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INTRODUCTION

Most men who now present with a clinical suspicion of early prostate cancer are otherwise healthy, driven by either an abnormal total PSA (tPSA) level or, less commonly, by an abnormal DRE. Patient expectations have risen globally, and this group seek a process that optimises tumour detection, and is both comfortable and of low risk. Prostate cancer will be identified in a significant minority. For the remainder the process needs to be sensitive enough to minimize false-negative results.

WHO IS A CANDIDATE FOR A BIOPSY?

The indications for TRUS of the prostate and biopsies (TRUS-B) have altered over the last 25 years. Currently the most common indication is an elevated tPSA associated with a normal DRE. In contrast, before 1991 an elevated tPSA (>4 ng/mL) in isolation was not considered an indication for biopsy. This trend was illustrated by Roberts et al. [1] who analysed data collected from Qimnsted county residents over a 17-year period. An abnormal DRE accounted for 69% of men proceeding to TRUS-B in the 1980s compared to 45% in the mid 1990s. Over the same period the percentage of men undergoing TRUS-B for a raised tPSA and normal DRE increased from 28% to 42%.

PSA AND DERIVATIVES

WHAT CONSTITUTES AN ABNORMAL VALUE?

The positive predictive value (PPV) of tPSA depends not only on the actual value, but also on the patient’s age. As a guide, the PPV of a tPSA of <4, 4.1–10 and >10 ng/mL is ~10%, 25% and 50–60%, respectively [2]. The 4 ng/mL threshold was initially set somewhat arbitrarily. For men with a normal DRE, 21–25% will have prostate cancer within a tPSA of 4.1–10 ng/mL [3,4]. At >10 ng/mL this value increases to 42% [4]. When considering the influence of an abnormal DRE, the PPV of a tPSA of >4 ng/mL becomes greater still. Bangma et al. [5] estimated that the PPV of a tPSA of >4 ng/mL alone was 17%, but when combined with an abnormal DRE was 65%. Similar values were reported elsewhere [1,6,7].

A lower threshold of 2.5 ng/mL has become increasingly popular in an effort to increase the chances of cancer being curable at diagnosis. Cancer detection rates of 22–27% have been reported in men with a tPSA of 2.5–4 ng/mL [4,8–10]. In this range, tPSA has a sensitivity of 67–80% and a PPV of ~22% [4]. In lowering the threshold the number of men undergoing unnecessary TRUS-B has increased, leading some authors to question whether tumours detected in this tPSA range are clinically significant. Such tumours are associated with more favourable pathological features [11], but even at this tPSA level aggressive pathology is encountered. To illustrate this, a recent study by Sokoloff et al. [12] reviewed histology from a series of 13 men who presented with a tPSA of <4 ng/mL and subsequently underwent radical prostatectomy (RP). From this group, 13 men had a final Gleason score of ≥7 and 20 had extra-prostatic tumour extension.

Age-adjusted reference ranges aim to increase tumour detection in younger men (≤8% in men aged 45–49 years) and reduce unnecessary biopsies in older men (21% reduction in men over 60 years old). The compromise is that 4% of tumours may be missed in older men [13].

Volume-adjusted tPSA indices perform better than unadjusted PSA assays. PSA density (PSAD) has had variable reviews as part of the cancer-detection algorithm [14–18]. Seaman et al. [17] determined the normal PSAD for men with PSA levels of 4–10 ng/mL to be <0.15; using a PSAD threshold of ≥0.12 it was calculated that a 16–55% reduction in biopsies could be anticipated. Again a compromise of 4–25% reduced tumour detection has to be considered. The limitation of PSAD is that it involves a calculation based on TRUS and as such is intrusive. PSAD has now been superseded by PSAD of the transition zone (PSADTZ). Several authors have found PSADTZ to be the most predictive volume-adjusted PSA derivative [18–20].

Whilst calculations such as PSADTZ may be of value in isolation, they are of most use when used as an integral part of an algorithm incorporating other factors such as free vs total PSA ratios (f/tPSA) [21].

Calculation of f/tPSA enhances tPSA specificity for values of 2.5–10 ng/mL (typically by ~90%) whilst avoiding the need for unnecessary biopsies in up to 20–30% of men [4,9] depending upon where the threshold is set. In the tPSA range 2.6–4.0 ng/mL, a threshold of 25% detects 85% of tumours, but avoids 19% of negative biopsies. A threshold of 30% detects 90% and avoids only 9% of negative biopsies [22]. For tPSA values of 4–10 ng/mL, the probability of finding a tumour is from 28% to 8% depending on whether the threshold is set at <15% or >25%, respectively [4]. Complexed PSA, when set at a threshold of 2.2 ng/mL, appears to be better than tPSA and to have comparable specificity to f/tPSA over the 2–4.0 ng/mL range [23].

Serial tPSA measurements of PSA velocity can aid in identifying men with prostate cancer. An increase of >0.75 ng/mL per year based on a minimum of three consecutive measurements taken over a 2-year period [24] was found for men who subsequently developed prostate cancer.

IS A DRE NECESSARY?

The DRE has long been an integral part of the assessment [25] and an abnormal DRE was considered an indication for biopsy, even
when the tPSA is < 4 ng/mL [2]. However, the influence of screening populations and stage migration towards earlier tumour stage at presentation limit the advantages of DRE in screened populations. Data from the European Randomised Study of Screening for Prostate Cancer have shown the DRE to have a PPV of only 2% for tPSA values of < 1 ng/mL, and 6.3% for tPSA of 3–3.9 ng/mL, respectively. Omitting a DRE in men with a PSA of < 3 ng/mL has not altered detection rates [28]. As PSA rises, so does the relative value of the DRE [5].

THE INITIAL BIOPSY

TRUS was originally used as a means of identifying hypoechoic lesions, which in turn were targeted under TRUS control. However, only 60–70% of prostatic carcinomas appeared to be hypoechoic on TRUS [27]. With the stage migration towards early cancer at diagnosis, TRUS is now most commonly used as a means of directing the prostate biopsy needle in a systematic, predetermined pattern.

SYSTEMATIC BIOPSIES

The probability of detecting prostate tumour on biopsies depends on three factors: the location of biopsies, the number of biopsies taken and the volume of the prostate. A good protocol should consider all of these.

SEXTANT

In 1989, Hodge et al. [28] described the first attempts at taking systematic ultrasonically guided prostatic biopsies from men with suspected prostate cancer. In doing so they not only showed the superiority of TRUS-B over digitally guided sampling, but also recognized that ultrasonographically normal prostate could harbour significant tumour. The technique was to take samples at three 1-cm intervals along the parasagittal plane from the base, middle and apical region. Whilst still popular, the technique has the limitation that it samples relatively little peripheral zone (PZ) tissue and a small overall proportion of prostate volume, resulting in a false-negative rate of 10–34% [29–33]. Bott et al. [34] showed that sextant biopsies identify 73% of tumours of > 0.5 mL, but only 18% of those < 0.5 mL. This observation, coupled with the stage migration of cancer at diagnosis towards earlier disease, probably explains the low success rate of sextant biopsies.

EXTENDED BIOPSY TEMPLATES

The combination of smaller-gauge biopsy needles and local anaesthesia has increased patient tolerance to taking more biopsies in any one sitting. It was estimated that extended 10–12 biopsy templates, using laterally placed cores, where the PZ is thickest, detect 24–38% more tumours than traditional sextant sampling [35–37]. Other potential benefits of taking more biopsies include better prediction of final Gleason score and identifying tumour bilaterality [8,38,39]. A significant proportion of tumours detected by extended templates have been shown to be clinically significant, defined as > 0.5 mL or ≥Gleason 7 [40], the difference being that such cancers are detected earlier by extended regimens. The impact on complication rates of taking more biopsies appears to be small [41].

Several biopsy templates have been described; as a rule, they incorporate sextant biopsies plus either additional lateral PZ, TZ or midline biopsies in various combinations. Makhlouf et al. [38] recommended a minimum of eight cores, Presti et al. [42] 10 cores, Babaian et al. [43] 11, Singh et al. [33] 12 cores and very recently Descavezaud et al. [44] 21 cores. Eskew et al. [45] used a fan-shaped 13-core biopsy template known as the ‘five-region technique’, increasing the number for larger prostates of > 50 mL.

Which areas should be biopsied? The relative importance of biopsy location has received much attention using either three-dimensional computer-simulated prostate models or by ex-vivo RP specimens. Whilst sextant biopsies in isolation may not be adequate they still are an important component of any extended template, additional biopsies complementing rather than replacing them [40,46,47]. Epstein et al. [40] studied 150 RP specimens, taking sextant biopsies plus nine additional samples (three midline and six posterolateral in apical, mid gland and basal locations). Had they only taken sextant biopsies, 25% of tumours would have been missed. Had only posterolateral samples been taken, 12% would have been missed. Their findings showed maximum tumour detection from sextant supplemented by additional posterolateral biopsies. Similarly, Bauer et al. [48], using a three-dimensional model, increased the detection rate from 84.8% to 96% by combining sextant with posterolateral placed biopsies. Ng et al. [46] used a 10-core strategy (sextant plus four lateral) and found that sextant biopsies alone detected only 17.5% of tumours, lateral biopsies alone 21.3% but both sextant and lateral sampling together accounted for 61.7% of positive biopsies. Fink et al. [47] chose to initially biopsy using sextants and then to re-biopsy adding six laterally placed PZ and four TZ biopsies, increasing tumour detection by 34%. They showed that the greatest impact was again using lateral sampling, TZ sampling adding little benefit. Chen et al. [49] used a stochastic computer simulation to show that the areas most commonly missed by sextant biopsies were midline PZ, inferior portions of the apico-lateral PZ (the anterior horn) and the TZ.

