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Invited editorial

Diagnosis, prognosis and management of incidentally found prostate cancer

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Summary. Incidentally discovered cancer of the prostate may be divided into focal and diffuse disease. The focal tumour tends to be of low grade and low-volume and in the majority of patients runs a clinically benign course. In 10–15% of untreated patients, however, progression occurs by 10 years after diagnosis. At the same stage of follow-up 30–63% of the patients have died of other causes, with no evidence of recurrence. In patients with low-grade focal cancer of the prostate, radical prostatectomy may be curative. An alternative management option is to closely observe these patients. Digital rectal examination, prostatic specific antigen, transrectal prostatic ultrasound and repeated prostatic biopsies can all make contributions to the follow-up of these patients.

Key words: Prostate – Cancer – Incidental – Al

Incidentally found prostate cancer is cancer detected histologically in tissue removed during prostatectomy for supposedly benign disease. It is divided into two types: focal and diffuse. Diffuse disease has a higher incidence of positive lymph nodes, capsular penetration, seminal vesicle invasion, progression and disease-related death than focal disease [14, 40, 41, 45]. For this reason, most urologists will offer radical therapy to patients with diffuse disease. The course and management of patients with focal disease is far less clear-cut and forms the basis of this review.

Focal, incidentally discovered prostatic cancer has for many years been considered little more than a pathological curiosity, with an essentially benign clinical course. Recent evidence, however, suggests that amongst those patients with focal disease and a longer life expectancy there exists a subset who are at risk of progression and may therefore benefit from radical treatment. This has rekindled clinical interest in this condition, and the treating physician is now faced with some difficult management decisions. It is intended that the contents of this review will present a rational basis on which such decisions can be made.

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Definition

All incidentally discovered carcinoma was initially classified as stage A in the Whitmore classification of prostatic cancer [56]. In 1975, Jewett pointed out that there seemed to be biological differences between focal and diffuse incidental prostatic carcinomas, and he suggested that these be divided into A1 (focal) and A2 (diffuse). He provided no more specific criteria than this [25]. Consequently many institutions have developed their own criteria to differentiate between focal, or potentially less biologically active tumours and diffuse, or more aggressive tumours. Most American institutions use the nomenclature of A1 and A2, and although there are many different definitions of these classifications they are usually based on a combination of the amount of tissue involved and the grade of that tissue. Perhaps the most commonly used staging system, in terms of amount of tissue involved, is that from the Johns Hopkins. This system estimates the percentage of previously marked tumour by naked eye examination of the slides. An "A1" tumour is one that occupies 5% or less of the total specimen [16]. Other authors have used 3 involved chips, 5 involved chips, 3 separate foci and < 50% of the specimen as their focal (A1) criteria, normally combining these with a requirement that the tumour be "well differentiated". The UICC TNM classification attempts to avoid these institutional interpretations of classification systems by defining strict staging criteria. Unfortunately, these "strict" staging criteria have themselves been changed with each revised edition of the TNM staging classification, leading to further confusion; also, there has been no allowance for the grade of the tumour. The proposed 1992

revision defines focal disease (T1a) as incidentally found tumour involving 5% or less of the specimen, but this still makes no allowance for grade [44]. More recently, the use of the ratio of chips with carcinoma to the total number of chips has been proposed as a method of differentiating between the biologically differing focal and diffuse incidental cancers [24, 49]. With this technique, not only was there good intra- and inter-observer agreement, but also as good a correlation with prognosis as with other definitions of focal disease. Humphrey and Vollmer also note that a continuous parameter, such as a ratio, may better reflect the continuous phenomenon that is the extent of tumour [24]. This theme is further developed by Lowe, who has derived probability tables for disease progression based on grade, age and extent of disease. He makes the point that there exists a spectrum of risk from incidental carcinoma of the prostate and that the simple division into focal and diffuse may not be sufficient [29].

Because so many staging systems exist, it is often difficult to compare the results. Worldwide consensus is needed, but until this is achieved it is important to explain precisely the system used when interpreting or reporting results. It is also important to keep in mind that all the systems are attempting to separate biologically differing diseases, that is a low-volume, low-grade malignancy with a very small risk of causing further problems from the more aggressive diffuse, but still incidental, tumours.

Lastly, mention should be made of the non-palpable malignancy detected by either ultrasonically guided or random biopsies. Although these tumours should probably be included within the "incidentally found" category, to date their natural history and definition have not been fully worked through.

Diagnosis and tissue sampling

Denton first demonstrated that the method of tissue sampling in transurethral resection of the prostate (TURP) specimens altered the rate of detection of "occult" prostatic carcinoma. He found that by the routine method of pathological examination at his institution the rate of detection of occult carcinoma was 6%, whereas step-sectioning (in which all fragments were blocked and sections taken at 1 mm intervals) demonstrated a detection rate of 21%. In other words, only 28% of the occult carcinomas of the prostate were being detected by their routine pathological methodology [13].

