Do low-grade and low-volume prostate cancers bear the hallmarks of malignancy?

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Prostate cancer is generally multifocal and consists of a dominant focus—measured by tumour volume and deemed the index lesion—and one or more separate, secondary tumour foci of smaller volume. Much laboratory and clinical evidence has shown that we need to rethink how we regard low-grade and low-volume prostate lesions. In this Personal View, we discuss why small, low-grade Gleason pattern prostate lesions, which are currently designated as prostate cancer, could be regarded as non-malignant. These lesions either do not meet the criteria of the hallmarks of cancer or robust evidence that they do so is absent, by contrast with large lesions with a high Gleason grade, which seem to cause most metastatic disease.

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Introduction

Diagnosis and treatment of localised prostate cancer has been a much debated topic and as such is fraught with controversy. This situation has not been helpful for men who are at risk of prostate cancer or who have been diagnosed with the disease.[1] The issues have been well described: overdiagnosis, underdiagnosis, missed diagnosis, misclassification of risk, overtreatment, and undertreatment. Despite a general acceptance that these issues are both real and important, few recommendations have been suggested to help to mitigate them.

One approach that merits some discussion is the reclassification of the generic term prostate cancer (when applied to disease localised to the prostate) into two subtypes—one that can be safely ignored, or better, not diagnosed and another that, if left untreated, would compromise either quality or quantity of life. Possible benefits of not diagnosing a lesion that is unlikely to affect a patient's life include reduction of the anxiety of living with a cancer diagnosis and avoidance of potential radical surgery that might not be of clinical benefit and could cause substantial side-effects. Even active surveillance would incur costs to the health-care system and the patient through additional clinical visits and biopsies.

Such a proposal is not totally new. A US National Institutes of Health and National Cancer Institute expert group meeting on active surveillance[2] stated that "because of the very favorable prognosis of low-risk prostate cancer, strong consideration should be given to removing the anxiety-provoking term 'cancer' for this condition". Additionally, Esserman and colleagues[3] have argued that "minimal risk lesions should not be called cancer", with these lesions perhaps instead being called "indolent lesions of epithelial origin (IDLE)". Others have offered similar opinions in the past year.[4,5]

Not all prostate cancers are destined to progress

The future behaviour of lesions that are identified early in the natural history of several cancers remains uncertain. Some will regress, others will remain stable, some will seem stable because of very long cell-doubling times, and a few will progress. Although lung cancer is one of the most lethal cancers in terms of the ratio of diagnoses to cancer-specific deaths, one in six individuals who die of causes other than lung cancer will have apparently malignant lesions at autopsy; these lesions are now termed pseudodisease in recognition of their non-malignant behaviour. Had these lesions been diagnosed during life rather than at autopsy, treatment would have resulted, but with little benefit to the patient and some harms and costs.[6] Thyroid cancer is closer to prostate cancer in terms of the burden of subclinical disease. The autopsy frequency of cancers in the thyroid gland in people who have died from causes other than thyroid cancer is one in two. This situation has led to such lesions being labelled papillary microcarcinoma.[7] Similarly, a National Institutes of Health consensus statement suggested that ductal carcinoma in situ of the breast should drop the word carcinoma from its name for the same reason.[8] Urologists and uropathologists are familiar with these issues. An increasing recognition that progression, metastases, and death are rare events in small renal masses has led to similar discussion about whether such lesions should also be deemed pseudodisease.[9] Low-risk, non-invasive bladder lesions have also been successfully reclassified from bladder cancer to papillary urothelial neoplasia of low malignant potential.[10]

We believe, as do many others, that it is time to apply the same reasoning to low-risk prostate cancer. Prostate cancer is generally multifocal and consists of a dominant focus (as measured by tumour volume), deemed the index lesion, and one or more separate, secondary tumour foci of smaller volume (figure 1). Much laboratory and clinical evidence has shown that we need to rethink the nomenclature we apply to low-grade and low-volume lesions.[11] We believe that small, low-grade Gleason pattern lesions, which are currently designated as prostate cancer, could be regarded as non-malignant. Using the framework provided by Hanahan and Weinberg,[12] we argue that these lesions either do not meet the criteria of the six hallmarks of cancer, or robust evidence that they do so is absent, by contrast with larger, high-grade lesions, which seem to cause most metastatic disease.