That Chen et al. [49] found the TZ to be a significant site for tumour is interesting. Whilst TZ cancer accounts for 20–30% of prostate tumours [50], < 3% men will have isolated prostate cancer detected on initial biopsies if TZ-directed biopsies are included [51]. The addition of TZ biopsies to initial sampling increases the overall detection rate by only 1.8–4.3% and consequently most authors do not recommend them on initial biopsy [19,29,47,51–53]. An exception can perhaps be made when the tPSA is high [54].

Epstein et al. [40] stressed the importance of apico-lateral biopsies. Recently Bott et al. [34] coined the term ‘anterior prostate cancer’ as being a source of missed diagnosis. Such cancers contains 75% or more of tumour located anterior to the urethra on RP specimens. These locations contain several components, including glands from the anterior horns of the PZ and TZ where they wrap around the urethra, along with fibromuscular stroma.

Not all authors agree on all points. Chen et al. [49] used computer models to analyse 180 RP specimens, containing 607 tumour foci, and concluded that the midline was an area that is a commonly overlooked location of tumour. Biopsy templates such as the five-zone technique incorporate three or more midline samples, depending on prostate size, with high detection rates [55]. In contrast, Epstein et al. [40] found midline biopsies to be of little value, identifying only three cancers of 124 found in 150 RP specimens. When midline
biopsies are taken, one pitfall is a greater risk of haematuria.

Whilst most work has centred on extending the areas sampled in any one sitting, Levine et al. [56] adopted a different approach, taking two consecutive sextant biopsy sets from the same patients, at one sitting, and in doing so increasing tumour detection by 30%. Can any biopsies be omitted? Philip et al. [57] showed that by omitting mid-zone parasagittal biopsies the overall tumour detection rate reduced by only 1%.

When an abnormality is seen on TRUS additional lesion-directed biopsies should be taken. This point was highlighted by Norberg et al. [30], who showed that had such biopsies been omitted, 15% of cancers would have been missed.

Whilst routine biopsy of the seminal vesicles is not indicated during TRUS-B [53], their invasion is a poor prognostic indicator and has led authors to take two biopsies just superior to the junction of prostate and seminal vesicles as a staging procedure [14].

NEEDLE DESIGN AND PUNCTURE TECHNIQUE

Most studies have focused on taking more biopsies to improve yield, but needle-core length also influences the detection rate as a consequence of providing more tissue for analysis [58]. The effect of altering the gauge of the needle from 14 G to 18 G is awaited with interest. Egevad et al. [59] investigated the effect of changing the needle orientation using a simulated three-dimensional model. Such minor changes in technique could potentially influence the detection rate, as early prostate cancer is most commonly situated under the capsule, near the point of needle entry. Changes in parallel movement had a greater influence on detection than rotating the needle tip.

SIZE MATTERS

Feneley et al. [60] showed that PSA-detected cancer tends to be found in larger-volume prostates than with cancer associated with a palpable lesion or diagnosed before PSA testing. This observation reflects the bias introduced by the effect of BPH on PSA. The larger the gland the lower the probability that a fixed number of prostatic biopsies will detect prostate cancer [61]. To overcome this, nomograms have been devised and validated, based upon prostate volume measurements (and age) to overcome this potential pitfall [52]. Such an inverse relationship could be explained by the fact that any given number of biopsies relatively under-samples larger (higher volume) prostates compared to the same number taken from a smaller gland. However, this may not be the only reason, for if it were, a preponderance of larger volume tumours detected in larger glands would be expected, whereas in practice the opposite has been reported [62]. Another theory is that as total prostate volume increases, so does the TZ volume, and consequently the proportion of PZ tissue in the cores taken is reduced. These combined influences could lead to a higher false-negative rate in larger glands (>50 mL) unless more biopsies are taken from such prostates. When Uzzo et al. [63] compared the detection rate of sextant biopsies according to size, they reporting a detection rate of 38% for glands of <50 mL compared to a 23% rate for > 50 mL. Some authors [42], but not all [62], have found it beneficial to take more biopsies from larger glands.

IMPROVING THE PATIENT EXPERIENCE

About 25% of men experience moderate to severe pain during TRUS-B [64,65], this being a greater problem in men aged >60 years [52]. Such discomfort may not only limit the potential number of biopsies taken using extended biopsy templates, but could also discourage those with high-grade prostatic intraepithelial neoplasia or persistent clinical suspicion of cancer from having subsequent biopsies. Irani et al. [66] highlighted the problem, reporting that 19% of men would potentially refuse a second biopsy without some form of analgesia or anaesthesia. Roehl et al. [22] reported that this figure may be as high as a third of patients.

There are two ways of reducing the discomfort, i.e. to ‘numb the prostate’ or ‘numb the patient’. Local anaesthetic infiltration of lignocaine or bupivacaine using fine-gauge spinal needles just before prostatic biopsies has become the most widely accepted means of ‘numbing the prostate’ [64,65], Most, though not all, studies have found it to be beneficial [67]. The relative importance of the exact location of infiltration remains disputed. Rabets et al. [68] stressed the importance of anatomy, identifying the hyperechoic notch between prostate and seminal vesicles (the ‘Mount Everest sign’), to ensure adequate blockade of the sensory fibres originating from the pelvic plexus. Costello and Costello [69] described a bilateral peri-prostatic plexus block, close to the seminal vesicles, whilst others advocated either infiltration of the prostatic capsule at the apex [65] or several injections into the prostatic base, plus additional bilateral injections to the middle and apex [70].

Topical intrarectal lignocaine gel has been reported to be both effective and easy to use [72], but others have been less enthusiastic and found it to be inferior to topical infiltration [73,74].

Anti-inflammatory agents have been used in an attempt to ‘numb the patient’. Haq et al. [75] used rectal administration of 100 mg diclofenac 1 h before TRUS-B in a double-blind, placebo-controlled trial, reporting significant benefit. By contrast, Moinzadeh et al. [76] found limited value in using 50 mg rofecoxib orally. Their greatest value may be when they are used in conjunction with local anaesthesia. Eskew et al. [45] found intravenous sedation to be of value where many samples are taken in one session, but its necessity has been disputed [77]. Stewart et al. [78] even described general anaesthesia for ‘saturation’ biopsies.

About 1% of men develop serious complications after prostatic biopsy, but most are haemorrhagic and transient. Complications include haematospermia in 36–50%, haematuria in 14.5–22.6%, rectal bleeding in 2.3%, retention in 0.2% and pyrexia in 0.8–3.5% [77,79]. Infections are uncommon in the era of fluoroquinolones, occurring after ~2.5% of biopsies, but are possibly under-reported. Haematuria is more common when midline biopsies are taken. In one series, 80% of men subjected to the ‘five region’ biopsy technique (which includes
three or more midline biopsies) had frank haematuria [65]. With the exception of haematospermia [77], complications do not appear to increase with extended biopsy protocols [41].

Retention remains a risk and Bozlu et al. [80] used tamsulosin, starting the day before investigation and for 30 days afterwards, to reduce voiding dysfunction after biopsies. Aspirin does not need to be discontinued before TRUS-B [81]. Antibiotics are now accepted as an integral part of patient preparation. Fluoroquinolones are highly effective against the Gram-negatives most frequently implicated in infections after biopsy, and are the most frequently used, either alone or combined with other agents such as gentamicin and metronidazole. Most authors give a dose before biopsy, but the exact duration described after biopsy has varied widely, some suggesting as long as 5 days of continuous prophylaxis [65,77]. Enlund and Varenhorst [82] recently reported 5 days of continuous prophylaxis [65,77].

varied widely, some suggesting as long as exact duration described after biopsy has authors give a dose before biopsy, but the use of cleansing enemas has been stated to be of value by some [77] and dismissed by others [83].

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Technical considerations when obtaining and interpreting prostatic biopsies from men with suspicion of early prostate cancer: Part 2

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GETTING MORE FROM THE BIOPSY REPORT

GLEASON SCORE

The Gleason score is the best predictor of final pathological stage. Evged et al. [1] recommended that the score rather than grade should be assigned wherever possible, even when only limited tissue is available for study. In their series an exact agreement between the biopsy and radical prostatectomy (RP) score was confirmed in 44% of cases, and overall 94% were within one Gleason score. The accuracy of pathological score allocation may improve when taking more biopsies [2].

PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)

High-grade PIN (HGPIN) represents the most likely precursor of prostate cancer [3] and is found in 0.7–23% of all prostatic biopsies [4]. HGPIN as such does not indicate a specific site at risk of synchronous cancer, but instead indicates a higher likelihood of detecting occult carcinoma in any area of re-biopsy. It is often situated close to cancer and correlates with the presence of higher-grade tumours [5]. Prange et al. [8] searched for HGPIN in the prostates of men undergoing cytoprostatectomy for bladder cancer, with no known prostate pathology, and confirmed that those men with HGPIN had a higher rate of prostate cancer than those without. The importance of reporting HGPIN found on needle biopsies is well established. In one of the classic studies, prostate cancer was discovered in 36% of men undergoing subsequent re-biopsy, compared with 13% of controls [7]. San Francisco et al. [4] discovered cancer in 24% of patients undergoing a second TRUS-guided biopsy (TRUS-B). HGPIN may be multifocal, occurring throughout the prostate [6], although in their series Green et al. [5] found it was most frequent at the apex.

The positive predictive value (PPV) of HGPIN increases when associated with an abnormal DRE, raised total PSA (tPSA), low free/total PSA ratio (f/tPSA) or adjacent glandular atypia [8–10]. Raviv et al. [11] identified HGPIN and an associated cancer in 33% of men with a tPSA of <4 ng/mL and 62% with >10 ng/mL. It was suggested that the volume of HGPIN affects the risk of prostate cancer more than simply by its presence [12,13] but this has been disputed [14].

'SUSPICIOUS' FINDINGS OF CANCER ON FIRST BIOPSY

Suspicious histology refers to 'atypical small acinar proliferation' (synonymous with 'atypical glands suspicious for cancer'). Several series identified prostate cancer on subsequent re-biopsy in 40–50% of men with such suspicious findings on initial biopsy [15–17]. Chan et al. [16] felt that all men with suspicious lesions should be re-biopsied, regardless of tPSA, or why the areas were considered suspicious.

PERCENTAGES

Calculating the percentage of biopsy tissue involved by tumour allows an approximation of tumour volume. These measurements work best when used with other variables such as tPSA, Gleason score and clinical stage [12,18]. Freedland et al. [19] used linear measurement of the cumulative tissue cores to calculate the overall percentage of tissue involved by tumour. By subdividing specimens into those with <20%, 20–40% and >40% cancer they were able to place patients into low, intermediate or high risk categories of biochemical failure after RP, when used in conjunction with PSA and Gleason sum. This calculation gave better results than the percentage of cores as a predictor of pathological stage. Grossklaus et al. [20] showed that the overall percentage of tumour per biopsy set was a good predictor of final pathological stage after RP. In a similar way, D'Amico et al. [18] used the percentage of positive biopsy cores (<34%, 35–50% and >50% tumour involvement) combined with PSA, score and stage to predict the outcome after localized treatment using three-dimensional conformal radiotherapy. One problem often encountered is needle-core specimen fragmentation before to processing, and Ickowski et al. [21] suggested it may be better to report the overall percentage of cores per specimen involved by tumour rather than percentage per core, to overcome this potential pitfall.

Hoedemaker et al. [22] found the predictive value of small focus of well differentiated tumour on needle biopsy to be poor unless tPSA was also considered. Those men with a tPSA of >4 ng/mL were significantly more likely to have high-grade cancer and larger tumour volume at RP than those with a tPSA of <4 ng/mL.

LOCATION OF TUMOUR/TUMOUR BILATERALITY

There are possibly two advantages to identifying the tumour location within the prostate. First, it establishes the presence of bilateral prostate tumour. Wills et al. [23] assessed the significance of bilateral positive biopsies, and when used in conjunction with Gleason score and number of positive cores they found that 87% of men with Gleason ≤6 and two ipsilateral positive cores had organ-confined disease, compared to half of men with contralateral bilateral positive biopsies. In high-grade tumours this association was lost. The second advantage is that tumour location may help to predict the final pathological stage or prognosis. Tombai et al. [24] individually labelled and processed biopsies to improve the prediction of final clinical stage. Miyake et al. [25] reported that positive cores from the anterior horn were associated with a higher probability of advanced disease. Badalament et al. [26] investigated the significance of cancer...
location, irrespective of bilaterality, and showed that in apical cores the percentage of tumour predicted the final pathological stage. As prostate cancer can be multifocal, taking more biopsies reduces sampling error, and thereby the chances of missing bilateral disease [2].

PERINEURAL AND SEMINAL VESICLE INVASION

Perineural invasion independently predicts pathological stage in men undergoing RP and should be reported when present on needle biopsies [27]. The presence of prostate cancer in the seminal vesicle biopsies is a poor prognostic index. Wynga et al. [28] took two biopsies, just superior to the junction of prostate and seminal vesicle, and identified cancer in 44% of men, effectively upstaging disease to T3 and thereby excluding men from consideration for radical surgery.

GETTING THE BEST FROM THE PATHOLOGIST

Relatively little work has been done to reduce the potential for observer errors in pathology reporting. van de Kwast et al. [29] studied the frequency of false-positive and false-negatives within the European screening project. The missed lesions tended to be small tumour foci of <3 mm. The most common reason for a false-positive diagnosis was atrophic change or adenosis. A reference pathologist, coupled with a low threshold for seeking a second opinion, has the greatest potential for reducing false-positive results [29].

HOW SHOULD MEN WITH NEGATIVE INITIAL BIOPSIES BE FOLLOWED?

Patients with an initial diagnosis of no cancer remain at risk of prostate cancer [30] and tumours missed on initial investigation are not necessarily small, indolent lesions [31]. Several studies have assessed what happens to such patients over a follow-up, to help quantify this risk. Bill-Axelson et al. [32] followed men over a 6-year period after negative biopsies, reporting that only 0.3% developed prostate cancer. Hayek et al. [33] followed 148 men with a normal DRE over 8-year period after TRUS-B. O'Dowd et al. [30] studied a large series of patients with an initial diagnosis of no cancer; 4.8% of patients had a repeat biopsy within 1 year, of whom 19.8% had cancer. Boddy et al. followed 164 men with an elevated tPSA and benign histology for 7 years [34]; 18 (11%) were subsequently diagnosed and two men died from prostate cancer. These reports highlight the need for a careful follow-up of this group of patients, especially in the initial period after biopsy.

REPEAT BIOPSIES: WHO, HOW AND WHEN?

Djavan [35] stated that 'repeating the biopsy will always increase the detection rate, no matter what was found on the initial biopsy.' The detection rate for a second set of TRUS-B is 10–20% [31,36,37].

WHO?

The European Association of Urology guidelines recommend re-biopsy for all men with a persistently elevated tPSA [38]. Precise values vary; Rietbergen et al. [39] indicated that all men with a tPSA of >4 ng/mL be re-biopsied irrespective of DRE or TRUS appearances. Djavan et al. [31] also stated that all those with a tPSA of >10 ng/mL should be included, but suggested using the f/tPSA (<0.30%) and PSA density of the transition zone (>0.26) to guide decision-making when the tPSA level was 4–10 ng/mL.

All men with HGPIN should have a repeat biopsy [31], irrespective of tPSA level [36]. PSA is still used in assessing the relative risk, but Weinstein and Epstein [40] reported that PSA was elevated in 90% of men with PIN + cancer, compared to only half of those with PIN but no cancer. Raviv et al. [11] indicated that HGPIN and a tPSA of <4 ng/mL was associated with cancer in a third of cases, compared to 62% where the tPSA was >10 ng/mL. Previously, low-grade (LG)PIN appeared to be a low risk for predicting cancer on subsequent biopsy [11,41], and for most authors has tended to elicit no further action unless an elevated tPSA, abnormal DRE or TRUS or low f/tPSA increased suspicion [10,31]. A recent article by Goeman et al. [42] questioned this principle when comparing PSA-matched groups, finding that 30% of those with LGPIN in initial biopsies had cancer on repeat sampling, compared to 27% of cases where HGPIN had been initially identified. Suspicious histology also warrants re-biopsy, with Lezkowski et al. [15] finding that up to 40% of such cases had cancer on re-biopsy.

The influence of total prostate volume on the detection rate of initial biopsies has been recognized for some time, but that of transition zone (TZ) volume has yet to be fully evaluated [43]. When the total volume is >45 mL and the TZ volume >22.5 mL one set of sextant biopsies is insufficient [31]. Remzi et al. [36] reported that total prostate volumes of <20 or >80 mL, and TZ volumes of <9.3 or >41 mL correlated with a low probability of cancer, potentially avoiding 7.1% and 10% of repeat biopsies, respectively. Nomograms have been constructed using features such as HGPIN, atypical acinar proliferation and cumulative number of negative cores, to identify those men likely to benefit from a repeat biopsy, and achieving detection rates of ~20% at the second sitting [37,44].

HOW?

By using systematic 10- or 12-core extended protocols that sample the lateral peripheral zone (PZ) [35,45], including apico-dorsal and posterolateral areas [31], cancer detection rates as high as 24–36% have been reported in men who had initial sextant biopsies. However, traditional sextant biopsies are still essential, as an integral part of those protocols that also target lateral PZ areas [31,46].

