section of the prostate showing two outlined tumour foci with corresponding individual Gleason scores. Small-volume cancers (<0.5 cm^3) are often multifocal and bilateral (pT2c cancer) (from Cheng *et al.*[42]).

cases, respectively (Figure 8).[42] Greene *et al.*[44] showed that >80% of prostates contain two or more widely separated tumours by the time of clinical diagnosis. Villers *et al.* found a somewhat lower rate of multifocality in resected prostate specimens (50%), but noted that, in those prostates with more than one tumour focus, 80% of the incidentally discovered tumours had volumes <0.5 cm^3. They commented that this was a proportion similar to that observed among incidentally diagnosed PCas in the specimen group retrieved following radical cystectomy.[45] These findings highlight the importance of understanding the pathogenesis and clinical implications of multifocality in prostate cancer (Figure 9).[4,7,46] The mechanism behind prostatic carcinogenesis probably involves a combination of environmental factors and inherited genetic predisposition. An underlying genetic predisposition could create a 'field effect', whereby further exposure to chemical and biological carcinogens leads to the formation of multiple precursor lesions. Through independent clonal expansion, these lesions evolve into spatially separated and distinct cancers (Figure 9).

Taking into consideration the average prostate weight (35 g) as well as the predominance of tumour multifocality, it would be unusual to identify a tumour involving more than one-half of one lobe (approximately an 8-cm^3 tumour) without involving the other lobe.[36] This argues against a distinct subclassification for tumours occupying more than one-half of a single lobe, but not involving both lobes (pT2b). Further study is needed to determine an optimal staging system for organ-confined PCa. The importance of tumour multifocality in the staging of prostate cancer is yet to be determined.[4,7] In our pathological review of 1274 patients undergoing radical prostatectomy for clinically localized prostate cancer using whole mount sectioning

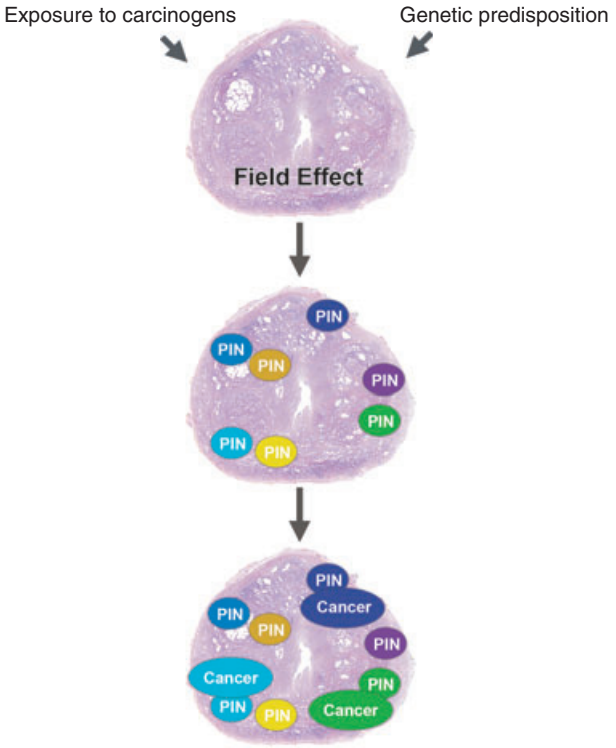

Figure 9. Carcinogenesis of prostate cancer (PCa). Representation of multifactorial aetiology leading to a field effect and progression from prostatic intraepithelial neoplasia (PIN) to multifocal prostate carcinoma. High-grade PIN is the precursor lesion of prostate cancer in a majority of cases, especially cancer arising in the peripheral zone. The relationship of PIN to PCa appears less certain for cancer originating in the transition and anterior zones (modified from Andreoiu and Cheng,[7] with permission).

and tumour mapping, tumour focality failed to predict biochemical recurrence both in univariate and in multivariate models.[47] No differences were seen in 5-year biochemical recurrence-free survival for unifocal (68%) and multifocal (69%) tumours ($P = 0.97$).[47] Conversely, unifocal cancer is not always associated with a favourable prognosis. In fact, half of the unifocal prostate cancers were associated with intermediate-risk or high-risk categories.[48]

A pT2 subclassification based on tumour volume (or tumour size) may be superior to the current 2010 pT2 staging classification based on the clinical impression of midline crossing and proportional occupation of a lobe.[49–51] Tumour size has been used widely as an important TNM staging parameter in numerous organ systems.[3] There was an excellent correlation between tumour size (maximum tumour diameter) and PCa volume.[49] We propose that maximum tumour diameter may be used for pT2 substaging (Table 4). The majority of cases with maximum tumour diameter ≤ 5 mm have a tumour volume ≤ 0.5 cm^3. It is well documented that

Table 4. Proposed changes for future pathological TNM classification of prostatic tumours*

Primary tumour (pT) – pathological		
pT0		**No evidence of residual tumour at prostatectomy**
pT1		There is no pathological T1 classification
pT2		Organ confined
	pT2a	**Largest tumour diameter** ≤ 5 mm
	pT2b	**Largest tumour diameter >5 mm; but** ≤ 16 mm
	pT2c	**Largest tumour diameter >16 mm**
pT3		Non-organ confined
	pT3a	Extraprostatic extension or microscopic invasion of bladder neck
	pT3b	Seminal vesical invasion
pT4		Invasion of **external sphincter**, rectum, **bladder** (**except bladder neck**), levator muscles, and/or pelvic wall
Regional lymph nodes (pN) – pathological		
pNX		Regional nodes not sampled
pN0		No positive regional nodes
pN1a		**Single positive regional lymph node, largest metastasis** ≤ 2 mm in greatest dimension
pN1b		**Single positive regional lymph node, largest metastasis >2 mm in greatest dimension**
pN2		**Multiple** (≥2) **positive regional lymph nodes**
Distant metastasis (pM) – pathological		
pM0		No distant metastasis
pM1		Distant metastasis
	pM1a	Non-regional lymph node(s)
	pM1b	Bone(s)
	pM1c	Other site(s) with or without bone disease. When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced

*Suggested changes are highlighted in bold.

patients whose cancer has a tumour volume ≤ 0.5 cm^3 and a Gleason score <7 (so-called 'insignificant PCa') have an excellent prognosis. It is interesting to note that each centimetre increase in maximum tumour diameter was associated with 70% increase in risk of recurrence in a previous analysis.[50] It has been documented that the median of maximum tumour diameter is 16 mm.[49] Therefore, it appears to be reasonable to use 5 and 16 mm as cutoffs for substaging of pT2 cancer. In the current proposal, pT2a tumours are organ-confined cancers with the largest tumour dimension ≤ 5 mm, pT2b tumours are organ-confined cancers with the largest tumour dimension >5 mm but ≤ 16 mm, and pT2c tumours are organ-confined cancers with the largest tumour dimension >16 mm (Table 4).

Further investigation is warranted to define the optimal cutoff for pT2 substaging and examine alternative approaches for pT2 subclassification.

Extraprostatic extension (stage T3a prostatic carcinoma)

Extraprostatic extension, i.e. cancer extending beyond the prostate gland capsule, has long been recognized as a poor prognostic factor, both for cancer progression and for patient survival.[52] In 100 necropsy and radical prostatectomy specimens, McNeal *et al.*[53] identified extraprostatic extension as a feature associated with tumour metastasis, seminal vesical invasion, and higher Gleason grade. Ohori *et al.*[54] found that extraprostatic extension was related to tumour progression in a multivariate analysis of 478 patients. In a series of 721 men who had undergone radical prostatectomy reported by Epstein *et al.*,[55] extraprostatic extension was an important variable for the prediction of cancer progression in a multivariate analysis model, especially for prostate cancers with Gleason scores of 5–7. On the basis of the importance of extraprostatic extension for tumour progression and patient prognosis, the AJCC and the UICC have incorporated extraprostatic extension into the unified TNM staging system since 1992, and assigned patients with extraprostatic extension to the T3 category.[2] Two key issues regarding the staging of pT3a cancers are diagnostic criteria for extraprostatic extension and an optimal subclassification system.