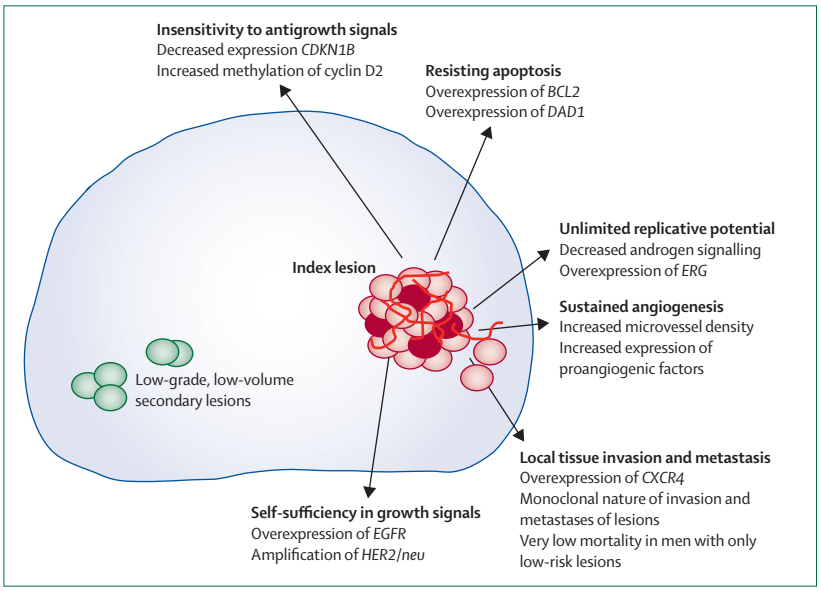

Figure 1: **Hallmarks of cancer as applied to the index and secondary lesions in prostate cancer**

The changing face of Gleason grading

In 1966, Donald Gleason first published his unique grading system for prostate cancer based solely on the architectural pattern of the tumour.[13] He developed a 5-point scale on the basis of the outcomes of 270 patients, in which patterns 1, 2, and 3 represented tumours that most closely resembled healthy prostatic glands, and patterns 4 and 5 represented tumours (or parts of tumours) that were increasingly anaplastic in appearance (figure 2, table).[14] An innovative aspect of this system was that, rather than assigning the worst grade as the grade of the carcinoma, the sum of the two most common patterns is calculated and reported as the Gleason sum score. For example, an area with predominantly pattern 3 disease and a small area of pattern 4 would be designated as Gleason 3+4=7. Since the Gleason system was introduced, pathologists have adopted modifications to the original grading system as described, to adapt it to modern needs (table).

Redesignation of cancer to non-cancer within the Gleason system is not new. The original 5-point ordinal scale described by Gleason is now rarely used. Instead, the scale starts at 3 and ends at 5—something that all clinicians struggle with when trying to explain it to patients. Gleason patterns 1 and 2, originally described by Gleason as changes consistent with malignant transformation, are now regarded as normal variants of the prostate architecture.[15] The redesignation of Gleason pattern 3 (possibly qualified by an upper threshold on volume) could be the next incremental step on a 40-year process of refinement of the Gleason classification system. For example, there has been an accepted grading shift upwards—one element of the so-called Will Rogers phenomenon[16]—with the changing definition of Gleason pattern 4 resulting in the regrouping of cases previously regarded as Gleason score 6 into the Gleason score 7 classification. In many cases of cancer in which the patterns would previously have been assigned to the lowest Gleason pattern 1, advances in immunohistochemistry have shown the presence of basal cells, identifying such cases as atypical adenomatous hyperplasia, a benign mimic of cancer.[17] Moreover, lesions with patterns 1 and 2 have been recognised as biologically similar to pattern 3, further discouraging their use (table).

Hallmark one: self-sufficiency in growth signals

> Tumour cells can generate their own growth signals and reduce their dependence on stimulation from the surrounding normal tissue microenvironment.

Ross and colleagues[18] used laser capture microdissection to extract cells from radical prostatectomy specimens from 23 men to create two subgroups, those with either exclusive Gleason pattern 3 (Gleason score 6) or those with exclusive pattern 4 (Gleason score 8). The investigators measured mRNA expression of 18 344 unique genes in the extracted cells, and noted differential expression of 670 of these genes between Gleason pattern 3 and Gleason pattern 4 lesions. The genes that were exclusively expressed in the pattern 4 tumours corresponded to those that are upregulated in embryonic, neuronal, and haemopoietic stem cells. Importantly, among these were *EGF* and *EGFR*. Overexpression of both of these genes is associated with independent cell proliferation and enhanced cell motility through several signal transduction mechanisms, including the MAPK, AKT, and RAS pathways. As well as the upregulation of *EGFR*, the investigators showed overexpression of *MAP2K4* and the EGF-activated promigratory gene *RALA*, and downregulation of *REPS2* (which negatively regulates EGFR via endocytosis), *PHLPP*, and *PML* (both of which inactivate the protein kinase phospho-AKT, which mediates growth-factor associated cell survival) in Gleason pattern 4 lesions.