These findings have been replicated by many other workers. Vollmer summarized results from 49 papers and 26454 patients, showing that complete sampling increases the detection of cancer from 10% to 24% in autopsy specimens, and from 7% to 19% in surgically removed prostates [55]. Thus, there can be no doubt that the harder one looks for occult carcinoma of the prostate, the more likely one is to find it. Moore has attempted to quantitate this phenomenon by drawing up probability tables [33]. From these tables he has calculated that to have a 99% probability of detecting cancer in a gland where there are 25 chips involved, only requires 16.7% of the total number of fragments to be sampled, whereas 60.1% and 99% of a gland would need to be sampled if only 5 and 1 chips were involved respectively. It is for this reason that the examination of all chips has been advocated by some [35]. To do so, however, places great additional strain on histological resources in both personnel and financial terms.

In an attempt to overcome this problem, Vollmer studied four different methods of partial chip sampling and found the sampling of five blocks of tissue to be the most effective method, missing only 5 of 61 cancers in 711 specimens [55]. Four of these were classified as stage 1, although no differentiation between focal and diffuse was made. Murphy et al. addressed this difference specifically. Based on previous data showing that 80% of American pathologists only examine the entire specimen if it weighs 10 g or less, they compared the detection rate of cancers in the first 10 g of tissue examined with that of the whole specimen. Using three different criteria for focal malignancies (5% or less, five chips or less, and three chips or less), they found that no diffuse cancers were missed, and in fact the examination of 6 g of tissue would have detected all the diffuse cancers by all of the three criteria. They did, however, miss a number of focal cancers, where they found a relationship between the amount of tissue examined and the detection rate. Only 82% of the focal cancers were detected after examination of 10 g, and to detect 90% 12 g would need to be examined [36]. This compares with the five block sampling of Vollmer, where his average of 2.5 g of tissue per block would have seen him sample 12 g on average.

Therefore, it would seem that the "biologically significant" diffuse cancers will be detected with the above partial sampling techniques, but that a number of the focal cancers will be missed. In the majority of cases this will be of no consequence to the patient, although it does leave a small risk (estimated at around 5% [45]) of missing a poorly differentiated tumour in a focal carcinoma and of missing focal cancer in young men. The method of sampling in any particular institution must be decided collectively between pathologists and urologists, with consideration given to potential risk to the patient of undiagnosed cancer, the policy of intervention following positive findings and the availability of histopathological resources.

Natural history and prognosis

Incidentally discovered carcinoma of the prostate accounts for roughly a quarter of clinically diagnosed prostatic cancers, and of these a half are designated as A1, or low grade and focal [42].

Vollmer, in his review of 49 papers, showed that with complete sampling of autopsy specimens there was a 25% incidence of incidental, clinically unsuspected prostate cancer [55]. This incidence is also known to increase with advancing age. Therefore 1 in every 4 men will die harbouring an incidental, clinically insignificant and unsuspected carcinoma of the prostate. However, the probability of an American male having a prostatic cancer diagnosed during his lifetime has been estimated at less

than 10% [47]. It is clear from the above that many prostatic cancers are clinically insignificant and have no impact on life expectancy. On the other hand, in the United States prostatic cancer has just surpassed lung cancer as the most commonly diagnosed cancer in males [46]. Furthermore, the mortality from the disease is also increasing, although at a lesser rate than the incidence, suggesting that although improved detection may account for a part of this increasing incidence there may well be a smaller genuine rise in the incidence of this cancer.

In 1972, Hanash et al. published a 15-year follow-up of untreated patients with carcinoma of the prostate. They found that the "stage A" patients had a life expectancy that correlated with expected survival [19]. In the same year Byar found, on reviewing his and four other series, a 1.9% death rate in "stage 1" patients not treated by radical prostatectomy [6]. Two years later, Correa et al. published a series in which they noted a clear difference between those patients with focal and diffuse incidental disease in terms of cancer progression and death rate [11]. This led Jewett to propose the division of incidental cancers into focal (A1) and diffuse (A2) categories [25]. As noted previously, the validity of this division has subsequently been confirmed.

The above studies showed a cancer death rate in untreated focal disease of 0–2%,and rate of death from other causes, in the absence of evidence of progression, of 35–57% over the duration of the studies, which had varying follow-up. Therefore most institutions adopted a conservative, expectant policy with focal incidentally found carcinoma of the prostate.

