

Six-Year Follow-Up of Untreated T1 Carcinoma of Prostate

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Abstract

Introduction: The management of T1 carcinoma of prostate remains controversial and the critical role of histopathology is often underestimated. **Materials and Methods:** A retrospective review was conducted on 27 cases of T1 prostate carcinoma diagnosed between 1980 and 1992, all of which were managed on a surveillance programme. Pathological material of 24 cases was available for re-examination by a single histopathologist without prior knowledge of the originally assigned grade. Gleason's scoring system was used in the current review. **Results:** Twenty-two (81.5%) were T1a and 5 (18.5%) T1b. Mean duration of follow-up was 77.3 months (1.0 to 159.0) and median age was 72.0 years (61.0 to 84.0). Twenty-five (92.6%) were originally graded as well differentiated, 1 (3.7%) was moderately differentiated and 1 (3.7%) was poorly differentiated. Three of the well-differentiated tumours were upstaged because of tumour volume. On review, differences in grading were noted in 13 cases (54.2%) and 11 (45.8%) were, as a consequence, upstaged. Progression was recorded in 5 cases (18.5%). Mean disease-free interval was 47.6 months (7.0 to 75.0) and mean serum PSA at progression was 34.2 ug/l (2.3 to 62.5). Four responded to delayed therapy. Mortality was recorded in 13 cases (48.1%) but cancer-specific mortality was only 7.7% (1/13). Mean age at death was 78.1 years. **Conclusion:** The importance of accurate grading and staging cannot be overemphasised given its pivotal role in subsequent management. The impact of age is also apparent and surveillance appears a reasonable option for those with limited life expectancy after diagnosis.

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Key words: Carcinoma, Gleason's, Prostate, Surveillance

Introduction

It is well known that T1 carcinoma of the prostate has varying biologic behaviour. Attempts to identify those at higher risk of progression have led to the subclassification into T1a (focal, low grade) and T1b (diffuse, high grade). It has been argued that T1a carcinoma of the prostate can be managed expectantly because of its long indolent natural history coupled with low rates of morbidity and mortality.^{1,2} The low-volume and low-grade status render the tumour clinically insignificant and these studies had confirmed the innocuous nature of T1a tumours. However, recent publications with extended follow-up suggest a higher than expected rate of progression and that definitive curative therapies may be more appropriate especially for younger healthy patients with life expectancy exceeding 10 years.^{3,4} Furthermore, the subclassification of T1 tumour is based largely on histopathologic findings. Its significance on subsequent management cannot be underestimated. This study focused on the outcome as well as the impact of histopathologic findings on patients with untreated carcinoma of the prostate who had extended follow-up.

Materials and Methods

Cases were culled from the department's tumour register from 1980 to 1992. T1 carcinoma of the prostate is defined as clinically non-palpable tumour diagnosed on histology after transurethral resection of the prostate (TURP) for benign prostatic hyperplasia (BPH). Our institution defines T1a as well-differentiated tumour involving less than 5% of resected prostatic chips. Additionally, all patients must have negative radionuclide bone scans. Those with suspicious DRE or positive / equivocal bone scans were excluded from the study. Other staging modalities such as computed tomograms of the pelvis, repeat TURP or post-TURP prostatic biopsy were not employed. Serum prostate-specific antigen (PSA) levels and transrectal ultrasound of the prostate (TRUS) were not available to the patients at the time of diagnosis. Follow-up information was obtained via patient visits, telephone interviews and the Singapore Cancer Registry. Follow-up assessment included routine DRE and serum PSA levels, when it became available, was conducted at intervals of 6 months to 1 year. TRUS biopsies and bone scans were performed where indicated.

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All pathological, clinical and biochemical records were examined. Pathological review consisted of retrieving all haematoxylin and eosin stained slides of the patients' TURP biopsies, restaining them when they had faded, regrading (Gleason's) and restaging them. A single pathologist with an interest in uro-pathology performed the regrading, without prior knowledge of the original assigned grade. Any subsequent biopsy material was also reviewed. At least 4 blocks of prostatic chips were routinely processed for histology; with all the chips submitted for evaluation if they filled 4 tissue cassettes or less.