Skacel and colleagues[19] used a tissue microarray of more than 300 tissue cores derived from radical prostatectomy specimens to show that *HER2/neu* proto-oncogene amplification, as measured by fluorescent in situ hybridisation, was associated with high tumour volume of greater than 2·0 cm³ (p=0·004). Amplification of *HER2/neu*, a member of the *EGFR* family, was almost exclusively confined to Gleason pattern 4 lesions rather than Gleason pattern 3 lesions.

Hallmark two: insensitivity to antigrowth signals

> Cancer cells must be able to resist the normal antigrowth signals that push them into a quiescent phase of the cell cycle or enter into postmitotic phases that ensure specific cell differentiation.

The D-type cyclins are associated with the regulation of transition from G1 to S phase during the cell cycle. Cyclin D2 is a direct target of MYC and it sequesters CDKN1B ($p27^{Kip1}$), a cell cycle inhibitor), which subsequently results in entry to the cell cycle.[20] Inactivation of cyclin D2 might be caused by aberrant promoter hypermethylation.

Using 101 radical prostatectomy specimens, Padar and colleagues[21] reported that maximum Gleason pattern 3 lesions had significantly greater frequencies of cyclin D2 methylation than did those that contained Gleason patterns 4 or 5. Transforming growth factor β (TGFβ) can impede growth by the induction of inhibitors of cyclin-dependent kinases, including CDKN1B. Also using radical prostatectomy specimens, Guo and colleagues[22] showed that there is progressively diminished CDKN1B immunostaining with increasing Gleason score in prostate neoplasms. All Gleason pattern 5 foci were completely negative for CDKN1B staining, which suggests that these cells are unresponsive to the growth-inhibitory effect of TGFβ. This loss of CDKN1B was associated with an increase in the proliferative index of high-grade prostate cancers.

Hallmark three: resisting cell death

> The ability of cancer cells to resist programmed cell death (apoptosis) is key to ensuring continued growth and proliferation.

True and colleagues[23] used laser capture microdissection to acquire specific subpopulations of prostate cancer cells consistent with lesions containing Gleason patterns 3, 4, and 5 from 29 radical prostatectomy specimens. They profiled transcript abundance using cDNA microarray analysis and developed an 86-gene model capable of differentiating between lesions that contain Gleason pattern 3 and those that contain higher patterns (4 and 5). This model was 76% accurate in characterising an independent set of 30 primary prostate lesions. One specific discriminatory gene identified was *DAD1*, a gene encoding defender against cell death 1, which is a downstream target of the NFκB survival pathway and displays an antiapoptotic function. DAD1 protein expression was measured by immunohistochemistry in tissue microarrays consisting of formalin-fixed radical prostatectomy tissue from 131 benign and 306 presumed cancerous samples. DAD1 protein concentrations showed a strong association with Gleason grade, with tumours of patterns 4 and 5 more likely to stain intensely compared with Gleason pattern 3.

Another more familiar antiapoptotic gene is *BCL2*, the role of which in carcinogenesis and castrate resistance in prostate cancer is well established. Fleischmann and colleagues[24] did immunohistochemical analysis on a tissue microarray of 3261 radical prostatectomy specimens and reported that *BCL2* expression was significantly upregulated in lesions with a high Gleason score (lesions that included Gleason patterns 4 and 5) compared with those that were only pattern 3.

Hallmark four: unlimited replicative potential

> Mammalian cells seem to have an inherent autonomous function, independent of cell-to-cell signalling, that limits their replicative ability. Cancers disrupt this intrinsic pathway.

Cells that transform into cancer have to be able to subvert this so-called brake on replication. We have some evidence that exclusive Gleason pattern 3 prostate lesions have this brake preserved and that high-grade cancers are more likely to have evolved a mechanism to overcome it. Tomlins and colleagues[25] provided some of this evidence from their well designed experiments. They used radical prostatectomy specimens (101 microdissected specimens from 44 individuals) to develop two phenotype tissue pools—one low-risk (exclusive Gleason pattern 3) and one high-risk (Gleason pattern 4 or higher). The high Gleason grade lesions showed decreased androgen signalling, similar to metastatic prostate cancer, which could reflect dedifferentiation and account for the clinical association of the grade of the high-grade lesions with prognosis. This finding was also reported by Hendriksen and colleagues,[26] who noted lower androgen signalling in high-grade Gleason pattern prostate cancer than in low-grade Gleason pattern lesions. The researchers suggested that localised prostate cancer cells become more aggressive by selectively downregulating androgen-responsive genes, which results in increased tumour cell replication and proliferation, dedifferentiation, or reduced apoptosis.

Another mechanism that is available to the cell to overcome the intrinsic brake on replication is gene translocation. The *TMPRSS2–ERG* translocation is one of the most prevalent genetic changes in prostate cancer, the presence of which results in overexpression of the ERG transcription factor, and therefore promotes proliferation.