Extraprostatic extension is defined pathologically by four criteria: cancer in adipose tissue, cancer in perineural spaces of large neurovascular bundles (in the posterolateral aspect of the prostate, at about 5 o'clock and 7 o'clock in transverse sections), cancer in anterior muscle, or cancer invading periseminal vesical soft tissue (Table 5; Figure 10).[12,56] As cancer in large neurovascular bundles or in anterior muscle is less common, recognition of extraprostatic extension usually depends on finding carcinoma cells in periprostatic adipose tissue.

Table 5. Diagnosis of extraprostatic extension (pT3a)

1. Cancer invading into periprostatic adipose tissue, with or without desmoplastic stromal response
2. Cancer invading into perineural spaces of large neurovascular bundle in the posterolateral prostate (at about 5 o'clock and 7 o'clock in transverse section)
3. Cancer in anterior prostate beyond normal confines of the prostate
4. Cancer invading periseminal vesical soft tissue

The prostate does not have a well-defined capsule. Ayala *et al.*[57] found that the capsule of the prostate is composed of fascicles of fibromuscular tissue, which constitute an inseparable component of the prostatic stroma. The outer surface of this fibromuscular tissue merges into the periprostatic connective tissue, and blends with periprostatic adipose tissue in some areas. Furthermore, these fibromuscular tissues are absent in the apex of the prostate. The authors concluded that a true capsule of the prostate does not exist.[58] In the absence of a common standard, various terms such as 'capsular invasion', 'capsular penetration' and 'capsular perforation' have been used in the literature, causing confusion. The term 'extraprostatic extension' was introduced recently to replace other terms.[11,56,59] Recognition of extraprostatic extension relies heavily on identification of carcinoma in periprostatic adipose tissue. However, the distribution of fat around the prostatic surfaces has not been well characterized. Hong *et al.*[59] systematically analysed 100 consecutively whole mounted prostatectomy specimens, and found that less than one-half of the prostatic surface was covered by adipose tissue (Figure 11). The absence of adipose tissue over large areas of the prostatic surface, especially the posterior surface, makes evaluation of extraprostatic extension difficult and unreliable. Further refinement of the TNM staging system, such as incorporatation of surgical margin status,[11,52,58,60–63] may be useful for prognosis and therapy stratification. In the current TNM staging system, it is recommended that a positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).[3]

As there is little periprostatic adipose tissue at the apex and anterior prostate, it is difficult to identify extraprostatic extension in these areas. For practical purposes, a diagnosis of extraprostatic extension should not be made from the apex of the prostate. The region of the anterior prostate is usually devoid of adipose tissue, making an unequivocal diagnosis of extraprostatic extension difficult. The anterior fibromuscular stroma of the prostate interdigitates with external

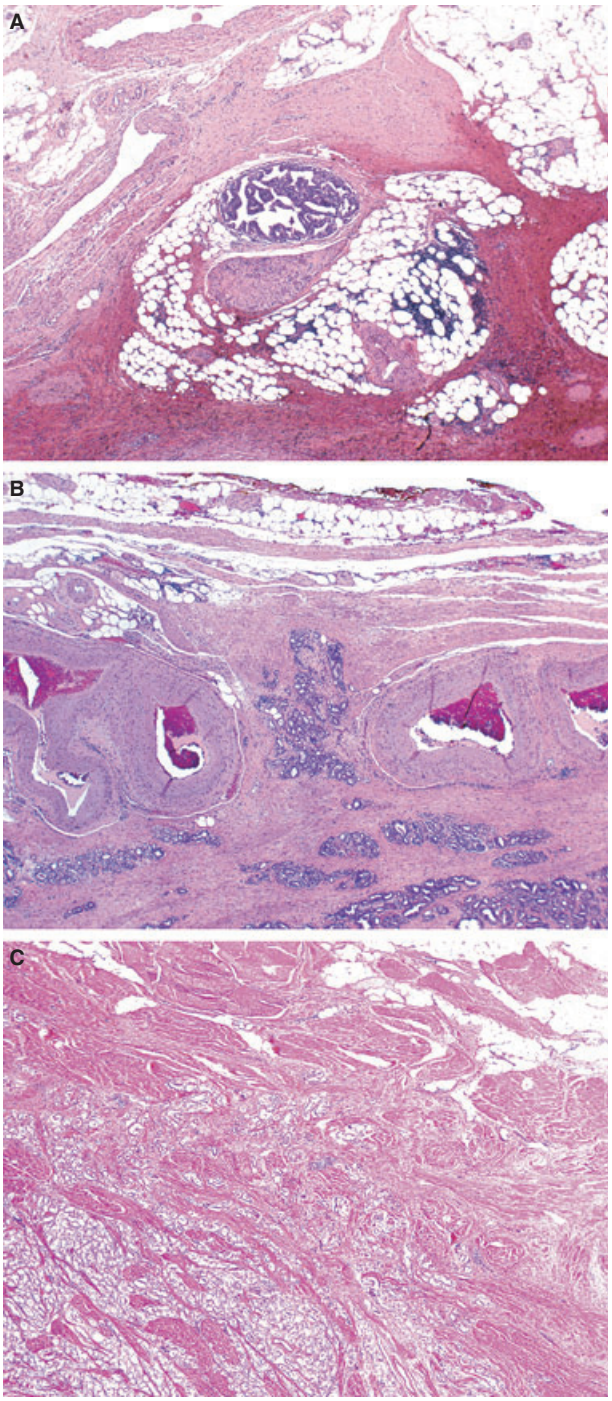

Figure 10. Extraprostatic extension (pT3a prostate cancer) is defined by cancer invading into periprostatic adipose tissue (**A**), cancer invading into perineural spaces of the large neurovascular bundle (in the posterolateral prostate) (**B**), and cancer in the anterior prostate beyond the normal confines of the prostate (**C**).

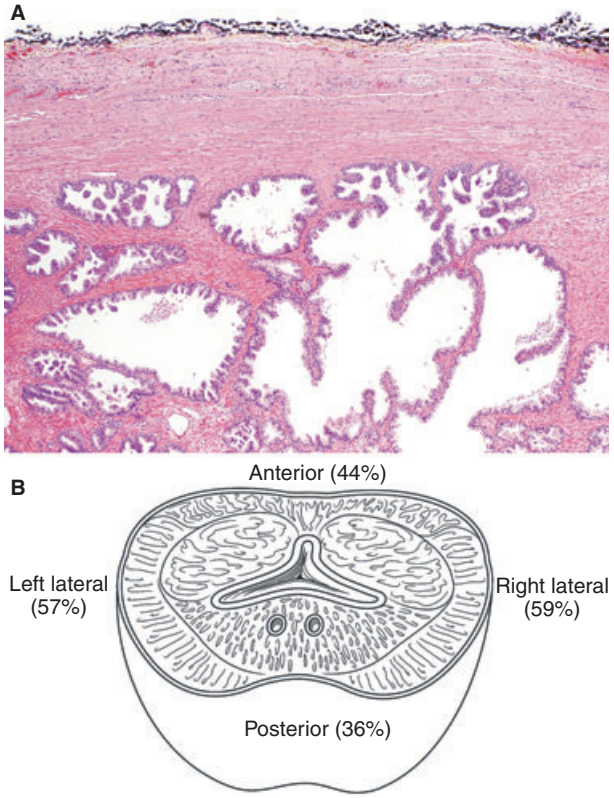

Figure 11. Distribution of periprostatic adipose tissue. **A**, Lack of periprostatic adipose tissue in the surface of the prostate. **B**, Less than half of the prostatic surfaces were covered by adipose tissue. The absence of adipose tissue over large areas of the prostatic surface, especially the posterior surface, makes evaluation of extraprostatic extension difficult and unreliable (modified from Hong *et al.*,[59] with permission).

smooth muscle and skeletal muscle adjacent to the pubic bone. Extraprostatic extension can be diagnosed in these areas only when there is unequivocal evidence of tumour extension beyond the normal confines of the prostate and beyond the rounded interface between the fibromuscular stroma and skeletal muscle.[12,56,64]

