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# Cancer Detected Incidental to Simple Prostatectomy (Stage A1)

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**Abstract** The incidence of stage A (incidental) adenocarcinoma of the prostate in transurethral resection (TUR) specimens is approximately 16%. This paper discusses the criteria for differentiating stage A1 versus stage A2 tumor, based on tumor volume and grade. Both the short-term (4 year) and long-term (8-10 year) natural history of untreated stage A1 prostate cancer are examined. Options to follow patients expectantly are presented. These include digital rectal examination and transrectal ultrasound. Specific problems relating to analyzing transrectal ultrasounds in patients who have had a prior TUR are addressed. Also, the unique aspects of transrectal ultrasound for stage A1 disease as it relates to the location of the lesion are expanded upon. The third option in the management of stage A1 disease is to monitor serum prostate specific antigen (PSA) levels. Areas covered include the sensitivity and specificity of PSA in general, and, in specific, serum PSA levels following TUR for stage A1 disease as a predictor of residual tumor. New data on a small group of patients who underwent delayed radical prostatectomy following diagnosis of stage A1 disease, where PSA data was available, are presented. The rationale for following patients with stage A1 disease by monitoring their serum PSA levels is supported by data from a group of men with normally sized prostates, benign prostatic hyperplasia, or cancer where longitudinal serum PSA levels were available. Finally, the option of radical prostatectomy for stage A1 disease is put forth. Data include a study of a large group of radical prostatectomy specimens performed for stage A1 disease. This includes the incidence of substantial tumor in this group and our ability to predict substantial tumor based on information obtained by TUR. In conclusion, a summary of the management of stage A1 disease in older versus younger men is presented.


**Key words:** adenocarcinoma, prostate, prostatectomy, PSA, TUR

Approximately 16% (range 13–22%) of transurethral resections (TUR) performed for presumed benign prostatic hyperplasia (BPH) reveal incidental (stage A) adenocarcinoma of the prostate [1–3]. Stage A (incidental) adenocarcinoma of the prostate is divided into those tumors which are relatively low volume and low grade (stage A1) and high volume, high grade tumors (stage A2). The definition of stage A1 disease is controversial. Tumor volume may be measured as number of TUR chips with tumor ($\leq 3$ chips or $\leq 5$ chips), percent of the specimen involved by tumor ($\leq 5\%$), percent of TUR chips with tumor, or actual tumor volume ($<1$ cc). Some authors require that stage A1 disease consists only of low grade tumor (Gleason sum $\leq 4$), while others allow the tumor to be low or intermediate grade. Furthermore, the definition of intermediate grade tumor is controversial; in the past, Gleason sum 7 tumor was included within this category. However, more recent studies have suggested that Gleason sum 7 tumor fares worse than Gleason sum 5 or 6 tumor and probably should be considered as high grade tumor. In 1981, Cantrell *et al.* studied the natural history of untreated stage A1 prostate cancer [4]. When a tumor occupied $\leq 5\%$ of the specimen and was not high grade, only 2% of the men progressed at 4 years. In contrast, when the tumor occupied over 5% of the specimen or was high grade, 33% progressed at 4 years. Based on these findings, stage A1 was defined as tumor occupying $\leq 5\%$ of the specimen and not high grade, with higher volume or high grade tumor defined as stage A2. Subsequent to this study, there have been several articles published on the long-term progression rate of untreated

**Table I. Long-Term Progression Rate of Stage A1**

| Author | Min. f.u.* (yrs.) | Progression | Mean Time (yrs.) to Progression | Dead of Other Causes |
|---|---|---|---|---|
| Zhang [9] | 5 | 13/132 (10%) | 7 | 11% (<5 yrs.) |
| Thompson [8] | 7 | 3/37 (8%) | 8.7 | 57% (1–77, mean 5.8 yrs.) |
| Epstein [6] | 8 | 8/50 (16%) | 7 | 25% (<8 yrs.) |
| Blute [5] | 10 | 4/15 (27%) | 10.2 | |
| Lowe [7] | 5 | 12/80 (15%) | | |

*Min. f.u. = minimum follow-up

stage A1 disease [5–9]. The progression rates in these studies have ranged from 8% to 27% with the minimum follow-up ranging from 5 to 10 years (Table I).

In general, studies showing higher progression rates have been those with longer follow-ups. Since the mean time to progression in these studies ranged from 7 to 10 years, studies with shorter follow-up are probably underestimating the risk of progression. It is also important to recognize that between 11 to 57% of the men in these studies died of other causes. Patients were not followed closely after the diagnosis of stage A1 and most had advanced disease at the time of progression; many died of cancer. Data from these long-term studies shed some light on the question of whether low volume intermediate grade tumor should be considered stage A1 or A2. In our data, as long as the tumor occupied $\leq 5\%$ of the specimen there was no difference in the progression rate at 8 years following diagnosis whether the Gleason sum was $\leq 4$ or 5–7 [6]. As mentioned earlier, the Gleason sum 7 tumor should probably be considered a high grade tumor and not as stage A1 disease. Indirect support for this comes from the rarity with which Gleason sum 7 tumor occupies $\leq 5\%$ of the specimen. Since prostate cancer volume and grade are correlated, the fact that Gleason sum 7 tumors are rarely small lends support to their classification as higher grade.