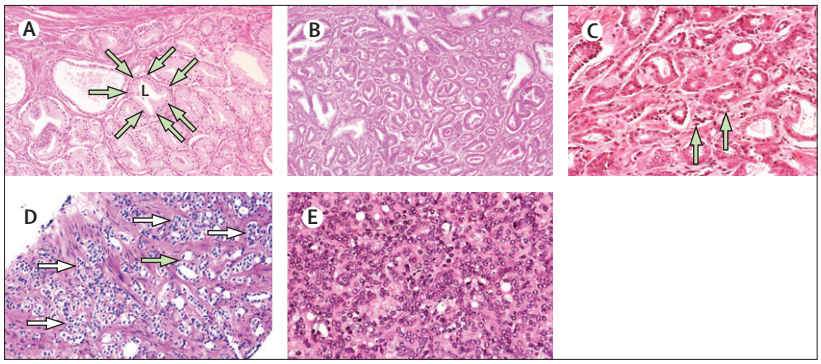

Figure 2: **Gleason grade patterns for prostate cancer lesions**
(A) Gleason grade 1 (arrows outline an individual prostate acinus; original magnification ×40. (B) Gleason grade 2 (original magnification ×40). (C) Gleason grade 3 (arrows show a small amount of individual cell infiltration into surrounding stroma; original magnification ×100). (D) Gleason grade 4 (increased stromal invasion; white arrows show some areas of gland fusion and poorly defined lumens; green arrow shows one of a few areas in which Gleason pattern 3 is present; original magnification ×40). (E) Gleason grade 5 (solid sheets of cells with no glandular structures and poorly differentiated cells; original magnification ×100). L=lumen.

	Original Gleason system	Modified system*
Gleason grade 1	Very well differentiated, small, closely packed, uniform glands in essentially circumscribed masses	Circumscribed nodule of closely packed but separate, uniform, rounded-to-oval, medium-sized acini (larger glands than pattern 3)
Gleason grade 2	Similar to pattern 1, but with moderate variation in size and shape of glands and more atypia in individual cells; cribriform pattern might be present—still essentially circumscribed, but more loosely arranged	Similar to pattern 1, fairly circumscribed, although a little infiltration might be seen at the edge of the tumour nodule; glands are more loosely arranged and not quite as uniform as pattern 1
Gleason grade 3	Similar to pattern 2, but substantial irregularity in size and shape of glands, with tiny glands or individual cells invading stroma away from circumscribed masses, or solid cords and masses with easily identifiable glandular differentiation within most of them	Discrete glandular units; typically smaller glands than seen in pattern 1 or 2; infiltrates in and among non-neoplastic prostate acini; substantial variation in size and shape; smoothly circumscribed, small cribriform nodules of tumour
Gleason grade 4	Large, clear cells growing in a diffuse pattern that resembles hypernephroma; might show gland formation	Fused microacinar glands; ill defined glands with poorly formed glandular lumina; large cribriform glands; cribriform glands with an irregular border; hypernephromatoid variant
Gleason grade 5	Very poorly differentiated tumours; usually solid masses or diffuse growth with little or no differentiation into glands	Essentially no glandular differentiation—composed of solid sheets, cords, or single cells; comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses

*Modified system grades defined by the International Society of Urological Pathology.[14]

Table: **Original Gleason scoring system and the 2005 modified system**

Although the association of *ERG* gene rearrangements and aggressive prostate cancer remains controversial, that such rearrangements have a substantial role in the transformation of some cancers is becoming apparent. Since *TMPRSS2–ERG* fusions lead to frequent changes in the *ERG* proto-oncogene in early-stage prostate cancer, investigation of this fusion in preneoplastic cells and multifocal lesions from the same patient has the potential to define its role in prostate cancer onset, progression, and heterogeneity. In fact, evidence suggests that ERG protein expression can be used as a surrogate marker for *ERG* genetic rearrangements. In a cross-sectional study[27] in which individual cancers from radical prostatectomy specimens with two to three tumour foci of various sizes and grades were analysed, the researchers established that ERG protein expression is significantly increased in tumours with large volumes and high Gleason grade, presumably as a result of this transcription factor promoting tumour growth and proliferation.

However, other evidence emphasises the uncertainty about the role of this particular gene fusion in prostate cancer development and progression. Furusato and colleagues[28] showed that *TMPRSS–ERG* fusions reside predominantly in the index lesion, but are also present in some secondary lesions and some histologically benign areas of prostate. Others[29] have shown a strong relation between expression of *TMPRSS2–ERG* fusion mRNA isoforms and pathological measures of clinical outcome (seminal vesicle invasion, extracapsular extension) in lesions from radical prostatectomy specimens. The same researchers also reported expression of the gene fusion in benign glands of the prostate.