The clinical outcome of patients with extraprostatic extension is variable.[54,65] There is a need to substage local invasion to stratify patients for further treatment. In the 1992 TNM system, tumour with extraprostatic extension was subdivided into two categories: unilateral and bilateral extraprostatic extension (Table 2). Subsequent studies failed to reveal a clinical outcome difference between these two categories.[66–68] In the 1997, 2002 and 2010 TNM systems, tumours with unilateral and bilateral extraprostatic extension are merged into a single pT3a group, without further subclassification. Several investigators have proposed subclassifying the degree of extraprostatic extension

Table 6. Three main proposals for subclassification of pT3a prostate cancer with extraprostatic extension (EPE)

Focal versus established EPE (Epstein *et al.*[65])
Focal: a few neoplastic glands outside of the prostate
Established: more extensive involvement
Focal versus non-focal EPE (Wheeler *et al.*[70])
Focal: tumour <1 high-power field and involves ≤ 2 separate sections
Non-focal: more extensive involvement
Radial distance of EPE (Sung *et al.*[69])
Radial distance of EPE: <0.75 mm
Radial distance of EPE: ≥0.75 mm

and have affirmed that greater extraprostatic extension signifies a worse prognosis (Table 6).[65,69,70]

Epstein *et al.* proposed subcategorizing extraprostatic extension into 'focal' and 'established' categories. Focal extraprostatic extension was defined as 'only a few neoplastic glands', whereas established extraprostatic extension would require 'more extensive extraprostatic spreading'.[65] In their series of 196 patients, the patients with focal extraprostatic extension had 82% progression-free survival at 8 years, whereas those with established extraprostatic extension had 65% progression-free survival at 8 years.[65] A five-level grading of capsular invasion with an objective and uniform definition of focal extraprostatic extension was proposed by Wheeler *et al.*[70] They defined cases with tumour invading the periprostatic adipose tissue or smooth muscle of the bladder neck as level 3, analogous to T3 in the TNM system. Among these advanced level 3 patients, if tumour was present outside the prostate to a depth of less than one high-power field on no more than two separate sections, they were subclassified as level 3 focal (L3F). The remaining patients with more extensive extraprostatic tumour were subclassified as level 3 established (L3E). Applying this more objective and uniform criterion, they found that patients with only focal extraprostatic extension (L3F) had a significantly better prognosis that those with non-focal extraprostatic extension (L3E).[70]

Recently, our group analysed the extent of extraprostatic extension by eight quantitative methods to determine which is best for substaging of pT3a tumours.[69] Univariate and multivariate analyses were performed to determine which measurement best predicted PSA recurrence. In the univariate analysis, the radial distance of extraprostatic tumour measured with an ocular micrometre was associated with PSA

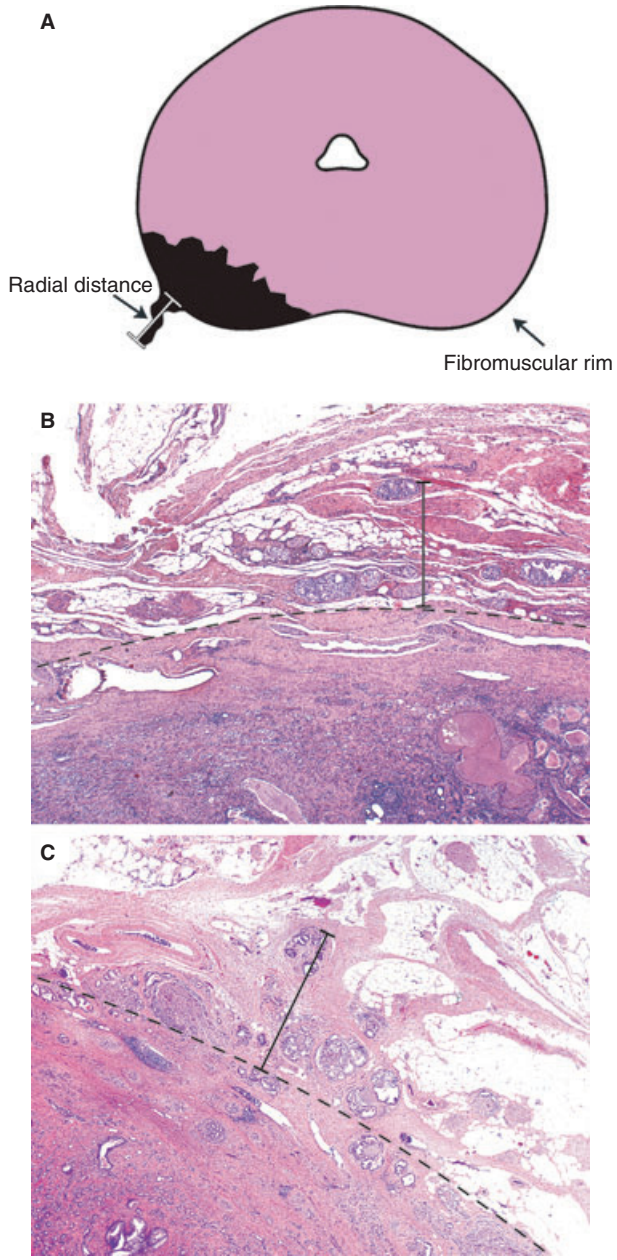

Figure 12. Subclassification of pT3a prostate cancer by radial distance. **A**, Illustration of measuring the radial distance of extraprostatic extension. **B**, **C**, Extraprostatic extension of prostatic adenocarcinoma with illustration of measurement of radial distance of extraprostatic extension (modified from Sung *et al.*,[69] with permission).

recurrence (Figure 12). In the multivariate analysis, radial distance remained an independent predictor of PSA recurrence (hazard ratio, 2.4; 95% confidence interval, 1.12–5.01; $P = 0.02$). Two- and 4-year PSA recurrence-free survival were 62% and 35%, respectively, for those patients with a radial distance <0.75 mm, as compared with 35% and 18%, respectively, for those with a radial distance ≥0.75 mm (Figure 13). The radial distance of extraprostatic extension measured with an ocular micrometre provided significant prognostic information for tumour recurrence. In comparison with other histometric predictors for T3 cancer behaviour, the ocular micrometre offered a more objective definition and a more accurate prediction of PSA recurrence. These advantages make radial distance of extraprostatic extension a potentially useful addition to a future TNM staging system.[69]

All three proposals for quantitation of extraprostatic extension (Table 6) are essentially volume-based.[65,69,70] The length of one high-power field for most microscopes is 0.55 mm. Therefore, Wheeler's proposal of 'focal' extraprostatic extension using one high-power field length as the cutoff is somewhat similar to Sung and Cheng's proposal of using a median radial distance of 0.75 mm as the cutoff.

Bladder neck invasion (stage T3a prostatic carcinoma)

In the 2010 TNM system, pT3a carcinomas include tumours with extraprostatic extension and/or microscopic bladder neck invasion. The incidence of bladder neck involvement by PCa ranged from 2.8% to 8.7% (Figure 14).[71]

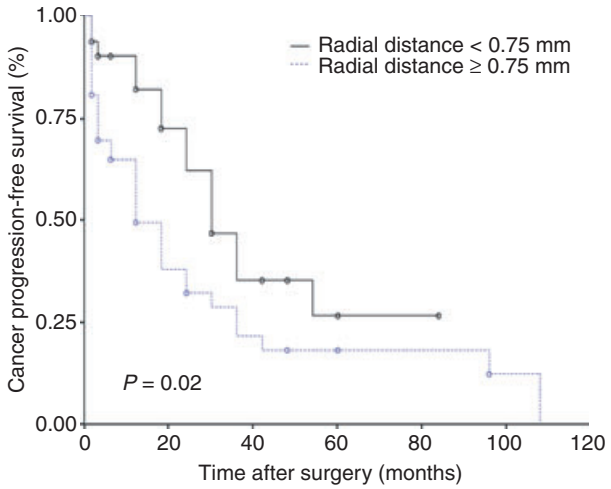

Figure 13. Kaplan–Meier curve [prostate-specific antigen (PSA) recurrence-free survival] for 83 patients with T3a prostate cancer stratified according to the radial distance of extraprostatic extension. The radial distance was analysed as a continuous variable and dichotomized for illustrative purposes according to the median value (0.75 mm) (modified from Sung *et al.*,[69] with permission).