Those with clinical and/or biochemical failure were deemed to have progressed. Local progression was defined as abnormal DRE with histologically proven upstaging to moderately or poorly differentiated carcinomas. Bony metastases had to be demonstrable on a positive bone scan. A history of bone pain with a negative bone scan was not accepted as evidence of metastases. A rising serum PSA trend indicated biochemical failure.

Results

During a 12-year period from 1980 to 1992, our institution managed 27 cases of T1 carcinoma of the prostate on a surveillance programme. Mean duration of follow-up was 77.3 months (range 1.0 to 159.0). Age at diagnosis ranged from 61.0 to 84.0 years (mean 72.4, median 72.0). Thirteen (48.1%) presented with lower urinary tract symptoms and 12 (44.4%) with acute retention of urine. All but 1 (96.3%) were Chinese.

Of these 27 cases, 22 (81.5%) were staged as T1a and 5 (18.5%) T1b. Our institution defined T1a as well-differentiated tumour involving less than 5% of resected prostatic chips. Twenty-five (92.6%) were originally graded as well differentiated, 1 (3.7%) was moderately differentiated and 1 (3.7%) was poorly differentiated. Three of the well-differentiated tumours were upstaged because of tumour volume.

The original slides/paraffin blocks of 24 cases were available for re-examination. In 3 cases, both the slides and paraffin blocks could not be retrieved. The number of

blocks of prostatic chips processed for histologic examination ranged from 1 to 19 (mean, median 4). There were 10 cases in which all the prostatic chips were processed for histological examination as they filled less than 4 blocks. Four blocks were examined in 9 cases; while in 5 cases, more than 4 blocks of chips were studied as the reporting pathologist submitted all the tissue for evaluation. Table I summarises the grading of the original and current histological review. Out of the 22 that were initially labelled as well differentiated, 12 (54.5%) were upgraded and 1 reread as ductal carcinoma. The single case of poorly-differentiated adenocarcinoma was regraded as moderately differentiated (Gleason's 3+2).

Table II summarises the impact of the current regrading on the stage of the cancer. Of the 13 cases that were regraded, 11 T1a cases were upstaged to T1b. The other 2 were originally T1b and the stage remained unchanged. One had tumour volume exceeding 5% and the other was down-graded from poorly-differentiated tumour to Gleason's 3+2.

Overall progression rate was 18.5% (5/27); with 18.1% (4/22) and 20.0% (1/5) for T1a and T1b, respectively. All who progressed were well-differentiated tumours, of which 4 were T1a. The fifth was staged as T1b due to tumour involvement of greater than 5%. The original histological material of 3 of these cases were available for review and 2 were regraded as moderately differentiated (Gleason's 3+4 and 3+2 respectively).

Table III summarises the clinical course of those who progressed. Mean duration to progression was 47.6 months (range 7.0 to 75.0). All had clinical failure with all developing abnormal DRE. Three were upstaged histologically following subsequent TRUS biopsy or TURP. One was negative despite two attempts of TRUS biopsies but showed a steadily rising PSA trend and bone scan was positive 3 years after initial detection of abnormal DRE. One had a positive bone scan at the time of detection of abnormal DRE and histological proof for local progression was deemed unnecessary.

TABLE I: COMPARISON BETWEEN ORIGINAL HISTOLOGIC GRADE AND CURRENT REVIEW

Original histology	No.	Regrading (Gleason's)	No.
Well differentiated	22	≤4	9
		5-7	12
		Ductal	1
Moderately differentiated	1	7	1
Poorly differentiated	1	5	1
Total	24		24

TABLE II: IMPACT OF CHANGE IN STAGE FOLLOWING REGRADING

Grade	Original		Restaging	
	T1a	T1b	T1a	T1b
Well differentiated/ Gleason's 2-4	19	3	10	—
Moderately differentiated/ Gleason's 5-7	—	1	—	14
Poorly differentiated/ Gleason's 8-10	—	1	—	—
Total	24		24	

Four had bony metastases with positive bone scans. Biochemical failure was observed in all 5 patients with serum PSA at progression ranging from 12.3 to 62.5 ug/l (mean 34.2).