Hallmark five: sustained angiogenesis

Neoangiogenesis is a normal physiological process that takes place during embryonic development and wound healing. The process is also necessary for tumours to break through the volume threshold of 1 mm diameter, since tumours larger than this cannot rely on the diffusion of oxygen from existing vessels.

Angiogenesis is probably necessary to support accelerated tumour growth, since the metabolic needs of the tumour must be met by an adequate blood supply.[30] Prostate cancer cells have the ability to produce several factors that promote new vessel formation. Malignant prostate cells secrete proangiogenic molecules such as VEGF, fibroblast growth factor 2, TGFβ, and cyclo-oxygenase-2. So the question arises, does this forced vascular proliferation occur preferentially in high-grade lesions or is it a transformation that is permissive for proliferation and dedifferentiation of prostate cancer cells? Raised VEGF and increased microvessel density are related to a poor prognosis in prostate cancer,[31] and a close association exists between the two. Moreover, this association seems to be more pronounced in high-grade and large tumours than in low-grade and small tumours.[32] In a well designed study, Mucci and colleagues[33] established that poorly differentiated tumours showed increased microvessel density and irregularity of the blood vessel lumen with reduced vessel size. After 20 years of follow-up, 44 of 572 men had either developed bone metastases or had died of cancer. Men with tumours that had the smallest vessel diameter at inclusion were six times more likely (95% CI 1·8–20·0) to develop metastatic prostate cancer or to die from the disease. Additionally, another subgroup was identified that had even greater propensity for clinical progression; men who had irregularity of vessel diameter were 17 times more likely (95% CI 2·3–128) to reach the same two endpoints. Microvessel density itself was not linked to cancer-specific mortality after results were adjusted for clinical factors.[33]

Other factors are either required or facilitate new vessel formation. Pasquli and colleagues[34] have added to the evidence that the drivers for new vessel formation are over-represented in prostate cancers that have high-grade elements. They showed a substantial upregulation of endocrine gland-derived VEGF or prokineticin protein expression in higher-grade lesions compared with exclusive Gleason pattern 3 lesions. Killingsworth and Wu[35] provided further insight, elucidating the mechanism by which new vessel formation takes place. The researchers studied pericyte interactions that were associated with new vessels using transmission electron microscopy. The interaction of endothelial cells from blood vessels with pericytes is essential for the process of prostate cancer neoangiogenesis, with pericytes increasingly acknowledged as molecular regulators of angiogenesis. Pericyte distribution was mapped from

α-smooth-muscle-actin-positive immune-stained histological sections and quantified by image analysis. Exclusive Gleason pattern 3 lesions had a microvessel pericyte density score that could not be distinguished from benign prostate tissue, by contrast with the scores of higher-grade lesions.

Hallmark six: tissue invasion and metastasis

> The potential for invasion into adjacent anatomical structures and spread to distant sites are key attributes of cancer cells. Most manifestations of prostate cancer do not have either of these properties.

Evidence exists that suggests the absence of invasive and metastatic behaviour in most prostate lesions. For example, when individual prostate lesions derived from one patient's primary prostate cancer specimen were implanted into mice, only one lesion out of three showed characteristics of local invasion and eventually formed metastases.[36] This work reminds us that as well as histological heterogeneity within any one prostate lesion there are, within the cancer, distinct elements with a range of biological potentials. The characteristics of those elements that are capable of metastatic spread are relevant to our argument. Elements that are permissive for cell migration seem to be comparatively overexpressed in higher-grade lesions than in exclusive Gleason pattern 3 lesions. The chemokine receptor CXCR4 is one of those elements that are upregulated in localised, high-grade Gleason pattern 4 lesions compared with Gleason pattern 3 lesions. This G-protein-coupled transmembrane receptor has a key role in the directional migration of cancer cells to specific metastatic sites in response to its ligand CXCL12. Additionally, CXCR4 upregulation has been associated with lymph node and bone metastasis in prostate cancer, possibly through activation of the *RAS* oncogene family member *RAP1A*, the expression of which is also upregulated in Gleason pattern 4 lesions relative to those containing only Gleason pattern 3. Investigators of other studies have suggested that hypoxia induces CXCR4 expression in tumour cells via hypoxia-inducible factor 1α.[37,38] Large volume tumours are much more likely to have central hypoxic areas than are small volume tumours. Expression of CXCR4 on the tumour cell membrane allows the cancer cells to migrate or metastasise away from the area of low oxygen tension, down a CXCL12 concentration gradient, to areas of high oxygen concentration. The ligand CXCL12 is secreted at especially high concentrations by lymph node and bone marrow stromal cells.