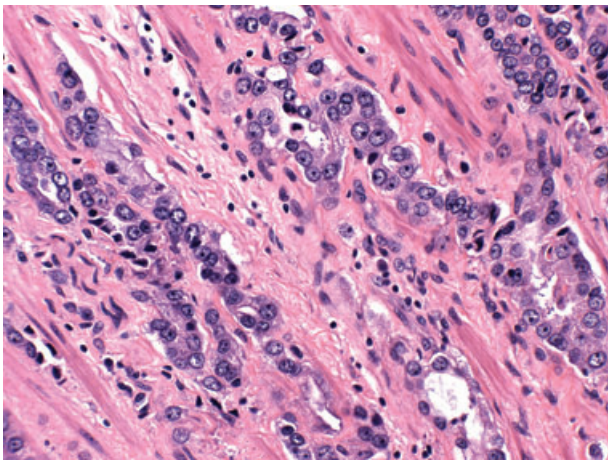

Figure 14. Bladder neck invasion (pT3a).

Bladder neck invasion has been characterized as pT4 cancer in previous editions of TNM staging systems. The recent literature[72–76] suggests that microscopic involvement of the bladder neck does not have independent prognostic significance. Therefore, resection specimens with bladder neck involvement should be classified as pT3, rather than as pT4. Other studies suggest that patients with bladder neck margin involvement have worse clinical outcomes than those without bladder neck margin involvement.[60,77] The difficulty regarding the significance of bladder neck involvement is compounded by discrepancies concerning the precise criteria for bladder neck involvement.[74,75] Some reports discuss bladder neck involvement that others would describe as bladder neck margin status.

Yossepowitch *et al.*[74,75] have evaluated the importance of bladder neck involvement in two separate studies. The authors found that microscopic bladder neck involvement was not an independent predictor of disease progression.[75] Similarly, Dash *et al.* examined the significance of bladder neck involvement for predicting PSA recurrence. Despite finding the bladder neck to be the site-specific positive margin with the highest PSA recurrence, their multivariate model found that mere bladder neck involvement was not a significant independent predictor of PSA recurrence ($P = 0.5$).[76] Although they did not find bladder neck involvement to be a significant predictor of progression, Dash *et al.*[76] found that the group with bladder neck involvement contained a larger proportion with high-grade tumours and extraprostatic extension. The authors suggested that a tumour that has escaped the prostate into the muscle of the bladder neck will have a worse prognosis and be likely to have a positive margin at that site.

Discrepancies between different studies may be attributed to differences in study design, patient populations, specimen handling, sample size, statistical methods, and the definition of bladder neck involvement. In the whole mount study, we utilized a standardized processing technique, and pathological data were prospectively collected. This study and the first study by Yossepowitch *et al.*[74] used a perpendicularly sectioned cone bladder neck margin to allow distinction of bladder neck involvement and bladder neck margin positivity. The study by Dash *et al.*[76] and the second study by Yossepowitch *et al.*[75] each relied upon different methods. In particular, Dash *et al.*[76] utilized a shave margin, in which tumour cells at the inked margin were defined as representing bladder neck involvement. This may have made the distinction of bladder neck involvement from bladder neck margin positivity difficult.

Öbek *et al.* compared the apex/urethra and posterior, anterior, lateral, posterolateral and bladder neck margins, using multivariate analysis. They found that bladder neck margin positivity was a significant ($P = 0.003$) independent predictor of disease progression.[77] The authors suggested that tumours with extracapsular extension and positive bladder neck margins may represent a more metastatic phenotype.[77] Similarly, in a study of 2712 patients, Blute *et al.*[60] evaluated multiple surgical margins and evaluated their impact on PSA failure. They found that the bladder neck was, after adjustment for Gleason grade, PSA, and DNA ploidy, the only positive margin site that was a significant predictor of PSA recurrence. They found 85% 5-year recurrence-free survival without a positive bladder neck margin, and 56% 5-year recurrence survival with a positive bladder neck margin.[60] These studies do not distinguish bladder neck margin positivity from bladder neck involvement without a positive margin, and the details on technique are limited.

Poulos *et al.*[71] analysed totally embedded and whole mounted radical prostatectomy specimens from 364 consecutive patients. Bladder neck involvement was found in 22 (6%) of the 364 patients. Univariate results indicated that bladder neck involvement was significantly associated with elevated preoperative PSA ($P < 0.001$), higher pathological stage ($P < 0.001$), larger tumour volume ($P < 0.001$), extraprostatic extension ($P < 0.001$), positive surgical margins ($P < 0.001$), and PSA recurrence ($P = 0.003$). In a multivariate logistic regression model controlling for pathological stage, Gleason score, and surgical margin status, bladder neck involvement was an independent predictor of PSA recurrence ($P = 0.04$). PSA recurrence was approximately three times as likely for

subjects with bladder neck involvement, after adjustment for other covariates, as for those without bladder neck involvement (adjusted odds ratio = 3.3, $P = 0.04$; Table 2). Patients with bladder neck invasion had a higher incidence of PSA recurrence than those with pathological stage T2 carcinomas ($P < 0.0001$). When PSA recurrence was used as an endpoint, no statistically significant difference was found between those with bladder neck invasion and those with extraprostatic extension (pT3a) ($P = 0.08$) or those with seminal vesical invasion (pT3b) ($P = 0.224$). These data demonstrate the importance of continued assessment of bladder neck invasion. This and other studies support placing tumours with bladder neck involvement in a stage that recognizes the prognostic implications of such involvement.[71]

Stage T3b prostatic carcinoma (seminal vesical invasion)

Stage T3b cancer is defined by invasion of prostatic carcinoma into the muscular wall of the seminal vesicle (Figure 15). Invasion of periseminal soft/adipose tissue should be considered as pT3a (extraprostatic extension), not pT3b, cancer. Because of the difficulty in distinguishing intraprostatic seminal vesicles from intraprostatic ejaculatory ducts, only cancer invasion into the extraprostatic portion of the seminal vesicles should be considered as seminal vesical invasion (pT3b cancer).[78]

PCa can invade the extraprostatic seminal vesicles by spreading along the ejaculatory duct (type 1), by direct invasion at the base of the prostate, by extending into periseminal vesicle soft tissue and then into the wall of the seminal vesicle (type 2) or, rarely, via discontinuous metastases (type 3).[79] Types 1 and 2 are often seen together. The prognostic importance of different types of seminal vesical invasion is uncertain.[80,81] The risk of relapse has also been stratified by the amount of seminal vesicle involvement.[80,82] However, further investigation is warranted before a recommendation can be made for routine practice.

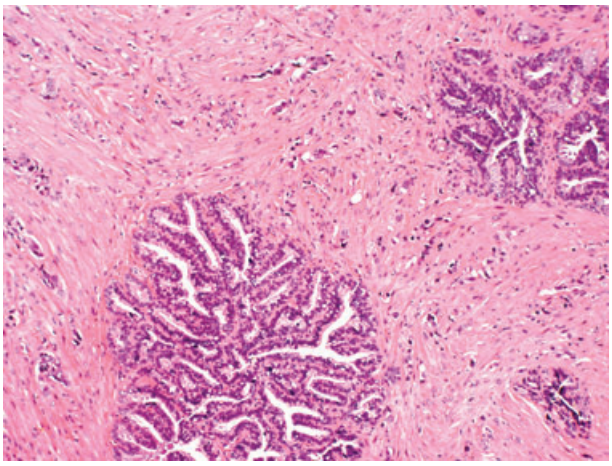

Figure 15. Seminal vesical invasion (pT3b).