Delayed therapies were instituted at progression. One patient underwent local external beam irradiation with an intention to cure. He remained alive with no clinical evidence of disease after 66 months from initial diagnosis. Palliative options were offered to the other 4 and they included orchidectomy (2), oral hormonal manipulation (3), repeat TURP (2) and palliative irradiation (1). Three responded with each having his serum PSA decreasing to 0.1 ug/l. The remaining patient, despite surgical orchidectomy, died of prostatic carcinoma 44.0 months after initial diagnosis. He was 81.7 years old then. Long-term follow-up showed that another subsequently died of an unrelated cause at age 80.2 years after 74.0 months of follow-up. One had stable disease and remained alive at 76 months follow-up. The last was well with no clinical evidence of disease at 76.5 months.

Progression-free survival was 74 months (range 1.0 to 159.0). Mean age of this group of patients at diagnosis was 73.0 years (range 61.0 to 84.0). Twelve died from unrelated causes. Death occurred at 50.5 months (range 1.0 to 112.0) after diagnosis and mean age at death was 78.1 years (range 69.3 to 90.7). Overall mortality was 48.1% (13/27) and cancer-specific mortality was 7.7% (1/13). This was the only case where the cause of death was directly attributable to prostatic carcinoma.

Discussion

Following Franks⁵ publication on the incidental finding of carcinoma of prostate in autopsies, controversies have

dogged the management of incidental carcinoma of the prostate. It has been found that not all T1 tumours behave innocuously. Attempts have been made to subclassify T1 tumours into T1a and T1b, whereby T1b tumours are deemed to have a higher risk of progression and thus warrant more aggressive therapy.^{1,2} However, controversies remain with regard to the optimal management for this group of patients.

As with any histologic grading system, a certain degree of individual subjectivity exists. The Gleason's system, however, is generally regarded as reproducible and readily learnt.⁶ As one of the distinguishing features between T1a and T1b tumours is histologic grade, the importance of accurate grading cannot be overemphasised. The discrepancy observed between the original assigned grade and the current review can be partially attributed to the fact that the Gleason's grading system was not universally espoused nor regularly applied in the earlier biopsies (Fig. 1). It is currently the norm, however, that all prostatic carcinomas are accorded a Gleason's grade and score in our institution.

Recommendations for optimal sampling of prostatic chips obtained from TURP specimens have been proposed, with McDowell et al⁷ advocating initial evaluation of 8 cassettes/blocks of chips, which is thought to be able to identify all T1b and about 90% of T1a cancers, and to process the remaining chips if a T1a cancer is found because of the potential of upstaging.⁸ In our study, all chips were examined in 15 cases; although admittedly, we were unable to fully optimise the number of blocks or proportion of chips examined, this being a retrospective review.

Theoretically, we can restage the 24 cases whose tissue

TABLE III: SUMMARY OF CASES THAT PROGRESSED

Case no.	Stage	Grade	Age (y)	Disease-free interval (months)	PSA at progression (ug/l)	DRE	Metastases	Treatment	Status	Age at last follow-up (years)	Regrading (Gleason's)
1	T1a	Well differentiated	72	43.0	40.8	Abnormal	Bone	Radiotherapy Orchidectomy	Dead at 74 months	80.2	Not available
2	T1a	Well differentiated	71	66.0	9.1	Abnormal	Nil	Radiotherapy	Alive (NED) at 66 months	76.5	Not available
3	T1a	Well differentiated	61	75.0	62.5	Abnormal	Bone	Radiotherapy Hormones	Alive (NED) at 75 months	67.3	2+2
4	T1a	Well differentiated	78	7.0	44.9	Abnormal	Bone	Radiotherapy Orchidectomy	Dead at 44 months	81.7	3+4
5	T1b	Well differentiated	70	47.0	13.6	Abnormal	Bone	Hormones	Alive with disease at 76 months	76.3	3+2