Most men have two to three distinct tumour foci in their prostate at presentation. Most of the tumour burden is usually contained within one of these foci. This dominant tumour by volume (which is strongly associated with grade) has been termed the index lesion because of its putative biological potential. Wise and colleagues[39] were possibly the first to develop this idea. They showed that Gleason pattern 4 and 5, volume of the largest tumour, and lymphovascular invasion were intraprostatic independent predictors of clinical prostate cancer progression. Other researchers[40] have noted that 80% of secondary foci are smaller than 0·5 cm³ and have the same volume distribution as do tumours found incidentally in patients that undergo cystoprostatectomy for bladder cancer. In most other solid cancer models of progression, tumour volume is a key determinant. The same is true, it would seem, of the prostate, although the evidence to support this assertion has taken some time to accumulate. Tumour volume has been proposed to be associated with prostate-specific antigen (PSA) recurrence[41] and prostate lesions smaller than 0·5 cm³ are almost always clinically insignificant because of the long doubling times of such lesions.[42] Several authors[43,44] have proposed that the threshold for significance of volume be placed higher, at 1·2 cm³, on the basis of data from the European large-scale randomised prostate cancer screening trial, in which volume thresholds of insignificant disease were calculated on the basis of models of lifetime risk estimates of prostate cancer diagnosis in screened and non-screened participants. The investigators showed that the minimum threshold tumour volume of the index lesion and total tumour were 0·55 cm³ and 0·70 cm³, respectively. However, after accounting for tumour stage and grade, the threshold volumes for the index tumour and total tumour were 1·3 cm³ and 2·5 cm³, respectively.[43,44]

A strong association also seems to exist between pathological and staging measures of poor prognosis (extracapsular invasion, seminal vesicle invasion, metastases) and individual cancer lesion volumes. Lesions measuring 0·5 cm³ or more had a one in ten chance of capsular invasion, whereas lesions measuring 4·0 cm³ or more had a one in ten chance of seminal vesicle invasion. Lesions measuring 5·0 cm³ or more had a one in ten chance of metastases.[45] Volume is an important determinant of grade (or vice versa); Gleason pattern 4 or higher is very rare in lesions that are not attributed index status.[46] If the volume of a lesion is a key attribute of progression, as it seems to be,[47] then multiplicity for any given overall tumour volume within a prostate should be a good prognostic sign. In other words, if 2 cm³ of tumour is distributed fairly equally among five separate lesions, the mean lesion volume will be less than 0·5 cm³. If, on the other hand, the cancer was unifocal (seen in about one in five men who present with prostate cancer), then the mean tumour volume will equate to the overall tumour volume—ie, 2 cm³. The primacy of the index lesion as a determinant of progression seems to hold.

The next question in relation to the volume of specific prostate cancer foci is about the biological potential of these small lesions. Tumour doubling times are the means by which this potential can be estimated. Schmid and colleagues[48] have reported that 79% of men with

previously untreated prostate cancer of all clinical stages, who had serial PSA measurements during a period of at least 12 months, had a tumour doubling time greater than 24 months. Primary tumour volumes that theoretically lead to distant metastases tend to be at least 4 cm³ in volume.[49] As such, with an estimated tumour volume doubling time of 2 years, it would take about 6 years for a 0·5 cm³ lesion to reach a volume of 4 cm³.

Although overwhelming evidence suggests that small tumours are very safe from a biological perspective, there remain some anomalies that remind us that our understanding is far from complete. Local invasion does not seem to be as closely linked to cancer foci volume as are metastases. Up to one in four tumours that show capsular invasion can be identified as non-index lesions,[50] and although tumours that are locally invasive do need to achieve some volume threshold, they do not necessarily have to be very large.[51] In fact, circulating tumour cells and occasionally lymph-node metastases have been reported in men who have lesions of 0·2 cm³ in volume.[52] In a series of 239 patients with tumour volumes of less than 0·5 cm³, investigators showed that 43 were poorly differentiated, 11 had extracapsular extension, six had positive surgical margins, two had positive lymph nodes, and seven progressed within 5 years.[53] Greene and coworkers[54] assessed DNA ploidy status, which is an independent prognostic factor for localised prostate cancer. Of 141 separate lesions in 68 patients, the investigators reported that 15% of those 0·01–0·1 cm³ and 31% of those 0·11–1·0 cm³ in volume were non-diploid. Thus, tumour volume in itself did not adequately predict the biological potential of prostate cancer and so should be combined with other factors, predominantly Gleason grade.