Green et al. [5] felt that when HGPIN occurred apically then particular attention should be directed at the apex on re-investigation, to exclude cancer. Other studies showed that biopsies directed solely in the area of PIN will miss 35% of cancers [41,47]. Thus, where PIN was identified initially, attention should focus not only on the same sites but also on remote sites [47–49]. Lui et al. [50] stated that the two primary indications for TZ biopsies are a persistently elevated/rising PSA and an enlarged nodular prostate with previous negative sextant biopsies. Fink et al. [51] went further and suggested that TZ sampling should be restricted only to those men with multiple repeated negative investigations. It would seem appropriate that when a cancer diagnosis is proving elusive then biopsies should also include tissue from the TZ. The actual technique is often understated, Lui et al. [50] giving one of the best descriptions...
...of how to obtain them. The needle should be placed near the midline and advanced through the capsule into the PZ to within 2–3 mm of the ultrasonographically defined TZ/PZ boundary before firing. Should the prostate extend far anteriorly, the needle should be pushed further through this boundary into the TZ before firing. Biopsies should be spaced at 1-cm intervals, the final number being governed by the TZ volume. The importance of apically placed biopsies was stressed by Chen et al. [52].

Others [53,54] used a 24-biopsy protocol (the ‘saturation’ technique) on men with previous negative sextants, achieving a 34% and 25% cancer detection rate, respectively. The technique was previously described; biopsies are initially taken from the extreme lateral basal portion of the prostate and then extended up to include the mid and apical zones [53]. The needle is then moved medially by rotating the probe through 20–30° axially. This process is repeated until the midline is reached, larger glands requiring more biopsies. Additional TZ sampling, taken just lateral to the midline at mid gland level, and targeted biopsy of hypoechoic lesions are also taken. Patel et al. [54] compared lateral and parasagittal biopsies, noting that all men with tumour had positive lateral biopsies but cancer was not identified in parasagittal tissue, independent of positive lateral biopsies. They felt that the parasagittal samples could be omitted from such a protocol with little detriment.

WHEN?

This to some extent depends on the indication for re-biopsy; in their review Djavan et al. [31] recommended, as a general rule, 6–12 months between initial and repeat investigation. This would certainly be true for those with an elevated tPSA as their primary indication. For PIN there is more debate. European guidelines state that when HGPIN is identified, immediate re-biopsy is indicated [55]. However, Lefkowitz et al. [56] concluded that for men who had HGPIN, with no other factors increasing the suspicion of cancer, and identified by 12-core sampling, the detection rate was sufficiently low on repeat sampling that immediate re-biopsy was unnecessary. Certainly TRUS repeated too early can introduce biopsy-related artefacts, e.g. hypoechoic areas caused by haematoma formation or capsular distortion after biopsy that mimic extracapsular extension. Montoriri et al. [3] suggested for HGPIN that they be repeated at 3–6 monthly intervals. Lewfowicz et al. [56] and San Francisco et al. [4] took the view that indications for re-biopsy could be guided by tPSA and DRE rather than happen as a matter of course.

HOW MANY TIMES IS RE-BIOPSY BEFORE REQUIRED BEFORE STOPPING?

At what stage does the risk of finding a clinically significant tumour reduce? This depends to a degree on whether or not initial biopsies were taken using sextant or extended regimens, most reports quoting values for earlier sextant systems. Keetch et al. [9] re-biopsied men who had a tPSA of >4 ng/mL or an abnormal DRE or TRUS appearance. On initial re-biopsy [second set] they had a 19% detection rate, on their third set 8% and on fourth or later sets, 7%. Zackrison et al. [57] followed patients who had a tPSA of >4 ng/mL or an abnormal DRE or TRUS appearance. On initial re-biopsy [second set] they had a 19% detection rate, on their third set 8% and on fourth or later sets, 7%. Zackrison et al. [57] followed patients who had a tPSA of >4 ng/mL or an abnormal DRE or TRUS appearance. On initial re-biopsy [second set] they had a 19% detection rate, on their third set 8% and on fourth or later sets, 7%. Zackrison et al. [57] followed patients who had a tPSA of >4 ng/mL or an abnormal DRE or TRUS appearance. On initial re-biopsy [second set] they had a 19% detection rate, on their third set 8% and on fourth or later sets, 7%.

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Abbreviations: (f, t, f/t) PSA, (free, total, free/total) PSA; TRUS-B, TRUS-guided biopsy; PPV, positive predictive value; RP, radical prostatectomy; PSAD, PSA density; TZ, transition zone; PZ, peripheral zone; LG/HGPIN, low-, high-grade prostatic intraepithelial neoplasia.
Gleason grading of prostate cancer in needle biopsies or radical prostatectomy specimens: contemporary approach, current clinical significance and sources of pathology discrepancies

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INTRODUCTION

Numerous grading systems have been designed for the histopathological grading of prostate cancer. The main controversies have been whether grading should be based on glandular differentiation alone or a combination of glandular differentiation and nuclear atypia, and whether prostate cancer should be graded according to its least differentiated or dominant pattern. The Gleason grading system, named after D.F. Gleason, is now the predominant grading system (Fig. 1A), and in 1993 it was recommended by a WHO consensus conference [1]. The Gleason grading system is based on glandular architecture; nuclear atypia is not evaluated [2,3]. Nuclear atypia, as adopted in some grading systems, correlates with the prognosis of prostate cancer but there is no convincing evidence that it adds independent prognostic information to that obtained by grading glandular differentiation (i.e. pattern of growth) alone.

The aim of this review is to evaluate the current clinical significance of Gleason scores in needle biopsies and radical prostatectomy (RP) specimens, and is also based on the results of a recent WHO-sponsored consensus [4,5]. This contribution includes an analysis of the effect of pathological evaluation in the differences in Gleason scores between these types of specimens.

GLEASON GRADING SYSTEM

The Gleason grading system defines five histological patterns or grades with decreasing differentiation. The primary and secondary pattern, i.e. the most prevalent and the second most prevalent pattern, are added to obtain a Gleason score or sum [3].

Gleason pattern 1 is composed of a very well circumscribed nodule of separate, closely packed glands which do not infiltrate into adjacent benign prostatic tissue. The glands are of intermediate size, and similar in size and shape. This pattern is usually seen in transition zone cancers (Fig. 1B). Gleason pattern 1 is exceedingly rare.

Gleason pattern 2 is composed of round or oval glands with smooth ends. The glands are more loosely arranged and not quite as uniform in size and shape as those of Gleason pattern 1. There may be minimal invasion by neoplastic glands into the surrounding non-neoplastic prostatic tissue. The glands are of intermediate size and larger than in Gleason pattern 1. The variation in glandular size and separation between glands is less than that seen in pattern 3. Although not evaluated in Gleason grading, the cytoplasm of Gleason pattern 1 and 2 cancers is abundant and pale-staining (Fig. 1C). Gleason pattern 2 is usually seen in transition zone cancers but may occasionally be found in the peripheral zone.

Gleason pattern 3 is the most common; the glands are more infiltrative and the distance between them is more variable than in patterns 1 and 2. Malignant glands often infiltrate between adjacent non-neoplastic glands. The glands of pattern 3 vary in size and shape and are often angular (Fig. 1D). Small glands are typical for pattern 3, but there may also be large, irregular glands. Each gland has an open lumen and is circumscribed by stroma. Cribriform pattern 3 is rare and difficult to distinguish morphologically from cribriform high-grade prostatic intraepithelial neoplasia. The latter shows the presence of basal cells; these are lacking in cribriform pattern 3 prostate cancer.

In Gleason pattern 4, the glands appear fused, cribriform or they may be poorly defined. Fused glands are composed of a group of glands that are no longer completely separated by stroma (Fig. 1E). The edge of a group of fused glands is scalloped and there are occasional thin strands of connective tissue within this group. The hypernephroid pattern described by Gleason is a rare variant of fused glands, with clear or very pale-staining cytoplasm.

Cribriform pattern 4 glands are large or they may be irregular with jagged edges. As opposed to fused glands, there are no strands
of stroma within a cribriform gland. Most cribriform invasive cancers should be assigned a pattern 4 rather than pattern 3. Poorly defined glands do not have a lumen that is completely encircled by epithelium.

In Gleason pattern 5, there is an almost complete loss of glandular lumina, with only occasional lumina apparent. The epithelium forms solid sheets, solid strands or single cells invading the stroma (Fig. 1F). Care must be applied when assigning a Gleason pattern 4 or 5 to limited cancer on needle biopsy to exclude an artefact of tangential sectioning of lower grade cancer. Comedonecrosis may be present.

GLEASON SCORES IN PROSTATE BIOPSIES

While the prime goal of the needle biopsy is to diagnose prostate adenocarcinoma, once carcinoma is detected further descriptive information on the type, Gleason score and amount of cancer forms the cornerstone for managing the patient, assessing the potential for local cure and the risk for distant metastasis [6–9].