In 1986, the group from Johns Hopkins reported extended follow-up of their series of untreated patients with focal disease [17]. They found that of those at risk (i.e. still alive) 8 years or longer after diagnosis, 16% (8/50) had progression of disease. They concluded that there was a significant risk in patients living 8 years or longer, and that this must be recognized in the management of young men with focal tumours and a longer life expectancy. This apparently higher progression rate with longer follow-up rekindled interest in the radical treatment of this condition. There are, however, three important points to note about this paper. The first is that it included patients with Gleason grades of 5–7, which many institutions would consider unsuitable for conservative management. The second is that if the study group as a whole is considered, then the progression rate is only 8.5% (8/94) and the death rate from carcinoma of the protate (including 2 patients with combined Gleason scores of 6 and 7) is 6.4% (6–94), but that there is also a 34.8% (27/94) risk of dying from a cause other than cancer in the same period. The last point is that of the 8 patients with progression, 6 died from their disease within 3.5–13 years after diagnosis. Also in 1986, Blute et al. reported their experience with a series of 15 men less than 60 years old with untreated "A1" disease who were at risk for more than 10 years [3]. Twenty-six percent (4/15) had disease progression 9–14 years after initial diagnosis. Three of these 4 patients had metastatic disease at the time of recurrence, but no patient had died from his disease. It should be noted that in their whole initial group, which included 8 patients upstaged to A2 after histological review, 30.4% (7/23) died from non-cancerous causes during the study period. These results tended to support the developing concept that there exists a higher risk of disease progression in patients with a longer life expectancy, but this is a small series and unfortunately the definition of A1 tumour (estimated volume of less than 1 ml) makes it difficult to compare the results with those of other series. In 1988 Lowe and Listrom published a paper analyzing the predictors of progression [29]. Because they have subdivided their patients according to grade, percentage of tumour and age, it is difficult to extract an average risk of progression for the focal group (less than 5% tumour and grade 1–4). The risk of progression at 10 years ranges from 6% (60-year-old) man with less than 1% involvement with a Gleason grade 2 to 3 tumour) to 36% (75-year-old man with 1–5% involvement with a Gleason grade 4 tumour). From a Kaplan-Meier curve of their group with cancer volume of 5% or less, the median time to progression was calculated as 17.5 years and the mean progression interval as 13.5 years. Unfortunately this group also includes 34 patients with larger volume tumour who had undergone attempted curative treatment. The fact that the Kaplan-Meier curves for grade <4 and volume extent $<5\%$ did not reach median time to progression, suggests that these 34 treated cases had an influence on progression within their "group 1". Thus, although not helpful in assessing the risk of progression for focal incidental carcinoma in general, Lowe and Listrom's paper does allow a better definition of this risk in any individual patient.

Three recent series have contributed further to the understanding of the prognosis of incidentally discovered focal carcinoma of the prostate. Thompson and Zeidman published a series of 60 patients with untreated focal disease and showed that of those at risk for greater than 7 years, 8% (3/37) had disease progression and all of these patients died from their disease [5]. During the study 57% (34/60) died from intercurrent illness. Roy et al. published in 1990 their series of patients followed for more than 10 years [41]. Sixteen percent (3/19) had disease progression, but none died a tumour-related death, while 63% (12/19) died from a cause other than cancer during the study period. In a further recent study, Zhang and co-workers reviewed 132 patients with "A1" carcinoma of the prostate with a mean follow-up of 8.2 years. Ten per cent of the patients followed for more than 5 years had progression of the disease, but none of these died from their cancer [59]. By extrapolating from these series and those of Blute et al. and Epstein et al., one can estimate that there is approximately a 10%–15% chance of progression of a focal low-grade incidental prostatic carcinoma at 10 years after diagnosis. Further, the risk of dying from such a carcinoma is probably 5% or less, while at the same time the risk of dying from an intercurrent illness is between 30% and 63%.

One further important point should be made about these studies on the natural history of untreated focal carcinoma, and that is that these are historical studies, many of which began over 20 years ago. As such, the follow-up for most of these patients would have been by

digital rectal examination, prostatic acid phosphatase and bone scan. The former is notoriously insensitive in this situation and the latter two can only detect metastasized malignancy. This may explain why so many of the patients that progressed did so with metastases and died of their disease. It is reasonable to expect a better detection of local progression with the use of modern aids such as prostatic specific antigen (PSA), transrectal ultrasound (TRUS) and systematically directed random biopsies. The impact of such monitoring is seen in the series of Zhang et al. [59], in which patients in the later part of their follow-up received all of these modalities. In 10 of the 13 patients whose cancers progressed, progression was local and the patients were able to be treated by radical means; 9 of these patients remain alive with no evidence of disease. Therefore, in the future we may well see an increase in the detected progression rate, but a decrease in the death rate, from focal disease.

From all of the above studies it is obvious that some patients with focal cancer have progression, but also that the majority do not. Although Whitmore's classical model for disease progression in prostatic carcinoma allows for development of metastatic disease directly from stage A disease [57], this event must be extremely rare. McNeal has shown that extraprostatic invasion and metastatic dissemination are a product of size and differentiation, with 1 ml being the volume of tumour probably required before the development of metastases [31]. Using this model, the assumption must be made that clinical progression of disease in focal cancer must arise from one of two sources. The first is the possibility of a sampling error, in that unrecognized tumour of greater volume and poorer differentiation remains undetected by the original prostatectomy. The other possibility is that the focal and well-differentiated tumour undergoes an "event" that causes it to grow in size and become more poorly differentiated.