The incidence of seminal vesical invasion is approximately 4% in the contemporary PSA screening era.[83] Ten-year biochemical recurrence-free and cancer-specific survival were 20% and 84%, respectively, among pT3bN0 cancer patients. High-risk clinical stage (more than cT2c) and high Gleason score (Gleason sum 8–10) remain the most important predictors of distant metastasis and of cancer-specific survival.[83]

Stage T4 carcinoma

Stage T4 tumour is defined by cancer invading into the rectum, levator muscle, and/or pelvic wall.[3] No further subclassification has been proposed. It should be noted that, in the prior TNM classification systems,[84,85] PCa with bladder neck involvement was classified within a unified T4 category. Tumour that is fixed or invades adjacent structures, such as the rectum, external sphincter, levator muscles, or pelvic sidewall musculature, is also classified as T4. As most T4 tumours are not excised, owing to extensive local invasion, incidental tumour infiltration of the bladder neck is the most common occasion in which resection specimens have been designated as pT4 in the past. We noted minor difference between clinical and pathological T4 tumours in the 2010 edition of TNM staging (Tables 1 and 2). To avoid confusion, it may be appropriate to adopt a uniform T4 definition. pT4 cancer should be defined as invasion of the external sphincter, rectum, bladder (except bladder neck), levator muscles, and/or pelvic wall (Table 4).

In a recent analysis of 17 Surveillance, Epidemiology, and End Results Program registries, Hsiao *et al.*[86] identified 615 patients with cT4N0M0 cancers. Patients with cT4N0M0 cancers appeared to have better survival than those with locally advanced disease (TxN1M0). The 5- and 10-year overall survival rates for locally advanced (cT4N0M0) disease were 59% and 40%, respectively. The corresponding 5- and 10-year prostate cancer-specific survival rates were 71% and 60%, respectively. For patients with nodal (TxN1M0) disease, the 5- and 10-year overall survival rates were 79% and 55%, respectively. The 5- and 10-year prostate cancer-specific survival rates were 84% and 68%, respectively. Interestingly, the difference in survival among patients with locally advanced (T4), node-positive and distantly metastatic stage IV cancer appears to be dependent on patient age, with older

patients having shorter overall survival and cancer-specific survival.[86]

Stage pT0 prostatic carcinoma (vanishing cancer phenomenon)

Goldstein *et al.*[87] first introduced the term vanishing cancer phenomenon, referring to cases with minute or no cancer on radical prostatectomy after a positive biopsy. They reported 13 patients with minimal (11 patients) or no (two patients) cancer in prostatectomy specimens. In two of the cases with no residual cancer on radical prostatectomy, the authors confirmed the identity of the biopsy and the prostatectomy tissue by DNA identity mismatch testing.

The incidence of pT0 cancer is approximately 0.4%.[88,89] The mean age is 62 years. At prostatectomy, the majority of patients with pT0 disease have high-grade prostatic intraepithelial neoplasia, and a few have atypical small acinar proliferation. It is difficult to identify pT0 patients preoperatively. However, these patients typically have preoperative PSA < 10 ng/ml, only one positive core biopsy, and a Gleason score of <7.[88] Descazeaud *et al.*[90] have described five characteristics that are frequently seen in patients with pT0 cancer: T1c clinical stage, preoperative PSA ≤ 15 ng/ml, one positive biopsy core only, Gleason score <7, and prostate weight ≥60 g. The prognosis of pT0 cancer is excellent, the patients being almost cured after surgery. Nevertheless, patient selection for the implementation of definitive therapy and careful consideration of active surveillance for appropriate candidates will minimize this occurrence.

Bostwick and Bostwick[91] found that 38 patients (0.56%) with no cancer on prostatectomy, identified among 6843 radical prostatectomies performed at the Mayo Clinic during a 30-year period, showed no disease recurrence or progression after a mean follow-up of 10 years. In their experience, the incidence of vanishing cancer declined 10-fold on comparison of prostatectomies performed before 1980 (2.1% incidence) with those performed in a more recent time interval, from 1993 to 1995 (0.2% incidence). They estimated the current incidence of vanishing cancer to be 2 per 1000 radical prostatectomies.[91] Epstein *et al.* reported a series of 46 patients, 35 with minute cancer and 11 with no residual cancer on prostatectomy. In 40 of these cases, they were able to document specimen identity.[92] In five of the six remaining cases, the results could not be interpreted because of technical problems, and in one case, the tissue from the biopsy with cancer did not match the tissue from the radical prostatectomy.

A report of pT0 disease after radical prostatectomy should raise concern among both surgeons and pathologists as to the underlying explanation for the absence of identifiable disease; urologists should question the appropriateness of definitive treatment and even the diagnosis itself. There is no full agreement on how to report and deal with the vanishing cancer phenomenon, and this situation has not previously been discussed between pathologists and urologists. It is a common view that if the biopsy is proven to be from a patient with negative radical prostatectomy findings, the pathological stage should not be given. Rather, in these cases, it appears valid to consider them to be pT2, as cancer was found in the prostate in the needle biopsy. One should bear in mind that it is almost impossible to completely rule out the possibility that the removed prostate still harbours PCa, even after extensive sampling. It is estimated that total embedding of the prostate samples only about 1% of the evaluable volume of the prostate. A total of 2678 sections in a 37.7-g prostate would be needed in order to sample the entire prostate specimen.[93] As no laboratory performs more than 2000 sections for a prostate, it is quite likely that very small cancers remain embedded in paraffin in pT0 cases.

The evidence suggests that pT0 cancer does exist and should be included in a future TNM staging system (Table 4). Caution is warranted in the diagnosis of pT0 cancer. In general, we recommend that the entire prostate should be embedded for histological examination before the diagnosis of pT0 cancer is made. However, for a very large prostate, it may not be absolutely necessary to embed the entire prostate if the original diagnosis of prostate cancer in needle biopsy has been confirmed.

Nodal classification (N staging)

Lymph node status has long been an important indicator of prognosis and disease status in cancer. The presence of lymph node metastasis in patients with prostate cancer indicates a poorer prognosis than in those without lymph node metastasis.[94–106] The presence of regional lymph node metastasis is designated as pN1 cancer (Figure 16). The current TNM classification does not further subclassify pN1 diseases.[3] The laterality or bilateral location of positive lymph nodes does not alter the nodal staging of prostate cancer. The regions of the pelvic lymph node dissected in a lymphadenectomy for PCa are the hypogastric, obturator, internal iliac, external iliac, lateral sacral, presacral and promontory sacral lymph nodes. Distant lymph node involvement is

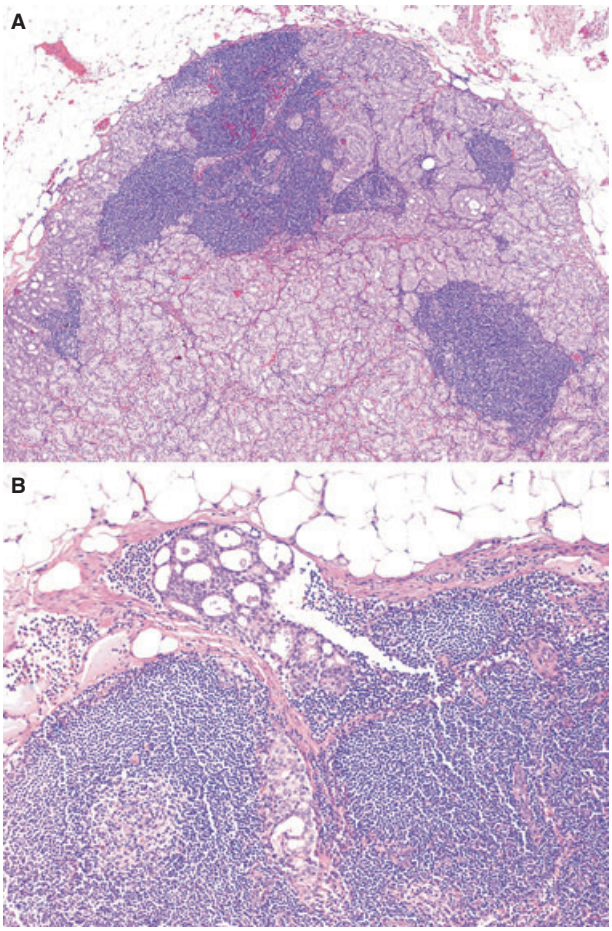

Figure 16. Lymph node metastasis from prostate cancer (pN1). **A**, The lymph node is almost completely effaced by metastatic prostatic adenocarcinoma. **B**, A minute focus of metastasis is present in this lymph node. Clinical outcome is linked to nodal tumour volume. However, the current nodal staging system does not take into consideration the nodal tumour volume. We propose new nodal classification based on the number of positive nodes and largest tumour metastasis (see also Table 4). In the new proposal, a single positive node with tumour metastasis ≤ 20 mm is classified as pN1a; a single positive node with tumour metastasis >2 mm is classified as pN1b; and multiple positive lymph nodes are classified as pN2.

regarded as M1 disease, despite the fact that it is lymphatic in nature. Distant lymph nodes are defined as lymph nodes that lie outside of the confines of the true pelvis. They include the aortic, common iliac, deep inguinal, superficial inguinal, supraclavicular, cervical, scalene and retroperitoneal lymph nodes.