THE GLEASON SCORE AS A PROGNOSTIC FACTOR

The Gleason score of adenocarcinoma of the prostate is the quintessential prognostic factor in predicting findings in the RP specimen (pathological stage), biochemical failure, local recurrences and lymph node or distant metastasis in patients receiving no treatment, radiation therapy, RP and other therapies including cryotherapy and neoadjuvant therapy [9–12]. The needle biopsy Gleason score also correlates with virtually all other pathological variables, including tumour volume and inked margin status in RP specimens, serum PSA levels and many molecular markers [6–9]. Specifically, Gleason scores of 7–10 are associated with worse prognoses, and tumours with Gleason scores 5–6 are associated with lower progression rates after definitive therapy. The predictive value of the Gleason score is enhanced when combined with other clinical variables, including a DRE and serum PSA levels. In recent years, nomograms have been developed to predict pathological stage at RP and disease progression after surgery or radiation therapy. Nomograms typically include pretreatment variables including clinical stage, Gleason score, serum PSA, amount of cancer in needle biopsy, etc. [9,11,13]. Based on statistical modelling of cumulative, prospectively accrued data on large consecutive series of patients, the nomograms have reasonable discriminatory ability to predict (depending on the patient cohort of the nomogram and statistical modelling) the pathological stage, seminal vesicle involvement, lymph node metastases, biochemical failure, small-volume organ-confined tumours, response to radiotherapy, etc. Such nomograms are used with increasing frequency in clinical practice by urologists and radiation oncologists to counsel their patients on the therapeutic options and potential risk for failure, based on the therapy they may choose. Inclusion of the needle biopsy Gleason score in all clinically valid nomograms is testimony to the prognostic and predictive power of this grading system and its central role in the contemporary management of patients with prostate cancer [9,11,13]. The Gleason score is also often used to determine eligibility for clinical trials, including those for watchful waiting [14,15].

While the pivotal role of the Gleason score in the needle biopsy is not in question, the method of reporting needs clarification for a few issues, including some not addressed in the original Gleason system [4]. The recommendations of reporting of the Gleason score in needle biopsies [4,16–18] are:

• Report the primary and secondary pattern, and assign a Gleason score.
• If one pattern is present, double it to yield the Gleason score.
• A Gleason score can usually be assigned even if the cancer is extremely small.
• In a needle biopsy with more than two patterns, the worst pattern must be reflected in the Gleason score, even if it is not the predominant or secondary pattern (see text).
• Provide a Gleason score for each separately identifiable involved core.
• A diagnosis of Gleason score 2–4 should not be made (see text).
• Do not report the Gleason score after hormonal or radiation therapy, except if the cancer shows no treatment effect.
• Provide a Gleason score for all adenocarcinoma variants, i.e. ductal, signet ring and mucinous.
• Do not assign a Gleason score for small cell carcinoma and sarcomatoid carcinomas, but specify the histological variant pattern.
• Provide a Gleason score for adenocarcinoma morphological patterns (e.g. hypernephroid, foamy gland, atrophic, pseudohyperplastic).

Optional
• Provide a composite (overall) Gleason score for all cores for the patient.
• Provide the percentage of tumour with Gleason pattern 4 in Gleason score 7.
Provide the percentage of tumour with Gleason patterns 4 and 5 in tumours with Gleason score 8–10.

The most significant new recommendation is to separately report the Gleason score for each recognisable core, irrespective of whether the cores are individually submitted (in individual containers signifying specific anatomical location, e.g. right base), or submitted together (more than one core, possibly sampling different areas of the prostate, e.g. three cores from the left apex, mid and base sent in one container). The needle biopsy core(s) with the highest Gleason score is often given the most weight in clinical decision-making and hence should be identifiable as a separate Gleason score, information which would be lost if individual cores were not graded. If extreme fragmentation makes grading of individual cores difficult, the emphasis should be to identify and provide information on the core with the highest Gleason score. A recent survey of the surgical members of the Society of Urologic Oncology indicated that 81% used the highest Gleason score in a positive biopsy, regardless of the overall percentage involvement, to determine their treatment plan [19]. This paradigm was also used in creating and validating the Kattan nomograms, Partin tables that are currently in wide clinical use [20,21]. Assigning an overall (composite) score is optional.

TERTIARY PATTERN

Another important change is the recognition and reporting of the tertiary pattern in needle biopsies [4]. Tertiary patterns are uncommon but when the worst Gleason grade is the tertiary pattern, it should influence the final Gleason score. For example: a case with primary Gleason pattern 3, secondary pattern 4, and tertiary pattern 5 should be assigned a Gleason score of 8; a case with primary Gleason pattern 4, secondary pattern 3, and tertiary pattern 5 should also be assigned a Gleason 8 (the secondary score being 4, based on the average of patterns 5 and 3 = 4; or Gleason score 9, pattern 4 + 5).

GLEASON 4 PATTERN IN GLEASON SCORE 7 TUMOURS

The data on the importance of the percentage of Gleason 4 pattern in Gleason score 7 tumours is rapidly expanding [22,23]. In recently generated nomograms, patients with Gleason score 4 + 3 vs 3 + 4 are stratified differently, underlining the importance of the relative amount of pattern 4 [23]. Whether or not the actual percentage of pattern 4 tumour should be included in the report is not clear, based on published data to date and, if this emerges as an important variable, meaningful discriminatory thresholds for percentage of pattern 4 will need to be defined.

GLEASON SCORE 2–4

The diagnosis of Gleason score 2–4 should not be made on needle biopsies [24]; the reasons for this are compelling. (i) Gleason score 2–4 cancer is extraordinarily rare in needle biopsies compared with TURP specimens; (ii) there is poor reproducibility among experts for lower grade tumours [25]; (iii) the correlation with the RP specimen score for Gleason 2–4 tumours is poor and about half of the RP specimens in one study had extraprostatic extension; and (iv) a 'low' score of Gleason 2–4 may misguide clinicians and patients into believing that there is an indolent tumour.

GLEASON SCORES IN RP SPECIMENS

The Gleason score assigned to the tumour at RP is the most powerful predictor of progression after RP.

Gleason scores 2–4 are rarely seen as the grade of the main tumour at RP for stages T1c or T2 disease. Tumours with these scores are typical in small multifocal incidental adenocarcinomas of the prostate, most commonly found within the transition zone [26]. Because these tumours are small and anterior they are rarely seen on needle biopsy. The situation where Gleason score 2–4 tumours represents the major tumour is in RP for tumour incidentally found on TURP (stages T1a and T1b). In one analysis of >2494 men with clinically localized adenocarcinoma of the prostate, Gleason score 2–4 was the grade of the main tumour in only 2% of the RP specimens [27]. This value represents a disproportionate number of T1a and T1b tumours compared to what would be seen in current practice, as this series encompassed older cases where RP for stages T1a and T1b disease was more prevalent. All men with only Gleason score 2–4 tumour at RP are cured [28].

Tumours with Gleason scores 5–6 at RP show a spectrum in biological behaviour, depending on other variables such as margin status and organ-confined status [28]. It is important to recognize that most tumours with these Gleason scores are cured, regardless of whether they show extraprostatic extension or positive margins.

Tumours with a Gleason score of 7 have a significantly worse prognosis than those with a Gleason score of 6 [28,29]. Given the adverse prognosis associated with Gleason pattern 4, it would be expected that whether a tumour is Gleason score 3 + 4 or 4 + 3 would influence the prognosis. There are several studies addressing Gleason score 3 + 4 vs 4 + 3 at RP, with somewhat conflicting results.

One study reported no significant survival advantage for Gleason pattern 3 + 4 over 4 + 3 [30]; however, the lack of statistical significance in that study might be ascribable to there being too few patients and the inclusion of patients with positive lymph nodes and/or seminal vesicle invasion. In another study [31] Gleason score 3 + 4 or 4 + 3 correlated with both stage and progression, but the median follow-up was only 25.8 months and the difference between the scores was independently predictive only in men with serum PSA values of <10 ng/mL and in those with organ-confined disease.

Several other reports show that Gleason score 4 + 3 has a worse prognosis than Gleason score 3 + 4, yet it was not reported whether it was an independent prognosticator [32,33]. Other studies show a significant difference in recurrence-free survival rate between patients with Gleason score 3 + 4 and 4 + 3 tumours, independent of surgical margins and extraprostatic extension [27,29]. Men with Gleason score 7 tumours were stratified into four different prognostic groups; those with the best prognosis had either Gleason score 3 + 4 or 4 + 3 and organ-confined disease, or had extraprostatic extension of any degree with Gleason score 3 + 4 and negative surgical margins. In the next worse prognostic group men had focal extraprostatic extension and only one adverse finding, meaning either Gleason score 3 + 4 with positive margins or Gleason score 4 + 3 with negative margins. The next worst prognostic group had established extraprostatic extension with again only one adverse finding in terms of
grade and margins. The patients with the worst prognosis were those who had focal or established extraprostatic extension and both adverse findings (i.e. positive margins and Gleason score 4 + 3). In a multivariate analysis, surgical margin status was more influential than the extent of extraprostatic extension in predicting progression after RP. It is unclear whether the adverse effect of positive margins relates to the intrinsic biology of disease or to the ability to achieve local control. Preoperative PSA levels did not add to the multivariate model.