There is evidence from three sources that such a change takes place in some, but not in all patients. Firstly, there is now considerable evidence to suggest that dedifferentiation of prostate cancer occurs [2, 4, 12]. Further indirect evidence for this event comes from the fact that the histology of radically removed prostates rarely differs from that of the cancer diagnosed at TURP, and that conversely, in Epstein's series, the histology on progression was that of intermediate or high grade tumour, whereas in the original specimen it had been low [17]. Evidence that many tumours remain dormant comes from the studies where focal tumour has been treated by radical prostatectomy. Between 83% and 92% of the radically removed specimens still have tumour present [16, 18, 40], but only 10–15% will progress within 10 years. A possible explanation as to why not all tumours progress comes from comparative data between Japanese and American men. While the Japanese men have a similar incidence of incidental [58] and histologically diagnosed prostatic cancer [10], they have a much lower incidence of clinical cancer in their own country. Furthermore, when they migrate to a high-incidence area they experience an increase in clinical cancer to a rate approaching that in the indigenous population [10]. This suggests that there may be external factors influencing the progression of focal incidental cancer to clinical disease.

Thus to summarize, the natural history of focal well-differentiated carcinoma of the prostate is largely one of a biologically benign disease, but in a small number of patients the disease has the potential to progress, and, historically, such progression has often been first detected at a stage when it has already metastasized.

Management of focal carcinoma of the prostate

Management of focal carcinoma of the prostate has included hormonal treatment, radiotherapy, radical prostatectomy and a conservative policy of observation alone.

Initially, most occult carcinoma of the prostate was treated either by radical local or hormonal treatment, but as it became apparent that the life expectancy of the group as a whole was as good as for the general population, and that this applied to both the treated and unteated groups, a more conservative approach was adopted. Two factors have rekindled interest in this condition. The first is that there are still cancer deaths amongst this group, and the second is that it appears that a longer life expectancy increases the chance of a clinical recurrence, or death from the disease. Therefore, authors have recently called for a reconsideration of the role of definitive treatment in the small subgroup of patients who are younger and have a longer life expectancy [17, 40, 41].

There is no doubt that the clinical course of focal carcinoma of the prostate can be influenced by radical treatment. In six series where these patients have been treated by radical prostatectomy there are only two recorded clinical recurrences, and in one of these the original differentiation is uncertain [7, 28, 34, 39, 43, 60]. Very little is known about the effect of radiotherapy on this focal, well-differentiated disease, but Kaplan et al., in a small series, had a 14% (3/22) recurrence rate in their "A1" patients treated by external beam radiotherapy, suggesting that this form of treatment may not be so effective in focal disease [26].

Hormonal treatment has never been shown to influence the clinical progression of incidentally discovered disease. Indeed in one study the actuarial survival of patients treated by stilboestrol was considerably worsened compared with placebo-treated patients in the control arm [20].

Although there is a paucity of information on treatment of this focal disease, it seems from the above data that radical prostatectomy is the treatment of choice. In offering such radical treatment it is important to remember that 8–17% of the patients will be rendered disease-free by TURP and will require no further treatment, and that even in Blute's series of patient less than 60 years age, 30% died progression-free during the period of observation, none of whom would have had any benefit from a radical procedure [3]. Therefore, one might expect that even in these younger patients with a predicted longer life expectancy, between 36% and 42% will definitely gain no benefit from radical treatment and that, according to current literature, only 10%–15% can be expected to have

disease progression at 10 years and therefore could "potentially" benefit from such treatment. Further, in offering radical treatment it should be kept in mind that at diagnosis it is very difficult to predict either those with a longer life expectancy or those in whom progression is going to occur. A further confounding influence in this decision is that Lowe and Listrom have shown increasing age to be associated with increasing risk of progression [29]. Therefore, while older men have a decreased life expectancy, they also have an increased risk within that decreased life expectancy, suggesting that it is not just the younger patients who are at risk of disease progression within their individual lifetimes.

The alternative to attempted curative treatment is to follow a conservative policy of observation and follow-up. The aim of such a policy would be to define any parameters early that would place the patient at increased risk of progression, and to detect any such progression at an organ-confined stage, leading to the selective use of radical treatment. Against such a policy is the observation in many series that patients with progression often have metastatic disease, and therefore a very poor prognosis, at the time of first evidence of progression. Although as yet unproven, it is very likely that modern diagnostic modalities will allow the earlier detection of local progression, before metastatic spread has occurred, and therefore give these patients a better prognosis. Any conservative policy must be both diligent and vigilant and must attempt to define as early as possible the small group that should be considered for radical therapy. This should be in two stages. The first is to restage the prostate after TURP in an attempt to detect possible errors to understaging. The second is to adopt a stringent follow-up policy aimed at detecting the development of progression as demonstrated by increased volume or grade in any residual tumour within the gland.