HANDLING OF PELVIC LYMPH NODE DISSECTION (PLND) SPECIMENS

Precise assessment of the metastatic status of pelvic lymph nodes is essential for staging, for prognosis, and for therapy selection. However, there is controversy about how to sample the tissue from PLND specimens in day-to-day practice. Some pathologists recommend submitting all of the pelvic lymphadenectomy tissue only for patients with a biopsy Gleason score >7. For cases with a biopsy Gleason score ≤ 7, they would only embed grossly identified lymph nodes. If palpable lymph nodes are sectioned entirely, there should be sufficient metastatic carcinoma detection sensitivity for correct staging. Xylene and other techniques for clearing fat have been used to improve lymph node retrieval.[78,107–109]

Extended PLND increases the number of lymph nodes recovered. When more lymph nodes are recovered with extended PLND, there is an increase in the number of patients identified with regional metastases.[94,110–113] In fact, there is a two- to three-fold higher incidence of metastasis detection with extended PLND.[114] Allaf *et al.*[115] found a higher proportion of occult metastasis when extended bilateral PLND was performed than when limited bilateral PLND was performed. They concluded that patients with a minimal nodal burden may benefit most from extended bilateral PLND.

Studies such as that by von Bodman *et al.* have shown that most patents with lymph node metastasis from prostate cancer have only one or two positive lymph nodes.[94,100,104] A subgroup of patients, those with a Gleason score ≤ 7 in the primary tumour, benefit most from removal of the metastatic disease. Thus, extended bilateral PLND should be performed in all patients with intermediate-risk to high-risk prostate cancer, not only to provide optimal staging, but also to provide the best therapeutic outcome.[94]

Weingartner *et al.*[116] proposed that 20 pelvic lymph nodes should be used as a guide for sufficient PLND. In one study involving 310 pelvic lymphadenectomy specimens, however, the authors found metastatic tumour in presumed adipose tissue rather than in grossly recognized lymph nodes in 6.5% of cases.[117] Approximately one case in 20 is misdiagnosed by examination of palpable lymph nodes only.[78,107,108] Montironi *et al.*[109,118] proposed that all adipose tissue from a PLND for radical prostatectomy should be submitted, as 6.5% of cases revealed lymph node disease that was not grossly recognizable at specimen dissection. Furthermore, the rate of correct prediction of lymph node disease is nearly 0% when fewer than 10 nodes are submitted, and rises to nearly 100% when ≥30 nodes are removed or submitted.[110] This further emphasizes the need for coordination between the urologist and pathologist in accurately assessing the nodes removed from PLND to achieve the greatest prognostic benefit for the patient. We recommend the submission of entire pelvic lymphadenectomy specimens to avoid missing positive lymph nodes.

It is generally thought that the reliability of staging for PCa improves with the number of lymph nodes recovered. Identification and counting of pelvic lymph nodes is more challenging than for from many other areas of the body, owing to the high rate of lymph node infiltration by adipose tissue. Tokuda *et al.*[119] found that the mean number of lymph nodes resected was 14.6 and that the median was 13. Despite the variation in number of lymph nodes recovered, there is a consensus that the number of lymph nodes found in a specimen should always be reported.[78] There is no set number of regional lymph nodes required for staging. Some authors suggest that at least 30 lymph nodes should be required,[120] but others have reported an acceptable median node retrieval of 13 lymph nodes.[78] Although the number of lymph nodes examined should be reported, there are other characteristics of lymph node metastasis, such as nodal tumour volume, that are more important in determining cancer-specific survival than the number of lymph nodes sampled (see further discussion below).

Frozen sections at the time of radical prostatectomy are of little clinical value. However, in the patient with a node suspicious of malignancy at the time of surgery or in a high-risk patient where more aggressive PLND is considered, the use of intraoperative frozen sections may be used to guide the approach and possibly to spare the patient unnecessary morbidity when the frozen section is negative.

It is useful to distinguish between micrometastatic and macrometastatic disease in patients with N1 disease. Patients with micrometastatic disease have a more favourable prognosis than those with larger metastases (see further discussion below). It is sometimes difficult to detect micrometastatic prostate cancer in lymph nodes. Frozen section diagnosis of metastatic disease in lymph nodes was, at one time, common practice; however, it is no longer used, because micrometastasis can be easily missed on frozen section examination.[121] It can even be difficult to identify micrometastatic disease on haematoxylin and eosin sections. Several new modalities, such as reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR, and immunohistochemistry, are currently being investigated to improve the detection of micrometastatic disease in patients with prostate cancer.[122]

NUMBER OF LYMPH NODES AND NODAL TUMOUR VOLUME

Despite the generally poor prognosis, long-term survival has improved in patients with node-positive disease.[94–104] Numerous studies have analysed the different characteristics of lymph node metastasis in order to determine which characteristics are prognostically significant. The clinical outcome in patients with lymph node-positive prostate cancer is largely determined by the characteristics of lymph node metastasis.

The biological aggressiveness of prostate cancer is closely linked to cancer volume. Overall, nodal cancer volume (measured by the grid method) appears to be the strongest predictor of systemic progression and of cancer-specific survival.[100,104] The factors that are important in predicting outcome include the diameter of the largest metastasis and the total metastatic tumour volume. We previously investigated the impact of nodal cancer volume on patient outcome, and found that the risk of distant metastasis in patients with regional metastasis increased in proportion to the nodal cancer volume when they were treated by radical prostatectomy and immediate androgen deprivation.[100,104] Patients with smaller lymph node metastatic volume had greater progression-free survival than those with extensive lymph node involvement. Five-year systemic progression-free survival was 100% in patients with nodal cancer volume <0.02 cm^3, as compared with 78% for those with nodal cancer volume ≥ 0.20 cm^3. Overall, nodal cancer volume was the best predictor of 5-year systemic progression-free survival among a wide variety of clinical and pathological factors. Metastatic tumour volume was strongly correlated with established prognostic factors, including Gleason grade, DNA ploidy, and cancer volume of the primary cancer. These findings suggest that nodal cancer volume is closely linked to the biological behaviour of metastasizing prostate cancer. It was noted that multiple foci of tumour metastases may be present in a single lymph node or multiple lymph nodes.[100] However, there was an excellent correlation between the maximum diameter of tumour metastasis (the largest metastasis) and total nodal tumour volume.[100] Patients with tumour metastasis ≤ 20 mm had an excellent prognosis.[100,104] Ten-year progression-free survival after radical prostatectomy and hormonal therapy was almost 100% among patients with tumour metastasis ≤ 2 mm.[100] It may be of value to incorporate the size of tumour metastasis (the largest tumour metastasis) in the N classification (Table 4).