The molecular association of individual lesions with lymph node metastases has added more force to the argument that, despite multifocality, prostate cancer disease progression is likely to be related to lesions that meet some minimum grade and volume thresholds. *TMPRSS–ERG* gene fusions seen in lymph node metastases are also found in the index lesion and not in small, low-grade satellite lesions[55] or secondary high-grade and high-volume lesions.[56] Results of one important study[57] showed that metastatic deposits taken from men in a rapid autopsy protocol shared one common cell of origin. However, the question of whether the metastatic clone originated from the index lesion is something that was not possible to address in this study because of the nature of the men from whom the tissue samples were taken (ie, they had been through first-line and second-line hormonal therapies in addition to chemotherapy in some instances, so the prostates were small and fibrotic, which made the delineation of individual lesions impossible).[58] Grasso and colleagues[59] also noted the monoclonal origin of lethal, castrate-resistant prostate cancer by sequencing the exomes of metastatic deposits in 50 lethal, heavily pretreated metastatic cancers obtained at autopsy.

Epidemiological evidence also supports the assertion that most prostate lesions, especially those of low volume and low Gleason grade, currently called cancer, do not show tissue invasion and eventual metastases. Evidence from post mortem studies has shown a frequency of one in three so-called prostate cancers in men who died of other causes. Similar frequencies are seen on assessment of prostates taken from cystoprostatectomy specimens from men who have undergone surgery for high-risk or invasive bladder cancer.[40] Therefore, since a third of men have prostate cancer that will not affect them in their lifetimes, it is unsurprising that small, low-grade lesions have low (or possibly absent) malignant potential.

This argument is lent support by findings from long-term radical prostatectomy outcome series. For example, Eggener and coworkers[60] showed that, of 9775 men who had Gleason 3 pattern in isolation confirmed on radical whole-mount prostatectomy specimens, only three died of prostate cancer in a 15 year period. In fact, when these three patients were reviewed, a small amount of Gleason pattern 4 was seen.[1] This finding cannot merely be accounted for by the success of surgery itself and is strong evidence that exclusive Gleason pattern 3 prostate lesions are not a metastatic phenotype. Others[61,62] have reported similar findings in smaller cohorts of patients, but using biochemical recurrence as a surrogate outcome measure.

The scientific literature about the advantages and disadvantages of active surveillance also helps the understanding of whether low-volume, low-grade disease behaves in a malignant way. Warlick and colleagues[63] investigated whether curability after surgery, which they defined as surgical pathological characteristics that would generally confer a greater than 75% chance of remaining biochemically recurrence-free at 10 years, was affected if treatment was delayed.[64] In other words, is the window of opportunity for cure—something that concerns patients and physicians alike when considering active surveillance—lost in men with small, low-grade disease who have delayed curative treatment? After comparing the burden of supposedly incurable cancer among patients undergoing delayed surgery at a median time of 26·5 months after diagnosis with that in patients undergoing immediate surgery (who would have been eligible for active surveillance) the investigators reported no association between adverse pathological changes on whole-mount specimens and the time period between diagnosis and surgery. Clinical experience with active surveillance suggests that an estimated risk of metastasis exists of less than 1% at 2–8 years[64] and disease-specific mortality of 1% at 8 years in men undergoing surveillance for low-risk disease as classified by a diagnostic transrectal ultrasound-guided biopsy. Early outcomes in men with intermediate-risk disease managed by active surveillance have also been encouraging.[65] Results of research that has assessed active surveillance have shown that all prostate cancer-related mortality occurred

in men who had been reclassified as higher risk and who were offered radical treatment. Therefore, reclassification of disease risk and subsequent radical treatment is likely to have occurred because of undersampling of the prostate rather than because of true progression. In other words, when compared with a more rigorous sampling strategy, transrectal ultrasound-guided biopsy undergrades and understages disease as a result of random and systematic errors in sampling the prostate.[66]

Clinical implications

When prostate cancer is identified from biopsies, the psychological connotations associated with having cancer mean that many men choose or are advised to undergo radical treatment that they stand little chance of benefiting from.[67] Most clinicians advising patients know that exclusive Gleason pattern 3 carries very little lifetime risk to the patient, but many still recommend radical treatments that carry high toxicity profiles. The principal driver remains uncertainty. More specifically, this uncertainty is in relation to the precision of risk stratification. The absence of precision means that the attribution of low risk is insecure in about one in three men who are deemed to be at low risk (exclusive Gleason pattern 3 disease), but in fact are not. If we could accurately identify men with Gleason pattern 3 lesions in isolation, these men would be very likely to be at much lower (possibly negligible) risk of death from prostate cancer than men previously attributed a Gleason pattern 3 diagnosis of cancer. If this situation came to pass, we might be in a position to reclassify exclusive Gleason pattern 3 lesions to a term that substitutes the word cancer for something else, such as IDLE.[3] Such a term would seem to be appropriate; if low-volume, low-grade lesions were reclassified as non-cancer or IDLE lesions and this change met with widespread professional acceptance, the immediate implications for clinical practice would be profound.