Modalities in the follow-up of focal prostatic carcinoma

A technique often promoted in the follow-up of A1 disease is the second-look TURP. The principle of this is to perform a second TURP within 3 months of the first to try and exclude sampling errors from the first procedure. For second-look TURP to be successful in staging the incidental carcinomas it should accurately reflect the findings in the residual gland, as shown by radical prostatectomy specimens. This is not the case, as is graphically demonstrated by the 70–82% of second-look TURPs that show no residual tumour [5, 8, 37, 59] compared with the 83%–92% of radically removed specimens that do have residual tumour [16, 18, 40]. Furthermore, only 4–20% of focal cancers are upstaged on second-look TURP [5, 8, 37, 53] compared with 13–69% on radical prostatectomy [16, 27, 37, 40]. It is therefore obvious that second-look TURP understages incidental carcinomas of the prostate. In his morphometric analysis of residual tumour in radically resected focal carcinomas, Epstein showed that much of the residual was at either the apex or periphery of the gland, particularly anteriorly [16]. McNeal supports the finding of a predominance of residual tumour anteriorly and peripherally by his own morphometric studies [32]. Further, Greene et al. found 67% of residual tissue in radical specimens lay beyond the verumontanum [18]. These are the potentially most difficult areas to assess by repeat TURP, and may explain the understaging that exists with this procedure.

Given the high incidence of understaging compared with radical specimens, the low incidence of upstaging, and the potential risk of making a subsequent radical operation harder, it is difficult to justify the routine use of second-look TURP in the further staging of focal carcinoma of the prostate, except, perhaps, in the situation where there is obviously a large amount of adenoma remaining. Paradoxically, both Lowe and Zhang showed that the risk of progression in non-treated patients was higher where residual tumour had been demonstrated in a second-look TURP [29, 59]. This probably reflects a larger total volume of tumour in these patients, which could presumably be detected by other biopsy techniques.

Although repeat TURP seems not to be useful in the management of this condition, needle biopsy may be. The peripheral zone of the prostate is ideally suited for transrectal ultrasonically guided biopsies. Ultrasonically guided biopsy of the prostate proved superior to digitally directed biopsy in a series by Hodge et al. in digitally suspicious glands [21]. They felt that the results could be further improved by the additional use of random systematic biopsies [22]. The ability of random systematic biopsies to detect unsuspected carcinomas in clinically non-suspicious prostates has recently been elucidated further. Vallancien et al. found that in 100 men with no suspicion of cancer on digital rectal examination, systematic biopsies detected 14 cancers, whereas biopsies of hypoechoic lesions demonstrated only 2 [52]. In a small number of patients with incidentally found prostatic cancer, Terris et al. modified their normal systematic biopsy technique (three biopsies on each side) by the addition of an additional four biopsies of the transitional zone. They detected substantial residual cancer in 47% of their patients with an incidentally discovered carcinoma, and in those that came to radical prostatectomy, histological examination revealed that patients identified by the modified biopsy technique had a mean residual cancer volume of 3.56 ml compared with 0.48 ml in patients with negative biopsies [50]. It is interesting to note that they only considered biopsies where there was a focus of greater than 3 mm as being positive. Systematically directed random biopsies can, therefore, not only access more easily the more peripheral parts of the gland, which are relatively inaccessible to TURP, but may also provide better histological information as to the extent of residual tumour. This may be particularly important in the case where the tumour detected by TURP is of peripheral zone origin and just the "tip of the iceberg" has been sampled.

The role of transrectal ultrasound (TRUS) in the detection of prostatic cancer has received increasing attention in recent years. While generally accepted as being poor in detecting focal carcinoma of the prostate, it may well have a role in the restaging and follow-up of these patients. A small series by Parra and Gregory detected both glands with residual tumour of greater than

1 cm when TRUS was performed 2 weeks after the initial operative procedure. These were identified by hypoechoic lesions in the peripheral zone [38]. Two recent series comparing TRUS after TURP with the radically removed specimen have further addressed the role of ultrasound in the identification of residual tumour after TURP. Egawa et al. detected 83% of residual cancers of more than 1.0 ml, 14% of cancers between 0.1 and 1.0 ml, and no cancers less than 0.1 ml in volume. Furthermore, their non-detected tumours had a lower Gleason sum (5.3 vs 6.1), and lower incidence of capsular extension (2% vs 20%) and seminal vesicle invasion (1% vs 20%) than those tumours detected as hypoechoic lesions by TRUS [15]. Terris et al. were not able to demonstrate a difference in mean cancer volume between their ultrasonically identified and non-identified residual tumours. They did not address grade, capsular penetration or seminal vesicle invasion [50]. Thus, while still not clear cut, there is some evidence that TRUS is capable of detecting many larger and more poorly differentiated tumours while not detecting the smaller and clinically insignificant residual cancers. TRUS is also potentially useful for looking at changes within a gland, or in the size of a gland, on a longitudinal follow-up. There is currently no literature on this topic. The final potential usefulness of TRUS in the follow-up of focal carcinoma of the prostate is as a guide to random systematic biopsies, if these are performed.