Fleischmann *et al.* made similar findings in their study. They found that the diameter of the largest metastasis was the strongest independent predictor for recurrence-free survival, disease-specific survival, and overall survival. They observed a quadrupled relative risk of cancer-related deaths for patients with large nodal metastases.[123,124]

The number of positive nodes (single versus multiple) may be the simplest way to stratify patients with N1 disease. In a study of 322 patients with lymph node metastasis, we found that patients with multiple regional lymph node metastases had an increased risk of death from disease. Patients with single lymph node involvement had a more favourable prognosis than those with two or three positive lymph nodes (Figure 17).[104] Among patients with a single lymph node metastasis, the 5- and 10-year cancer-specific survival rates were 99% and 94%, respectively. After adjustment for extraprostatic extension, seminal vesical invasion, Gleason grade, surgical margins, DNA ploidy, preoperative serum PSA concentration, and adjuvant therapy, the hazard ratio for death from prostatic carcinoma among patients with a single lymph node metastasis as compared with patients without lymph node metastasis was 1.5. However, the hazard ratio for death from prostatic carcinoma for those with two positive lymph nodes was 6.1.[104] A study by von Bodman *et al.*[94] found that the 2-year recurrence-free probability was 65% in men with one positive lymph node, 48% in men with two positive lymph nodes, and 10% in men with three or more positive lymph nodes.

We propose that a tumour with a single positive node should be classified as N1 disease and a tumour with two or more positive lymph nodes as N2 disease. N1 cases may be further stratified on the basis of the size of tumour metastasis (Table 4). A single positive node with largest metastasis ≤ 2 mm should be classified as pN1a; a single positive node with largest metastasis >2 mm should be classified as pN1b.

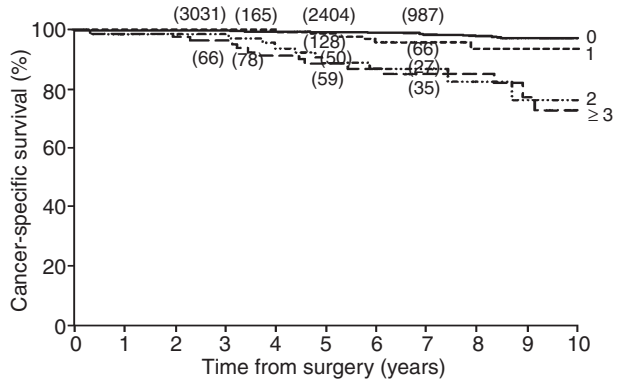

Figure 17. Kaplan–Meier curves for 3463 patients with prostate carcinoma who were treated by radical prostatectomy and bilateral pelvic lymphadenectomy (with or without adjuvant hormonal therapy) according to the number of positive lymph nodes (0, 1, 2, or ≥3). Numbers within parentheses represent the numbers of patients still under observation at 3, 5, and 7 years (modified from Cheng *et al.*[104]).

MICROMETASTASIS

Of special interest in the prostate is the recent attention given to micrometastases. Currently, there is no distinction between micrometastasis and macrometastasis in the staging system for prostate cancer. The significance of micrometastasis versus macrometastasis continues to be controversial. The cutoff point between a micrometastasis and macrometastasis is also different in various studies with regard to patient outcome. Some authors define micrometastasis as being larger than 0.2 mm but not larger than 2 mm.[123] Others have used cutoffs of 3 mm[96] and 5 mm.[110] We define micrometastases by single cells or small clusters of cells not more than 0.2 mm in greatest dimension involving the lymph node. Because of the small size of micrometastases, most reports use cytokeratin immunohistochemical staining to aid the pathologist in their detection. Specifically, Weckermann *et al.*[125] cited the use of immunohistochemistry to detect nine of 20 micrometastases in their study of samples that were negative with haematoxylin and eosin staining. Further reports have demonstrated a benefit of cytokeratin staining in increasing the sensitivity of nodal involvement detection in high-risk patients.[122,126]

Studies have shown that patients who have the micrometastatis surgically removed have increased survival as compared with those without PLND who subsequently develop nodal metastases.[96,104,115,127] For example, a favourable clinical outcome has been seen in patients in two studies with lymph node metastases <2 and <3 mm.[96,127] Defining minimal lymph node metastasis (micrometastasis) as the largest dimension of nodal metastasis being ≤ 5 mm, Schmid *et al.*[128] found that patients with micrometastasis had improved progression-free and overall survival as compared with those with more extensive lymph node involvement (median follow-up, 86 months). In contrast, Sgrignoli *et al.*[129] found no difference in the risk of distant metastasis, whether the largest dimension of metastasis was >5 mm or not, in 113 node-positive patients. Fleischmann *et al.*[123] found that micrometastasis had no adverse impact on 5-year survival, whereas patients with metastatic disease measuring >10 mm had a quadrupled risk of death. Their studies and others have concluded that the size of the largest lymph node metastasis is the only factor with an independent impact on PSA recurrence, disease-specific survival, and overall survival. It is more important to report the largest size of metastasis than to record the total number of positive lymph nodes.

LYMPH NODE DENSITY

The concept of lymph node density has received increasing attention in prostatic adenocarcinoma. Lymph node density is defined by the number of positive nodes divided by the total number of lymph nodes sampled. Most studies, regarding whether or not the extent of lymph node metastasis is a prognostic marker, have relied only on the number of positive lymph nodes. The prognostic significance of positive lymph node numbers has been documented in some but not all reports. In a series of 120 consecutive lymph node-positive patients between 1974 and 1987 with a median follow-up of 48 months, Steinberg *et al.*[127] found that both the percentage of positive lymph nodes and the frozen section diagnosis were significant predictors of progression in multivariate analysis. The raw number of positive lymph nodes, on the other hand, was not significant in either univariate or multivariate analysis. A positive patient benefit has been reported when the number of nodes removed reduces the lymph node density to <15%.[111,130] Cai *et al.*[131] found that lymph node density is a more important predictor of outcome than the number of positive lymph nodes when a limited dissection is performed. In their study, when the density was >33%, there was a worse prognosis than when it was ≤ 32%. Bilateral lymph node involvement also resulted in an adverse prognosis.

EXTRANODAL EXTENSION

Extranodal extension refers to cancer perforation through the lymph node capsule into perinodal tissue (Figure 18). The importance of extranodal extension in regional lymph node metastasis is controversial, especially with regard to its significance for treatment. Although treatment may not cure such patients, regional lymph node recurrence may be the only manifestation of cancer progression in some patients. Extranodal extension is a frequent histological finding in lymph nodes with prostate cancer, but its prognostic significance has not been established. We evaluated the impact of extranodal extension on survival and its association with other clinical and pathological characteristics in patients who were node-positive.[132] More than half of the patients who had prostate cancer with regional lymph node metastasis had extranodal extension. When the presence of extranodal extension was correlated with preoperative PSA, Gleason score, pathological stage, and nodal cancer volume, extranodal extension was not associated with worse patient outcome. Patients with extranodal extension had the same distant metastasis-free or cancer-specific survival as those without extranodal extension.[132] These findings have also been supported by other studies.[123]

Conversely, in a study of 69 node-positive patients, Griebling *et al.*[133] found that 55% had evidence of extranodal extension. With a mean follow-up of 2.9 years, 19 patients (28%) died of prostate cancer. The authors found that Gleason score and extranodal extension were both independent predictors of cancer-specific survival in patients with node-positive prostate cancer. The inconsistencies regarding the prognostic significance of extranodal extension between studies may be attributable to differences in the size of the study population, statistical methods, patient selection factors, or therapy. The presence of extranodal extension does not seem to have an adverse outcome in patients with regional lymph node metastasis who are treated initially by radical retropubic prostatectomy, bilateral pelvic lymphadenectomy, and androgen deprivation therapy.

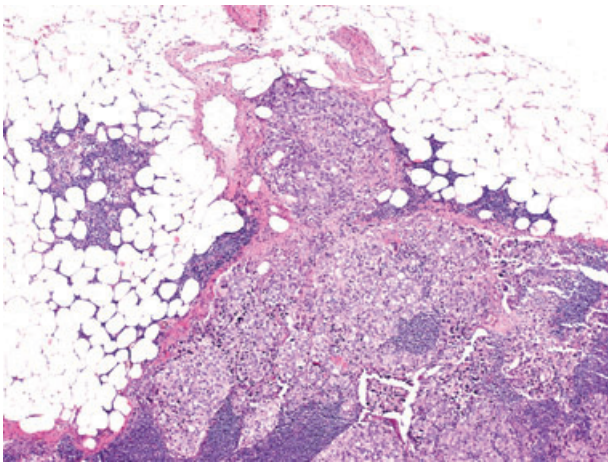

Figure 18. Extranodal extension of lymph node metastasis.