Gleason score 8–10 tumour accounted for only 7% of the grades at RP at one large centre [27]. Typically, men with Gleason score 8–10 tumours have highly aggressive tumours and present at an advanced stage, such that they are not amenable to local therapy. Even in more recent series 70–91% of men with Gleason score 8–10 tumour do not present with organ-confined disease [34,35]. Overall, patients with Gleason scores 8–10 at RP have a 15% chance of having no evidence of disease at 15 years after surgery [27]. Although there are few men in each study and the follow-up fairly short, it was reported than when Gleason score 8–10 tumour is organ-confined the prognosis is significantly better [30,35–37].

PERCENTAGE GLEASON PATTERN 4/5

The group from Stanford has been a strong proponent of using the proportion of high-grade tumour as the preferred method for grading prostate cancer. However, the percentage of pattern 4/5 is only strongly predictive for progression at the extremes (>70% or <20% pattern 4/5) [38]. It has not been shown that classifying tumours based on the percentage of pattern 4/5 is more predictive than stratifying patients into Gleason scores 2–4, 5–6, 3 + 4, 4 + 3 and 8–10. Furthermore, assessing the percentage of Gleason pattern 4 is often difficult, as patterns 4 and 3 are often intimately admixed. Further difficulty in asking pathologists to derive a specific percentage of pattern 4/5 stems from studies showing interobserver variability in grading tumours with Gleason scores 5–7 [39]. Therefore, while an accurate measurement of the percentage of Gleason pattern 4 may not be practical, distinguishing Gleason score 3 + 4 from 4 + 3 is simpler and more likely to be part of a routine pathological examination.

TERTIARY GLEASON PATTERN

Within RP specimens, as a result of there being more tumour available for histological examination, a higher proportion of cases are found to contain more than two grades. Aihara et al. [40] found an average of 2.7 different Gleason patterns per case and over half of cases contained at least three different grades in a series of 101 RPs. There is no consensus about how to grade these tumours, as the Gleason system only accounts for the primary and secondary patterns. The other controversy is how to grade tumours which are >95% of one pattern, where there is only a very small percentage of higher grade tumour. For example, if a tumour is composed of >95% Gleason pattern 3 and <5% pattern 4, some experts would assign a Gleason score 3 + 3 = 6, as it was proposed that there must be >5% of a pattern present for it to be incorporated within the Gleason score. Others might grade the tumour as Gleason score 3 + 4 = 7. In the only studies to address this issue, the existence of a high-grade component, even it constituted <5% of the whole tumour, had a significant adverse influence on the overall biological behaviour [41]. The progression rate of Gleason score 5–6 tumours with a tertiary component of Gleason pattern 4 is almost the same as that of a pure Gleason score 7 tumour. Gleason score 7 tumours with tertiary pattern 5 are associated with progression rates after RP approximating those for a pure Gleason 8 tumour. However, there was no such significance in cases of Gleason score 8 with tertiary pattern 5, partly because of the limited sample size, yet it is also likely that Gleason score 8 tumours are already so advanced that the existence of pattern 5 elements makes no difference. Consequently, when a tumour contains tertiary high grades, the tumour should be graded routinely with a comment in the report noting the presence of the tertiary element [42].

CORRELATION AND SOURCES OF DISCREPANCIES BETWEEN NEEDLE BIOPSY AND RP GLEASON SCORES

There have been several studies addressing the correlation between Gleason scores in needle biopsies and corresponding RP specimens. Although earlier studies used the thicker (14 G) needle biopsies [43,44], more recent series are based on thin-core (18 G) needles used in conjunction with biopsy guns and TRUS guidance. Sextant or other methods of systematic sampling are typical in the more current series. In a recent compilation of data on 3789 patients from 18 studies, there was exact correlation of Gleason scores in 43% of cases and plus or minus one Gleason core unit in 77% [45]. Under-grading of carcinoma in needle biopsy is the most common problem, occurring in 42% of all reviewed cases. Importantly, over-grading of carcinoma in needle biopsies may also occur, but this was only found in 15% of cases. In general, adverse findings on needle biopsy accurately predict adverse findings in the RP specimen, whereas favourable findings on the needle biopsy do not necessarily predict favourable findings in the RP specimens, largely through sampling error.

SOURCES OF DISCREPANCIES

Perhaps the most important factor is sampling error, which relates to the small amount of tissue removed by thin-core needle biopsies. The average 20-mm, 18-G core samples are ~0.04% of the average gland volume (40 mL). The most common type of sampling error occurs when there is a higher grade component present within the RP specimen which is not sampled on needle biopsy [46]. This typically occurs when a needle biopsy tumour is graded as Gleason score 3 + 3 = 6. In the RP specimen there is a Gleason pattern 4 which was not sampled on the biopsy, resulting in a RP Gleason score of 3 + 4 = 7.

In some instances under-grading results from an attempt to grade very small areas of carcinoma, so-called ‘minimal’ or ‘limited’ adenocarcinoma [47]. Scores of minimal adenocarcinoma in needle biopsies show a reasonably strong correlation with RP scores, but the Gleason scores do not have the same power to predict extraprostatic extension and positive margin status as they do in non-minimal carcinomas [47].

Over-grading can result from sampling error in cases where the high-grade pattern is selectively represented in needle biopsy. It may only represent a very minor element in the RP specimen. Even the same cancer focus may have different grades, depending on the area sampled.

BORDERLINE CASES

The other source of discrepancy between biopsy and RP is borderline cases. In the
description of the Gleason grading system there are some cases that fall at the interface between different patterns, where there will be interobserver variability and possible even intra-observer variability [48].

**PATHOLOGY ERROR**

Pathology error is most common when pathologists assigned a Gleason score of ≤4 on a needle biopsy which in fact was Gleason score 5–6. Many pathologists under-grade needle biopsies by confusing quantitative changes with qualitative changes. When there is a limited focus of small glands of cancer on needle biopsy, by definition this is a Gleason pattern 3 (this consists of small glands with an infiltrative pattern). Taking a biopsy of truly low-grade adenocarcinoma of the prostate could not result in just a few neoplastic glands, but rather would be more extensive, as low-grade adenocarcinoma grows as nodules of closely packed glands rather than infiltrating in and amongst normal glands. Under-grading may result from difficulty in recognizing an infiltrative growth pattern or failing to recognize the presence of small areas of gland fusion [48].

**PATHOLOGISTS’ EDUCATION AND EXPERIENCE**

The pathologists’ experience in grading thin-core needle biopsies can also influence the overall correlation with RP results. With experience, pathologists recognize grading pitfalls, in particular that Gleason scores of 4 and lower are almost non-existent in the needle biopsy. Furthermore, small areas of fusion in the presence of a predominantly grade 3 background are recognized and will yield a Gleason score of 7, which often correlates well with RP results [49].

**INTRA-OBSERVER AND INTEROBSERVER VARIABILITY**

Reproducibility studies can be categorized as intra-observer and interobserver; for investigations of intra-observer agreement of Gleason grades, exact agreement was reported in 43–78% of cases [49,50], and agreement within plus or minus one Gleason score unit was reported in 72–87% of cases. Gleason wrote that he duplicated exactly his previous histological scores about half the time. Highly variable levels of interobserver agreement on Gleason scores were also reported, at 36–81% for exact agreement and 69–86% of observers within plus or minus one Gleason score unit. The reproducibility of Gleason grading can be improved by recognizing problematic areas and educating physicians via meetings, courses, website tutorials and publications that specifically focus on the Gleason grading system [51].

**CONCLUSIONS**

The Gleason grading system for prostatic carcinoma, based on glandular architecture, is the dominant method worldwide in research and in daily practice. The Gleason grading system should be used in all prostatic tissue samples, including needle-core biopsies and RP specimens. Its prognostic value was tested in a large population with a long-term follow-up that included the use of survival as an endpoint. The Gleason grading system shows a reasonable degree of correlation between biopsy and RP specimens. Several sources of discrepancy between these types of specimens have been identified. Further educational endeavours are needed to arrive at a greater consensus and accuracy in the use of the Gleason system.

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Abbreviations: RP, radical prostatectomy.
Therapeutic approaches in metastatic renal cell carcinoma

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INTRODUCTION

The global incidence of renal cancer is continuously increasing [1]; in 2002, >200 000 cases were registered worldwide, with >85 000 patients in Europe alone. The incidence of RCC, which accounts for ~3% of all adult malignancies, is gradually increasing at a rate of ~2.5% per year [2]. RCC is the most lethal carcinoma of the genitourinary tumours, with >40% of patients dying from their tumour, compared to the ~20% who will die from bladder or prostate cancer [3]. Of patients with RCC, 20–30% present with metastatic disease and 20–40% undergoing nephrectomy for clinically localized RCC will develop metastases [4]. About a third of patients develop metastatic disease; common sites include the lung, liver, bone, brain and adrenal gland, as well as lymph nodes and local recurrences. RCC has the capacity to appear almost anywhere in the body, with often more than one organ system being involved in the metastatic spread. Eventually up to half of patients will have metastatic disease after nephrectomy. Hence, the prognosis in metastatic RCC is very poor, with a median survival of 6–12 months and a 5-year survival rate of <10% [2,5]. Currently surgery is considered the reference standard in localized and often in metastatic RCC. If surgery is unsuitable therapeutic regimens based on interleukin-2 and interferon-α are acknowledged treatments [6–10], but response rates, especially in second-line therapies, are very low, rendering successful therapy almost impossible. Recent advances in proliferation-inhibiting agents have created new options for these patients.