Prostatic specific antigen (PSA) is a prostate-specific tissue marker, but unfortunately not carcinoma-specific, being elevated in many benign conditions. Like TRUS it is insufficiently specific to be useful in the diagnosis of focal disease, but may well be of use in the assessment of such disease after initial prostatectomy. Carter et al. found that after TURP, which theoretically removed most of the benign component contributing to PSA levels, all patients with a post-operative PSA of 1 ng/ml or less had residual tumour volume of less than 0.5 ml, while all those with >10 ng/ml had a volume of greater than 0.5 ml [9]. Similarly, Voges (using the Yang kit) reported that 7 of 8 patients with a PSA of 1 ng/ml or less had residual cancer of 0.4 ml or less, while of those with PSA >2.5 ng/ml, 19 of 20 had a residual tumour volume of more than 0.9 ml [54]. The relationship of post-operative PSA to residual tumour volume was also demonstrated by Hudson et al., when they found that 15 patients with a PSA level between 0.6 and 3.5 ng/ml had no elevation of PSA or evidence of progression over a follow-up period of 15–120 months [23]. As the volume of malignancy has a relationship with serum PSA [58], then it could also be predicted that, in the absence of significant residual adenoma, an elevated PSA level after TURP would probably represent significant residual disease and that a rising PSA as a product of time would represent increasing local disease, prompting repeat biopsy and possible definitive treatment.

Digital rectal examination (DRE) cannot by definition, detect incidental carcinoma of the prostate. The high rate of metastatic disease as first evidence of recurrence in the follow-up of these patients also suggests that it is a very insensitive and late predictor of recurrence.

There is little information on the use of intracellular prognostic indicators, other than grading, in the follow-up of focal disease. However, in a small paper from McIntire et al., flow cytometry was able to predict progression accurately in 11 focal cancers [30], and ploidy has been shown to correlate with both progression and prognosis in untreated prostatic cancer patients [1, 2]. While it is too optimistic to hope that any one of the various intracellular parameters will reliably predict all patients whose disease will progress, in combination with the follow-up techniques mentioned above they may prove helpful in identifying those most at risk and therefore most likely to benefit from radical treatment.

Thus, a conservative management policy in this condition must include two stages. The first is to assess any possible staging error after TURP, such as significant volume of residual tumour, or tumour of worse grade. A combination of PSA, transrectal ultrasound and ultrasonically guided prostatic biopsies is probably the best way to achieve this. If such errors are excluded, then the second stage of a conservative management policy must be to attempt to detect early any signs of cancer progression within the gland which would prompt a reconsideration of radical treatment. A rational approach to this would be to perform serial digital rectal examinations, PSA determinations and ultrasonic studies, and to use a change in these as the indication for further biopsies.

Conclusion

There are several differing definitions for low-volume, low-grade incidentally discovered tumour. These all attempt to separate the clinically less significant focal disease from the more active diffuse disease. The incidence of the disease is proportional to the amount of tissue sampled, which may have important clinical implications in the younger population having a benign prostatectomy. Although the majority of patients will have no further problem with their disease, there is a small subgroup who are indeed at increased risk. The treatment options in these patients are either radical therapy or an expectant policy of close follow-up. In most patients radical prostatectomy is curative at this stage, but the majority would be treated unnecessarily. Conversely, there is a risk with expectant policies that any disease progression may be beyond radical treatment at the time of diagnosis. Therefore any such policy must be stringent and should probably include physical examination, transurethral ultrasound, prostatic specific antigen and liberal use of prostatic biopsies, looking for a change in either size or differentiation of the tumour.

References

1. Adolfsson J, Ronstrom L, Hedlund P, Lowhagen T, Carstensen J, Tribukait B (1990) The prognostic value of modal deoxyribonucleic acid in low grade, low stage untreated prostate cancer. J Urol 144:1404
2. Adolfsson J, Tribukait B (1990) Evaluation of tumour progression by repeated fine needle biopsies in prostate adenocarcinoma: modal deoxyribonucleic acid value and cytological differentiation. J Urol 144:1408