First, research into novel detection strategies and therapies is likely to need substantial rethinking. At present, new tissue and imaging biomarkers are usually tested for their ability to find all cancer on the basis of the transrectal ultrasound-guided biopsy. In fact, hundreds of millions of pounds have been spent on the discovery of an elusive biomarker during the past two to three decades, on the premise that the outcomes from the transrectal ultrasound-guided biopsy are the gold standard. However, this test detects clinically insignificant, possibly non-malignant lesions (which incorrectly designates the patient a true positive). A third of all men diagnosed with prostate cancer are estimated to have clinically insignificant disease.[64,68,69] Furthermore, transrectal prostate biopsies can miss a clinically significant cancer that is likely to progress and metastasise within a man's lifetime (which incorrectly designates the patient a true negative). 40% of men who test negative on biopsy are estimated to have cancer;[68,70] of these, a third have clinically significant cancer based on lesion volume and presence of high grade.[69]

Second, a recalibration of what is deemed cancer is likely to substantially reduce the overdiagnosis and overtreatment burdens with which we are all familiar. Clinicians could rely on tests that target measurable malignant disease rather than attempting to find all lesions. Imaging intrinsically cannot detect every focus of Gleason pattern 3. A recalibration of what is deemed malignant would mean that we should not expect these imaging modalities to do so. The performance characteristics of multiparametric MRI, for example, coupled with an intensive sampling strategy, in being able to rule out 0·5 cm^3 lesions with a negative predictive value of about 90–95%, is arguably an ideal test.[71] A large multicentre study is in progress that is assessing the reproducibility of such imaging in men at risk before any biopsy, against a reference standard that can be applied in all men and not only those who undergo surgery (NCT01292291). The key with imaging is that it could provide an accurate volume with indicators of high Gleason grade before biopsy and act as a triage test to identify men who need biopsies, which would allow men with no clinically significant cancer to avoid entering the diagnostic pathway altogether.[72]

Third, when compared with other solid organ malignancies, prostate cancer is an outlier. Treatments for breast, renal, thyroid, liver, and pancreatic cancers all include tissue-preserving therapies, if appropriate, which are dependent on location and burden of the cancer. These specialties in oncological surgery developed tissue preservation, as opposed to Halsted principles for wide surgical margins, because of upstream diagnostic methods that rely on identifying measurable (by palpation or imaging) disease that can undergo targeted sampling followed by targeted treatment. The transrectal ultrasound-guided prostate biopsy has led to the reverse approach for prostate cancer. Random and blind sampling has forced our hands as clinicians, so that we have to apply radical whole-gland principles because the exact disease statuses of regions of the prostate are

Search strategy and selection criteria

We searched PubMed and Medline for relevant publications from the past 10 years (Jan 1, 2002 to April 16, 2012), and supplemented the results of our search with key articles from before this period when appropriate. Publications were selected for their findings of differences between lesions in each of the six hallmarks of cancer criteria. We used the search terms "prostate cancer" AND "multifocal" OR "index lesions/tumo(u)r OR "secondary lesions/tumo(u)r". Separate searches with these terms were supplemented by those with terms related to each hallmark of cancer. Searches were supplemented by authors' personal bibliographies. Only articles published in English were included.

unknown. So, if multifocality is overlooked in other organs by targeting only the measurable index lesion—that which is largest by size and has elements of the highest grade—that targeting these lesions in prostate cancer might be sufficient to lead to acceptable, possibly equivalent, cancer control rates to whole-gland therapy is a reasonable hypothesis. In prostate cancer, one strategy could be to target lesions that meet widely acceptable thresholds for clinically significant cancer. Focal therapy certainly leads to reduced genitourinary and rectal side-effects, if the results of early prospective studies are reproducible across populations, centres, and surgeons.[73–75] However, the key will be to design longitudinal cohort and comparative effectiveness studies that assess medium-term and long-term cancer control. Such research will need to focus on the natural history of untreated benign and low-volume, low-grade prostate lesions.

Contributors

HUA conceived the Personal View, and MA and HUA did the database searches and identified relevant articles. HUA and MA jointly wrote the first draft. AF and ME fully took part in redrafting the report and in ensuring its scientific correctness. All authors redrafted the report through several iterations and approved the final submitted version.

Conflicts of interest

ME and HUA received funding from USHIFU, GlaxoSmithKline, and Advanced Medical Diagnostics for clinical trials. ME received trial funding from Steba Biotech. ME is a paid consultant to Steba Biotech and USHIFU. ME and HUA have previously been paid consultants to Oncura (GE Healthcare). MA and AF declare that they have no conflicts of interest. None of these funding sources had any input or role in the production of the report.

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