NEPHRECTOMY

To date the benefit of surgery in metastatic RCC has not been well accepted; because of low survival rates with metastatic disease, some centres refuse nephrectomy when the initial diagnosis confirms metastasis. Recently two studies compared the outcome of patients treated with systemic immunotherapy and previous nephrectomy vs systemic immunotherapy alone. The first was by the South-west Oncology Group in the USA, which enrolled 241 patients; it showed a median overall survival of 11.1 months in 120 patients treated with nephrectomy plus interferon, and 8.1 months in 121 patients treated with interferon alone. As the patients were not stratified in risk groups according to performance status, types of metastases or presence of measurable disease, the difference in the survival of 3 months in the two groups was low but significant [11]. Another study by the European Organization for Research and Treatment of Cancer overcame this problem and included 85 patients. In the nephrectomy arm the median overall survival rate was improved to 17 months, compared to 7 months in the interferon-only arm [12]. Taken together both studies showed that nephrectomy should be demanded as standard therapy in primary metastatic RCC [11–13].

IPSILOateral ADRENALECTOMY AT THE TIME OF NEPHRECTOMY

Removal of the ipsilateral adrenal gland in patients with RCC treated by nephrectomy was a widespread standard since Robson described the operation in 1969. With the emerging use of modern imaging techniques routine adrenalectomy has become a matter of dispute. The most recent retrospective study included 1635 patients treated at one institution between 1980 and 2000. In all, 1010 patients had a radical nephrectomy plus ipsilateral adrenalectomy, whereas in 625 there was no simultaneous adrenalectomy. In 5.5% of patients with simultaneous adrenalectomy there were metastases in the adrenal gland. Cancer-specific survival rates (75% vs 73% for adrenalectomy vs none) and postoperative complication rates (7% vs 8%) did not differ significantly between the groups. For 30 metastases in the adrenal gland on preoperative staging, the false-negative rate was 23% associated with a tumour stage of >pT3 [14–16]. Thus adrenalectomy should only be used in groups with a higher tumour stage and poor prognosis.

RESECTION OF THE METASTATIC MASS

Surgical removal of one or several metastases can lead to long-term survival in >30% of affected patients [17–20], but the results depend on the location of the lesions. Cure rates are better with metachronous metastases, with a long disease-free interval and fewer systemic symptoms [21]. Resection is also suitable in local recurrence [22–24], pancreatic [25–27], hepatic [17] and adrenal metastases [5,16,28]. If occult lymph node metastasis is resected with initial nephrectomy most patients benefit significantly [29–31]. Consequently survival is increased and the response to immunotherapy might be enhanced [31,32]. The resection of lung metastases is especially associated with prolonged survival. In a series of 191 patients with pulmonary metastases from RCC who had surgery, the overall 5-year survival rate was 36.9%. The 5-year survival rate after complete metastasectomy and incomplete resection was 41.5% and 22.1%, respectively. The survival was significantly longer for patients with fewer than seven pulmonary metastases, compared with those with more than seven (47% vs 14.5%) [33–35]. Thus resection should be regarded as standard treatment in pulmonary metastases.

Ablation of metastases and small primary RCC using cryotherapy with or without a laparoscopic approach is effective, especially in hepatic metastases. Survival rates of up to 37% after 5 years were reported [36]. In single cases there was histopathological confirmation of complete destruction of all vital cancer tissue [37]. Hence experience is limited to date, and diligent monitoring is required more frequently than after surgery [38].

Ablation of canceous lesions using radiofrequency techniques is described in several metastatic sites, e.g. the liver, lymph nodes, abdominal or primary or secondary renal tumours [39-45]. In 582 patients treated with radiofrequency ablation for metastatic disease, complications included five (1.4%) deaths and seven patients with a liver abscess, with five pleural effusions, five skin burns, four with hypoxaemia, three with pneumothorax, two small subcapsular haematomas, one acute renal insufficiency, one haemoperitoneum, and one needle-tract seeding. Minor complications required no specific treatment [40]. The mean diameter of lesions treated to date is ~4.0 cm, with a maximum of 10 cm. Overall local control rates after 1 year were reportedly 91%; with a 1-year survival rate of 79% [45]. Thus long-term data and further histopathological results should be awaited.

SURGERY OF BONE METASTASIS

Osseous metastases secondary to RCC are usually associated with a poor prognosis for the patient’s survival. There are rare data confirming the benefit of surgery for these lesions. With 45 patients treated within 10 years, Duer et al. [46-49] reported a survival of 49% after 1 year, 39% after 2 years and 15% after 5 years. Only the extent of the disease and the latency period between primary tumour diagnosis and first detection of osseous metastasis were identified as independent factors of survival. Astonishingly, eight patients who had wide resection of a solitary osseous metastasis combined with nephrectomy all survived during a mean (range) follow-up of 69 (24-76) months. Thus patients who present with single osseous metastases are candidates for aggressive surgical treatment, with curative intent.

RADIOThERAPY

Radiotherapy has shown only limited effects in treating metastasis; the main effect is the palliation of bone pain. Bone metastases or local recurrences are widely viewed as poor prognostic signs for successful immunotherapy for metastatic RCC. Some data suggest that the combination of radiotherapy and chemo-immunotherapy may induce a synergetic antitumour effect for treating bone metastases or local recurrences from RCC [50]. If untreated, 4-11% of patients develop brain metastasis in the later stages of the disease, with a very short survival [51,52]. Whole-brain radiation therapy (WBRT) can give median survival times of 3-8 months [53], with a response rate of 30-65% and a reduction in symptoms in 80% of patients within 3 weeks [54,55]. In a randomized multi-institutional trial directed by the Radiation Therapy Oncology Group, WBRT with or without no stereotactic radiosurgery boost was compared in patients with one to three brain metastases; 167 patients were assigned to WBRT and stereotactic radiosurgery, and 164 WBRT alone. The median survival time was better in the combined group, at 6.5 months vs 4.9 months for WBRT alone [56]. However, outpatient gamma-knife radiosurgery is also an effective and minimally invasive method for multiple brain metastases from RCC. Particularly for selected patients with limited extracranial disease, it should be recommended as being the method of choice to control intracranial disease [56-58].

CHEMOTHERAPY

To date, many different chemotherapeutic regimens have been tried and none confirmed as being effective in metastatic RCC. Amato [59] reviewed 72 cytotoxic chemotherapeutic agents used alone or as two-drug combinations; the results in 3502 adequately treated patients reflected an objective response in only 5.5%, thus rendering RCC a chemotherapeutically resistant cancer. These findings are consistent with other large series of patients treated with chemotherapy alone, which also showed no or only very limited response [60,61].

Even newer agents had no significant effect; oxaliplatin tested in the FOLFOX-4 regimen showed no benefit, but with considerable toxicity [62]. As well capetabine, gemcitabine, irinotecan and topotecan showed only limited or no activity [63-66]. Thus taxanes have no positive effects for patients with metastatic RCC [67].

A combination of gemcitabine and 5-fluorouracil showed response rates of up to 17%, with no relationship to previously described risk factors [68]. Thus this regimen provides a modest improvement over historical chemotherapy approaches [66,68].

In metastatic sarcomatoid RCC there is newer evidence that chemotherapy might be beneficial. In a recent collaborative study at two institutions, 18 patients with RCC (10 sarcomatoid, eight other) were treated with doxorubicin combined with gemcitabine. Two patients had a complete response, five a partial response, three a mixed response, and one had stable disease. The median duration of response was 5 months. These data suggested that the combination of doxorubicin and gemcitabine has antitumour activity in patients with sarcomatoid RCC. A prospective investigation of this combination in RCC is warranted [69].

THALIDOMIDE

Thalidomide has shown immunomodulatory effects such as inhibition of TNF-α and angiogenesis, and stimulation of interleukin-10 and T-cell function, thus rendering it a potential agent for treating metastatic disease, especially when chemotherapeutic regimens fail [70-72]. Dose-related toxicity with thalidomide is usually limited to sedation, neuropathy and constipation [73-75]. In six Phase II studies, 144 patients were assessable for evaluating thalidomide treatment; 25-72% had stable disease for a limited period [76-80] and the overall response rate was 6%. The time to progression did not differ from historical results in untreated patients, but not compared to a control arm. Finally, in a phase II study there was no clinically significant effect of high-dose thalidomide in metastatic RCC in 26 patients [81].

IMMUNOTHERAPY

The rationale for immunotherapeutic approaches in metastatic RCC is based on the late occurrence of metastases, varying tumour growth, increased incidence of RCC in immunocompromised patients and occurrence of spontaneous remissions [82-86].