3. Blute M, Zincke H, Farrow GM (1986) Long-term follow-up of young patients with stage A adenocarcinoma of the prostate. J Urol 136:840
4. Brawn PN (1983) The dedifferentiation of prostate carcinoma. Cancer 52:246
5. Bridges CH, Belville WD, Insalaco SJ, Buck AS (1983) Stage A prostatic carcinoma and repeat transurethral resection: a reappraisal 5 years later. J Urol 120:307
6. Byar DP and The Veterans Administration Cooperative Urological Research Group (1972) Survival of patients with incidentally found microscopic cancer of the prostate: results of a clinical trial of conservative treatment. J Urol 108:908
7. Byar DP, Corle DK and The Veterans Administration Cooperative Urological Research Group (1981) VACURG randomised trial of radical prostatectomy for stages 1 and 2 prostate cancer. Urology 17 [Suppl] 7
8. Carroll PR, Leitner TC, Yen B, Watson RA, Williams RD (1985) Incidental carcinoma of the prostate: significance of staging transurethral resection. J Urol 133:811
9. Carter HB, Partin AW, Epstein JI, Chan DW, Walsh PC (1990) The relationship of prostate specific antigen levels and residual tumour volume in stage A prostate cancer. J Urol 144:1167
10. Carter HB, Piantadosi S, Isaacs JT (1990) Clinical evidence for and implications of the multistep development of prostate cancer. J Urol 143:742
11. Correa RJ, Anderson RG, Gibbons RP, Mason JT (1974) Latent carcinoma of the prostate: why the controversy? J Urol 111:644
12. Cumming JA, Ritchie AWS, Goodman CM, McIntyre MA, Chisholm GD (1990) Dedifferentiation with time in prostate cancer and the influence of treatment on the course of the disease. Br J Urol 65:271
13. Denton SE, Choy SH, Valk WL (1965) Occult prostatic carcinoma diagnosed by the step section technique of the surgical specimen. J Urol 93:296
14. Donohue RE, Mani JH, Whitesel JA et al. (1982) Pelvic lymph node dissection: guide to patient management in clinically locally confined adenocarcinoma of the prostate. Urology 20:559
15. Egawa S, Greene DR, Flanagan WF, Wheeler TM, Scardino PT (1991) Transurethral ultrasonography in stage A prostate cancer: detection of residual tumour after transurethral resection of the prostate. J Urol 146:366
16. Epstein JI, Oesterling JE, Walsh PC (1988) The volume and anatomical location of residual tumour in radical prostatectomy specimens removed for stage A1 prostate cancer. J Urol 139:975
17. Epstein JI, Paull G, Eggelston JC, Walsh PC (1986) Prognosis of untreated stage A1 prostatic carcinoma: a study of 94 cases with extended follow-up. J Urol 136:837
18. Greene DR, Egawa S, Neerhut G, Flanagan TM, Wheeler TM, Scardino PT (1991) The distribution of residual cancer in radical prostatectomy specimens in stage A prostatic cancer. J Urol 145:324
19. Hanash KA, Utz DC, Cook EN, Taylor WF, Titus JL (1972) Carcinoma of the prostate: a 15 year follow-up. J Urol 107:450
20. Heaney JA, Chang HC, Daly JJ, Prout GR Jr (1977) Prognosis of clinically undiagosed prostatic carcinoma and the influence of endocrine therapy. J Urol 118:283
21. Hodge KK, McNeal JE, Stamey TA (1989) Ultrasound guided transrectal core biopsies of the palpably abnormal prostate. J Urol 142:66
22. Hodge KK, McNeal JE, Terris MK, Stamey TA (1989) Random systematic versus directed ultrasound guided transrectal core biopsies of the prostate. J Urol 142:71
23. Hudson MA, Bahnson RA, Catalona WJ (1989) Clinical use of prostate specific antigen in patients with prostate cancer. J Urol 142:1011
24. Humphrey P, Vollmer RT (1988) The ratio of prostate chips with cancer: a new measure of tumour extent and its relationship to grade and prognosis. Hum Pathol 19:411
25. Jewett HJ (1975) The present status of radical prostatectomy for stages A and B prostatic cancer. Urol Clin North Am 2:105
26. Kaplan ID, Bagshaw MA, Cox CA, Cox RS (1991) Radiotherapy for incidental adenocarcinoma of the prostate. In: Altwein JE, Faul P, Schneider W (eds) Incidental carcinoma of the prostate. Springer, Berlin Heidelberg New York, p 167
27. Larsen MP, Carter HB, Epstein JI (1991) Can stage A1 tumour extent be predicted by transurethral resection tumour volume, percent or grade? A study of 64 stage A1 radical prostatectomies with comparison to prostates removed for stages A2 and B disease. J Urol 146:1059
28. Lehman TH, Kirchheim D, Braun E, Moore R (1968) An evaluation of radical prostatectomy for incidentally diagnosed carcinoma of the prostate. J Urol 99:646
29. Lowe BA, Listrom MB (1988) Incidental carcinoma of the prostate: an analysis of the predictors of progression. J Urol 140:1340
30. McIntyre TL, Murphy WM, Coon JS et al. (1988) The prognositic value of DNA ploidy combined with histologic substaging for incidental carcinoma of the prostate gland. Am J Clin Pathol 89:370
31. McNeal JE, Bostwick DG, Kindrachuk RA, Redwine EA, Freiha FS, Stamey TA (1986) Patterns of progression in prostate cancer. Lancet I:60
32. McNeal JE, Price HM, Redwine EA, Freiha FS, Stamey TA (1988) Stage A versus stage B adenocarcinoma of the prostate: morphological comparison and biological significance. J Urol 139:61
33. Moore GH, Lawshe B, Murphy J (1986) Diagnosis of adenocarcinoma in transurethral resectates of the prostate gland. Am J Surg Pathol 10:165
34. Morton RA, Steiner MS, Walsh PC (1991) Cancer control following anatomical radical prostatectomy: an interim report. J Urol 145:1197
35. Mostofi FK (1986) Prostate sampling. Am J Surg Pathol 10:175
36. Murphy WM, Dean PJ, Brasfield JA, Tatum L (1986) Incidental carcinoma of the prostate: how much sampling is adequate? Am J Surg Pathol 10:170
37. Parfitt HE, Smith JA, Gleidman JB, Middelton RG (1983) Accuracy of staging in A1 carcinoma of the prostate. Cancer 51:2346
38. Parra RO, Gregory JG (1989) Transrectal ultrasound in stage A1 prostate carcinoma. Urology 34:344
39. Paulson DF (1991) Does detection of small-volume prostatic adenocarcinoma by ultrasound or magnetic resonance imaging provide improvement in disease control? In: Altwein JE, Faul P, Schneider W (eds) Incidental carcinoma of the prostate. Springer, Berlin Heidelberg New York, p 140
40. Paulson DF, Robertson JE, Daubert LM, Walther PJ (1988) Radical prostatectomy in stage A prostatic adenocarcinoma. J Urol 140:535
41. Roy CR, Horne D, Raife M, Pienkos E (1990) Incidental carcinoma of the prostate: long term follow-up. Urology 36:210
42. Schmidt JD, Mettlin CJ, Natarajan N et al. (1986) Trends in patterns of care for prostatic cancer, 1974–1983: results of surveys by the American College of Surgeons. J Urol 136:416
43. Schroeder FH, Blom JHM, Hop WCJ, Mostofi FK (1983) Incidental carcinoma of the prostate treated by total prostatectomy: the prognostic impact of microscopic tumour extension and grade. World J Urol 1:15
44. Schroeder FH, Hermaneck P, Denis L, Fair WR (1992) The TNM classification of prostate cancer. Prostate [Suppl 4]:129
45. Sheldon CA, Williams RD, Fraley EE (1980) Incidental carcinoma of the prostate: a review of the literature and critical reappraisal of classification. J Urol 124:626
46. Silverberg E, Boring CC, Squires TS (1990) Cancer statistics, 1990. CA 40:9
47. Silverberg E, Lubera JA (1986) A review of the American Cancer Society: estimates of cancer cases and deaths. CA 36:9
48. Stamey TA, Kabalin JN, McNeal JE et al. (1989) Prostate specific antigen in the diagnosis and treatment of adenocarcinoma of the prostate. II. Radical prostatectomy treated patients. J Urol 141:1076