CANCER DEDIFFERENTIATION AND NODAL GLEASON SCORE

A critical issue in cancer biology in many organs is dedifferentiation. Dedifferentiation is a recognized consequence of disease progression, and occurs in both epithelial and mesenchymal neoplasms. It may occur within a primary tumour over time, or it may be evident in metastatic cancer histology. Dedifferentiation to a higher histological grade is associated with increased biological aggressiveness in many cancers. It is clear that, in prostatic carcinoma, the tumour may undergo dedifferentiation within the primary cancer or within metastases, as seen in other carcinomas.

In previous studies, we demonstrated the morphological heterogeneity of metastasis in prostate carcinoma.[101] Correlation of the Gleason score in the lymph node with that of the primary tumour is important. Dedifferentiation can occur in metastatic deposits in lymph nodes (Figure 19). In a study of 242 patients with lymph node metastases, 45% had a nodal Gleason score higher than the Gleason score of the primary tumour. We found that patients with dedifferentiation had a higher rate of systemic disease progression than those without dedifferentiation. When only Gleason grade of the primary tumour was controlled for, the relative risk associated with dedifferentiation at metastatic sites is clinically significant. However, when the analysis was adjusted to include total lymph node tumour volume, the relative risk for dedifferentiation decreased and was no longer found to be clinically significant or independently predictive.[101]

Cher *et al.* demonstrated that lymph node-positive patients with a low cellular proliferative fraction in lymph node metastases had a significant survival advantage over those with a high proliferative fraction. In their study, histological grade and pathological stage of primary cancer were not as significant for predicting outcome. Thus, the behaviour of lymph node-positive prostate cancer is more closely linked to the biological aggressiveness of the metastatic cancer than to that of the primary cancer.[134] Cher *et al.*[134] hypothesized that patients with a high proliferative fraction in lymph node metastases are more likely to have increased nodal cancer volume and are more likely to develop distant metastasis than those with low proliferative rate cancer. Boormans *et al.*[96] reported that, in addition to nodal cancer volume (described as the diameter of the largest metastasis in their study), nodal Gleason score >7 is associated with adverse outcome. An important consideration when assessing Gleason score in lymph node metastases is the high rate of multifocal disease representing multiclonality for high metastatic Gleason score patients.[7] Therefore, the Gleason score of a single examined node may not represent the entire clinical picture for the patient.

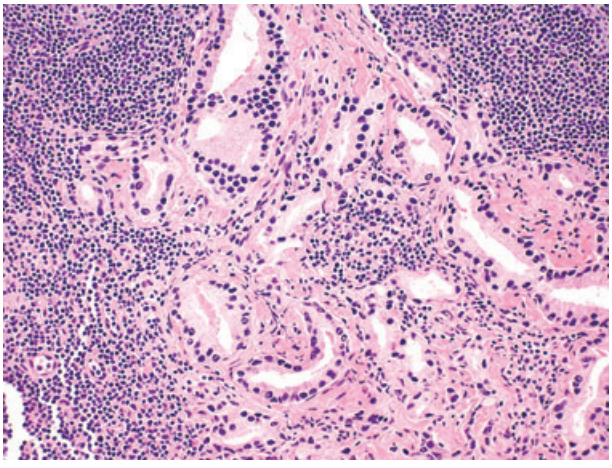

Figure 19. Lymph node metastasis with low-grade (Gleason pattern 3) prostate cancer.

Hofer *et al.*[135] evaluated 201 patients with lymph node-positive disease who were treated with radical prostatectomy, PLND, and early hormonal deprivation. Although they found that higher Gleason patterns in lymph node metastases were associated with a higher risk of PSA progression, a multivariate analysis revealed that only the nuclear grade of the primary cancer and the presence of metastatic disease in lymph nodes were independently associated with PSA recurrence. PCa does undergo dedifferentiation. However, the metastasis Gleason score may not be as important in the staging and prognosis of PCa as other characteristics of lymph node metastasis, such as metastatic tumour volume.

TREATMENT AND OUTCOME

The management of lymph node-positive patients remains controversial.[95,104,136] Although treatment may not cure such patients, regional lymph node metastasis, and not PSA recurrence, may be the only manifestation of cancer progression in some patients. Two decades ago, McCullough and Leadbetter[137] stated, 'some 5-year and occasional 10-year survival as well as an occasional cure is possible (after radical prostatectomy) even when positive nodes are found'. Treatment of patients with regional lymph node metastasis has improved in recent years. Cancer cure is possible, especially among patients with a low nodal cancer burden.[100,104,106,136,138] Briganti *et al.*[106] found that prostate cancer patients with lymph node involvement who were treated with radical prostatectomy, extended PLND and adjuvant treatments had a favourable long-term outcome. They also noted that, when patients were not treated with adjuvant hormonal therapy, those with fewer positive lymph nodes had a significantly better outcome than those with a higher number of positive lymph nodes. One other point of interest is that several studies have demonstrated an excellent cause-specific survival (83% at 15 years) in patients with DNA diploid tumours undergoing both radical prostatectomy and androgen deprivation.[99] The usual number of positive lymph nodes in patients with prostate cancer is low, with only one or two lymph nodes containing metastatic disease in most patients.[94] For patients with metastatic disease,

a subgroup with Gleason grade 7 or less in the primary tumour benefit the most from removal of the metastatic disease. Therefore, patients who fall into this subgroup should undergo an extended bilateral PLND in order to provide optimal staging and the best therapeutic outcome.[139,140]

The presence of lymph node metastasis generally indicates a worse prognosis than in patients without lymph node metastasis. However, some patients with lymph node metastasis have long-term survival. Favourable characteristics of regional lymph node involvement include low nodal tumour volume and small nodal tumour size. Despite the fact that these characteristics of lymph node metastasis are more favourable than other staging criteria in the metastatic setting, the AJCC system for PCa does not have different subclasses for node-positive disease (N0 versus N1). Our understanding of lymph node-positive prostate cancer is rapidly increasing with the emergence of novel imaging techniques, such as molecular imaging, and of systems with which to detect circulating tumour cells, such as CellSearch. As detection of lymph node metastasis and biological assessment of lymph node metastasis have improved, we are better able to subclassify patients with metastatic prostate cancer. Subclassification of patients with lymph node-positive disease would improve the accuracy of patient prognosis estimation. A better understanding of patients with lymph node metastasis should lead to treatments allowing for improved clinical outcome.

Conclusion

Accurate staging is critical for patient management. An ideal staging system should accurately reflect the natural history of cancer at the primary site, describe the total cancer burden, assess the extent of spread at the time of diagnosis, and stratify patients into prognostic groups for treatment planning. Standardization of terminology and diagnostic criteria also allows comparison of treatment results between different institutions. The development of a staging system with both clinical and pathological accuracy is essential for understanding the biological characteristics of prostate cancer, determining prognosis, and planning appropriate therapeutic management. Although the 2010 revision of AJCC/UICC prostate cancer staging represents an improvement over previous systems, several important issues have not yet been resolved. There is a need to improve stage T1a/b stratification with newly available data. The current subclassification of pT2 cancer is largely clinically irrelevant. A future TNM classification may consider a tumour size-based substaging system for pT2 cancer. Given the abundantly demonstrated multifocal, multiclonal nature of prostatic carcinogenesis, there has been an ongoing struggle in trying to arrive at a clinical staging system that correlates well with pathological staging and with long-term prognosis. The current nodal classification without subgroups is inadequate to address the clinical need. Identification of patients at the greatest risk of systemic progression will help in the selection of appropriate initial therapies. The data suggest that the inherent biological aggressiveness of metastatic prostate cancer is closely linked to the total lymph node cancer burden. Assessment of nodal cancer volume is useful for predicting systemic progression in lymph node-positive PCa patients, and should be incorporated in a future TNM staging system.

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