DRE: digital rectal examination

NED: no evidence of disease

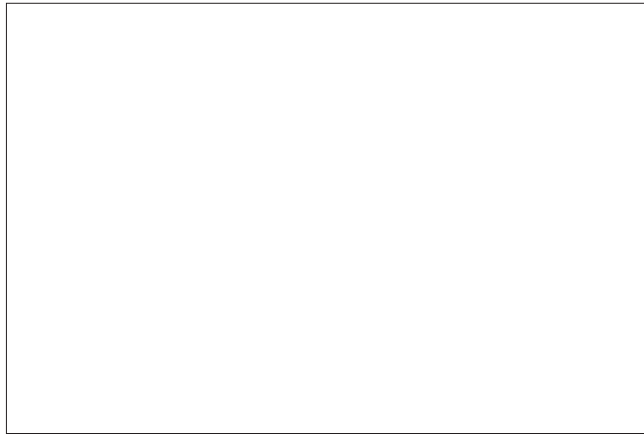


Fig.1. Prostatic adenocarcinoma that was initially labelled as well differentiated, but histologic review revealed fused acini (upper field) corresponding to Gleason's pattern 4, juxtaposed to more discrete malignant glands of Gleason's grade 3 (lower field) (Haematoxylin and eosin, original magnification $\times 100$).

specimens were available for regrading. Ten would have been staged as T1a and 14 as T1b. The new overall progression would have been 12.5% (3/24); with 10.0% (1/10) for T1a 14.3% (2/14) for T1b, respectively. These

figures are comparable with current literature.⁹ Presumably more aggressive therapy would have been offered to those upstaged to T1b rather than managing them on surveillance.

However, Table IV, which is a summary of the 13 cases that were regraded, shows that 10 of the newly upstaged cases did not progress. Two of them who progressed were originally staged as T1b and had refused therapy. There was only 1 instance of newly upstaged T1b who progressed. It was also the only case who died from carcinoma of the prostate. Definitive therapy, if accepted by the patient, could possibly have altered the outcome. However, he was 77 years old at the time of diagnosis and survived 3½ years before succumbing to the disease. Aggressive therapy, given the limited life expectancy, may not have been beneficial.

The varying definition of T1a has not helped either. Whilst most authorities agree that poorly-differentiated carcinoma should be regarded as T1b, there is no uniform criteria for T1a tumours. Some consider the grade of the tumour only¹⁰ while others include tumour volume as an additional criterion. A focal tumour is more likely to follow

TABLE IV: SUMMARY OF CASES THAT WERE REGRADED

Case no.	Original grade	Current grade	Original stage	Current stage	Progression	Status	Cause of death
4	Well differentiated	3+4	T1a	T1b	Yes	Dead	Prostate carcinoma
5	Well differentiated	3+2	T1a	T1b	Yes	Alive with disease	—
6	Well differentiated	2+3	T1a	T1b	No	Dead	Pneumonia
7	Well differentiated	3+2	T1a	T1b	No	Dead	Pneumonia
8	Well differentiated	3+4	T1a	T1b	No	Dead	Myocardial infarct
9	Well differentiated	3+3	T1a	T1b	No	Dead	Myocardial infarct
10	Well differentiated	3+3	T1a	T1b	No	Dead	Septicaemia
12	Well differentiated	2+3	T1a	T1b	No	Alive (NED)	—
16	Well differentiated	3+2	T1a	T1b	No	Dead	Colonic carcinoma
18	Well differentiated	3+3	T1a	T1b	No	Dead	Not known
24	Well differentiated	4+3	T1a	T1b	No	Alive	—
25	Poor differentiated	2+3	T1b	T1b	No	Alive (NED)	—
27	Well differentiated	2+3	T1a	T1b	No	Alive (NED)	—