49. Svanholm H, Starklint H, Barlebo H, Olsen S (1990) Histological evaluation of prostatic cancer. III. Reproducibility of assessment of tumour volume and its possible significance for prognosis. APMIS 98:237
50. Terris MK, McNeal JE, Stamey TA (1992) Transrectal ultrasound imaging and ultrasound guided biopsies in the detection of residual carcinoma in clinical stage A carcinoma of the prostate. J Urol 147:864
51. Thompson IA, Zeidman EJ (1989) Extended follow-up of stage A1 carcinoma of the prostate. Urology 33:455
52. Vallancien G, Prapotnich D, Veillon B, Brisset JM, Andre-Bougaran J (1991) Systematic prostatic biopsies in 100 men with no suspicion of cancer on digital rectal examination. J Urol 146:1308
53. Vicente J, Chechile G, Algaba F (1989) The role of repeat transurethral resection in stage A1 carcinoma of the prostate. Eur Urol 16:325
54. Voges GE, McNeal JE, Redwine EA, Freiha FS, Stamey TA (1992) The predictive significance of substaging stage A prostate cancer (A1 versus A2) for volume and grade of total cancer in the prostate. J Urol 147:858
55. Vollmer RT (1986) Prostate cancer and chip specimens: complete versus partial sampling. Hum Pathol 17:285
56. Whitmore WF Jr (1956) Symposium on hormones and cancer therapy: hormone therapy in prostatic cancer. Am J Med 21:697
57. Whitmore WF (1990) Natural history of low-stage prostatic cancer and the impact of early detection. Urol Clin North Am 17:689
58. Yamabe H, ten Kate FJW, Gallee MPW et al. (1986) Stage A prostate cancer: a comparative study in Japan and the Netherlands. World J Urol 4:136
59. Zhang G, Wasserman NF, Sidi AA, Reinberg Y, Reddy PK (1991) Long-term follow-up results after expectant management of stage A1 prostatic cancer. J Urol 146:99
60. Zincke H, Blute ML, Fallen MJ, Farrow GM (1991) Radical prostatectomy for stage A adenocarcinoma of the prostate: staging errors and their implications for treatment recommendations and disease outcome. J Urol 146:1053