TOXICITY AND SIDE-EFFECTS

Systemic cytokine therapy often is associated with ‘flu-like symptoms in almost every patient. Other side-effects are fatigue and vascular leakage. Besides substantial side-effects on the intestinal organs (i.e. hepatitis, gastrointestinal bleeding, recurrence of
selected cases, inhalation therapy may have beneficial effects on pulmonary metastases even after the failure of previous systemic immunotherapy [97]. Interferon-α combined with vinblastine alone failed to show better efficacy [7]. Atzpodien et al. [99,100] developed a combined scheme using interleukin-2 and interferon-α subcutaneously, combined with 5-fluorouracil. Of 41 patients treated with this combination there were seven complete (17%) and nine partial responses (22%), with an overall objective response rate of 39%. Another 15 patients (37%) were stable throughout therapy. The overall survival was 24 months [99]. The high response rates associated with this triple therapy should be regarded as the standard, especially as it is applicable in an outpatient setting.

Recent studies have attempted to improve this response rate by adding the potential antitumoral agent and vitamin A metabolite 13-cis retinoic acid (CRA) to this triple therapy. In two large series there was no additional effect of CRA [7,101]. At present the relationship between the doses of interleukin and interferon and the outcome awaits verification in a prospective randomized trial.

Over 6 years, the Groupe Français d’Immunothérapie enrolled 782 patients in successive multicentre trials using cytokine regimens. The presence of biological signs of inflammation, short intervals from renal tumour to metastases (<1 year), elevated neutrophil counts, liver metastases, bone metastases, patient performance status, the number of metastatic sites, alkaline phosphatases and haemoglobin levels were predictive of survival [102,103]. Consequently, the subgroup of patients presenting with at least three factors predictive of rapid progression should no longer be considered candidates for cytokine trials in France [102,103] (Table 1). However, a small subgroup of patients with good performance status and only one metastatic site had the highest probability of response (37%) when using a combination of interleukin-2 and interferon-α [9,102–104].

Motzer et al. [105–108] described a simple predictive model of tumour outcome. In 670 patients with advanced RCC, pretreatment features associated with a shorter survival on multivariate analysis were a low Karnofsky performance status (<80%), high serum lactate dehydrogenase (≥1.5 times upper limit of normal), low haemoglobin (below the lower limit of normal), high ‘corrected’ serum calcium (≥100 mg/L), and no previous nephrectomy. The median time to death in 25% of patients with no risk factors was 20 months; 53% of patients had one or two risk factors and the median survival time in this group was 10 months. Patients with three or more risk factors had a median survival time of 4 months. Thus, clinical and basic laboratory findings are so far the best predictive variables in metastatic RCC.
ANTIBODY TREATMENT

G250 (WX-G250, Wilex, Munich, Germany) is a chimeric monoclonal antibody of the subclass IgGl, that recognises an antigen preferentially expressed on cell membranes of clear cell RCC (>90%) and that is not expressed in normal proximal tubular epithelium. In most cases staining of G250 in expressed in normal proximal tubular subclass IgGl, that recognises an antigen accumulation in cancer tissue was detectable [10]. Recently a study of 36 metastatic patients was conducted with unconjugated G250 to assess safety and efficacy; 10 patients had stable disease, one a complete response and one a significant regression during the follow-up. The median survival after treatment started was 15 months [111]. Phase II trials optimizing treatment schedules with both conjugated and the unconjugated WX-G250 combined with cytokines are complete and will be published shortly. A phase III clinical trial but in the adjuvant situation in high-risk patients is to start within the year.

TUMOUR VACCINE THERAPY

Three different kinds of cell-based vaccines for RCC are currently under investigation; isolated tumour cell suspensions, gene-modified tumour cells and dendritic cells (DCs) expressing RCC-associated antigens. Clinical results to date are sparse. With autologous tumour cells in an adjuvant setting the 5-year survival rate was improved [112]. In another study, DC vaccination was associated with stable disease in 71% of 22 patients, with a duration of up to 19 months, with three (14%) having an objective response. The median time to progression was 5.7 months [113–115]. Thus these results are within the range of monotherapeutic approaches with other immunotherapeutic agents. Cultured tumour lysate-loaded DC vaccines also generated only a limited clinical response [113–115]. Further results should be awaited before this therapeutic approach can be recommended for the standard treatment of patients with metastases and a low tumour burden.

BONE MARROW TRANSPLANTATION

Metastatic RCC may be susceptible to a graft-vs-tumour T lymphocyte response promoted by allogeneic stem cell transplantation. To date, studies have a high exclusion rate of screened patients because of missing HLA-matched siblings, ineligibility and tumour progression during the treatment phase. Some patients failed to achieve a durable donor engraftment and thus regained host-derived haematopoiesis with disease progression. As yet no prolonged complete remissions have been reported, with only about a third of patients showing a response or stabilization. Major toxicities include grade 3 and 4 acute and chronic graft-vs-host disease, fatal sepsis and CNS bleeding. Hence significant morbidity and mortality limit the eligible patient population [117–129].

ANTI-ANGIOGENIC THERAPY

Angiogenesis is, amongst other processes, regulated by vascular endothelial growth factor (VEGF). Tumour cells have the capacity to over-express the VEGF receptor (VEGFR) that stimulates three major receptors located on vascular endothelial cells, i.e. VEGF-1, –2 and –3. Expression of these growth factors in RCC correlates with the potential for tumour metastases, pathological stage of renal cancer and survival [130–132]. Agents targeting VEGF are effective in treating metastatic RCC. Bevacizumab (Avastin) is a recombinant, humanized monoclonal antibody that selectively binds to VEGF, thus depleting plasma stores of soluble VEGF and depriving VEGFRs of their ligand [133]. SU11248 is a broad-spectrum inhibitor of the VEGFR, platelet-derived growth factor receptor (PDGFR), FLT3 and KIT [134]. BAY 43–9006 targets VEGFR-2, –3 and PDGFR-α tyrosine kinases [135,136] (Table 2).

In a randomized, placebo-controlled, phase II study, high-dose bevacizumab significantly prolonged the time to disease progression in patients with metastatic RCC (4.8 vs 2.5 months; P < 0.001 vs placebo). The progression-free survival rate in 39 patients treated with bevacizumab was 64% after 4 months and 30% after 8 months. There was no significant effect on overall survival, with only four of 39 patients showing a partial response [137].

SU11248 was effective in metastatic RCC; in a phase II trial, 21 of 63 patients (33%) met the RECIST criteria for a partial response and 23 (37%) the criteria for stable disease. There was progressive disease in 30% of patients. Of the patients responding with at least stable disease, the median time to follow-up was >6 months [134]. Hence, this new drug seems to be effective in treating metastatic RCC, with a phase III trial still recruiting.

BAY 43–9006 disrupts the Raf/MEK/ERK pathway at the level of the Raf kinase and therefore VEGFR signalling [135,136]. BAY 43–9006 has shown preliminary single-agent activity in four phase I and one phase II clinical trials conducted in patients with advanced solid tumours, including RCC [136]. In a randomized discontinuation trial study, patients received BAY 43–9006 for a 12-week induction phase; those with metastatic RCC who had tumour shrinkage of ≥25% (responders) continued to receive open-label BAY 43–9006 (37 patients), whereas those whose tumour burden remained within 25% of baseline (stable disease) were randomized to BAY 43–9006 or placebo (45). Seven patients with tumour growth of >25% (progressive disease) were withdrawn from the study. After a further 12-week treatment period, 25 of the 63 evaluable patients (40%) showed a response, 18 had stable disease and 15 had progressive disease. Of the patients who progressed beyond 12 weeks, 88% receiving open-label BAY 43–9006 (37) and 41% randomized to BAY 43–9006 (38), were
progression-free at 24 weeks. The median progression-free survival time in these groups was 48 and 23 weeks, respectively [136]. Phase II/III studies investigating BAY 43–9006 in metastatic RCC are currently recruiting [136,138].

Another angiogenic surface molecule is endothelial growth factor (EGF); to date three clinical trials with substances disrupting the EGF-related signalling have been reported [139–143]. The monotherapeutic use of either of these substances failed to induce any response in metastatic RCC. With gefitinib (Iressa) there was no complete or partial response in 18 patients, although gefitinib was effective in nonsmall cell lung cancer [143,144]. With the high-affinity monoclonal antibody ABX-EOF, there was a major response in three (one complete response) and minor response in two of 88 patients included in the trial. After 8 weeks half the patients had stable-disease, with a median progression-free survival of 100 days [140,141]. Currently there is a phase II/III study recruiting.


CONCLUSION
Therapeutic approaches to metastatic RCC comprise many methods that can only be adapted to the patient’s situation by a multidisciplinary effort. If aggressive surgical interventions and systemic therapies are combined, the prognosis of formerly untreatable patients can be dramatically improved. Thus, acceptable survival and at least a significantly longer time to progression are achievable even in metastatic disease. Risk stratification should primarily consider the patient’s clinical status and basic laboratory findings.

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Abbreviations: WBRT, whole-brain radiation therapy; CRA, 13-cis-retinoic acid; DC, dendritic cell; VEGF(R), vascular endothelial growth factor (receptor); EGF, endothelial growth factor; PDGFR, platelet-derived growth factor receptor.