NED: no evidence of disease

an indolent course as opposed to a diffuse tumour. Different estimates of tumour volumes have been used, ranging from arbitrary figures of less than 3 or 5 foci¹¹ to a calculated value of less than 1 cm³.⁴ A more restrictive definition of including only well-differentiated tumours involving less than 5% of resected prostatic chips has also been used, which is that adopted for our study.⁹

These variations have resulted in differing reports in the rate of progression. Cantrell et al¹² based on a definition of T1a as that not including poorly-differentiated tumours and involving less than 5% of prostatic chips, reported a progression rate of 2% with a 4-year follow-up for T1a and 33% for T1b. Thompson and Zeidman¹¹ reported a low rate of 5% progression in their cohort of 60 patients at 7.5 years using a different definition of A1 (less than 5 foci). Zhang et al,⁹ using a stricter definition, still recorded a 10% progression at 8.5 years. Brawn et al,¹⁰ on the other hand, adopted a looser definition where tumour volume was not part of the criteria for T1a and still found a 5.4% progression rate. However, this study was not reflective of true surveillance as therapy was provided for 38 (51.3%) of the T1a cases in their series.

These low progression rates led to the early conclusion that low-grade incidental carcinoma was clinically insignificant and could be managed on a surveillance programme. Epstein et al³ challenged this notion when they showed that 16% of patients progressed at 8 years despite using a strict definition of T1a tumour. Other publications with long follow-up seem to support their findings.^{4,9}

Our institution has traditionally adopted a restrictive definition of T1a—well-differentiated tumours comprising less than 5% of prostatic chips. T1b patients would be managed more aggressively. However, 5 patients originally staged as T1b wished to be managed expectantly and were thus entered into the surveillance programme. This unique cohort allowed us to study their natural history in tandem with the rest of T1a cases.

Delayed therapies instituted at the time of progression appeared effective. Cancer-specific mortality was only 7.7%. Only 1 death was directly attributable to prostatic carcinoma and even that was at 4 years after initial diagnosis, at an advanced age of 81 years. Although 2 of the 3 who were alive had clinical evidence of disease, all were symptom-free at 7 years follow-up. Most studies reported high mortality rates but the cause of death was usually not due to carcinoma of the prostate^{3,11,13} and a similar trend was observed in this series. In fact, survival for this group of patients is comparable to a similar group of men who had histologically proven BPH.¹⁰ These findings were further supported by recent publications on clinically localised carcinoma of the prostate, which had large numbers of patients and follow-up of at least 10 years.^{14,15}

The importance of age was apparent. The average age of our patients at diagnosis was 72.4 years and mean age at progression was 74.4 years. Mean age at death was 78.1 years and mortality occurred at 4 years after initial diagnosis, the majority of which were from unrelated causes. It therefore seemed prudent to manage this group of patients on a surveillance programme rather than subject them to more aggressive therapies.

It is clear that progression can still occur after a long interval and there appear to be no predictive factors to further identify those at risk. Number of tumour foci had no correlation with chance of progression.¹¹ A stricter definition of T1a^{3,9} needs further refinement to better identify those at higher risk of progression.

The critical issue appears to be accurate staging which is largely dependent on the histopathologic reporting. Subsequent management plans hinge on accurate subclassification and this is particularly pertinent given the higher rate of progression for T1b disease. This fact may be less apparent in elderly patients with limited life expectancy. However, it assumes great importance in a younger patient with expected good quality of life even at 10 years.

Conclusion

Accurate evaluation of the behaviour of T1a tumours requires a large number of patients and long follow-up. Although limited in these aspects, this review shows that surveillance is a viable option for T1a tumours. Of particular importance is accuracy in histological grading and staging. Consideration for life expectancy is equally important given the long duration to progression. It may therefore be worthwhile to have a histopathologist with an interest in urologic pathology to review the histologic findings. Surveillance can be offered to those with a life expectancy of less than 10 years. Although it is not our institution's standard practice to manage a young T1a patient with longer life expectancy aggressively, it seems appropriate to offer alternative options other than surveillance given the significant long-term progression rate.

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