There are several options in following patients with stage A1 disease. Digital rectal examination cannot be counted on to detect progression in stage A1 disease, since patients with stage A2 tumor who have significant tumor volume are still non-palpable [10]. Transrectal ultrasound has relatively low sensitivity and specificity in detecting prostate cancer. In a recent multi-institutional cooperative study group of clinically confined adenocarcinoma of the prostate, only 72% of lesions >1 cm were detected by ultrasound [11]. Detecting stage A carcinoma by ultrasound is even more problematical, with a specificity of only 37% in one recent study [12]. This lower specificity was in part due to the presence of scar tissue around the TUR site which mimicked a tumor. Transrectal ultrasound also appears to have a lower sensitivity in detecting stage A carcinoma. In a recent study of 20 tumor foci $\geq 5$ mm, only 11 were identified by transrectal ultrasound. Most of those missed were present centrally and anteriorly [12]. This region is a common site of stage A carcinoma, and is difficult to study by transrectal ultrasound since BPH can radiologically mimic carcinoma. Repeat TUR has also been proposed as a means of following men with stage A1 disease. Repeat TUR cannot be counted on as a curative procedure since at least some of the foci in stage A1 disease are present, either peripherally up against the prostatic capsule or apically, areas which are inaccessible by TUR [13]. Repeat TUR has also been proposed as a staging procedure for stage A1 disease [14–18]. However, most of the studies have demonstrated that <10% of patients with stage A1 disease who undergo repeat TUR are upstaged to stage A2 disease. Furthermore,

although patients who have residual tumor at TUR appear to have a higher risk of progressing, those with no residual tumor at repeat TUR still may progress.

The newest modality which has been proposed to follow patients with stage A1 disease is the serum prostate specific antigen (PSA) level. The problem with serum PSA is that many patients with BPH will have levels above 4 ng/ml using the Hybritech technique. In addition, patients with serum PSA levels <4 ng/ml may still have adenocarcinoma of the prostate with capsular penetration, seminal vesicle invasion, or even lymph node metastases [19]. It has been proposed that in patients who have undergone a TUR, the confounding factor of BPH can be removed so that serum PSA levels will more accurately reflect the tumor volume. In a recent study from our institution, 22 men who underwent radical prostatectomy for stage A1 prostate cancer were studied to correlate the residual tumor volume with their post-TUR serum PSA level. In men with serum PSA levels <1 ng/ml there were only small residual tumor volumes, in contrast to the few men who had serum PSA levels over 10 and had higher tumor volumes [20]. However, almost half the men had indeterminate serum PSA levels between 1–10 ng/ml with varying extent of residual tumor volume. Analysis of a small group of men from our institution who underwent delayed radical prostatectomy following the diagnosis of stage A1 disease revealed that five had normal serum PSA levels at the time of radical prostatectomy. Although two of these five men had a low grade tumor confined to the prostate, the remaining three had either a high grade tumor, positive margins, positive seminal vesicles, or positive lymph node metastases. This small group of men demonstrates that following men with stage A1 disease until their serum PSA level goes above normal does not ensure detection of tumor at a curable stage. However, serial PSA levels in these men were not obtained following diagnosis but only at the time of progression several years following diagnosis by TUR. The current recommendation for the use of serum PSA levels as a means of following men with stage A1 disease is to analyze serial PSA measurements. Monitoring the change in PSA over time is based on the following facts: (1) PSA increases with increasing tumor volume; (2) the contribution of cancer to serum PSA level is ten times that of BPH; and (3) prostate cancer has a more rapid rate of growth than BPH. In a recent study from our institution it was demonstrated that serum PSA levels in those with BPH increased only slightly over time, whereas those who eventually were shown to have prostate cancer showed a more rapid rise in their PSA level [21]. Consequently, it was felt that one could monitor the rate of change of serum PSA levels in patients diagnosed with stage A1 prostate cancer. A rise in serum PSA level even to a level below normal could trigger a work-up for progression of disease.

Finally, we have studied a large group of radical prostatectomies performed for stage A1 disease [22]. Six percent of these cases showed no residual tumor; approximately 74% showed minimal residual tumor; and 20% had substantial residual tumor. Substantial residual tumor was defined as either high tumor volume, stage C disease, or high grade tumor. High tumor volume was defined as over 1 cc of total tumor volume, which was based on the finding that this was the median tumor volume for stage A2 and B tumor [10,23] (Fig. 1). Of the 64

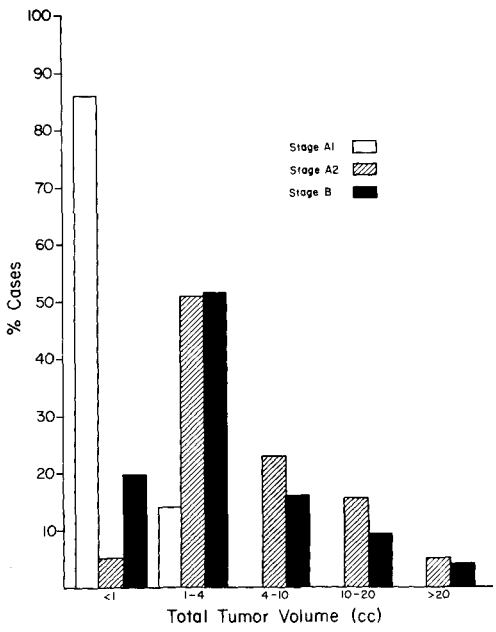


**Fig. 1.** Total tumor volume of stage A1 compared to stages A2 and B adenocarcinoma of the prostate.

cases studied, 13 showed substantial tumor; of these, seven had over 1 cc of tumor, five cases showed capsular penetration, and one case had Gleason grade 4+5=9 tumor. One could not predict using pre-operative pathologic parameters which cases had minimal versus substantial tumor. These pathologic parameters were TUR percent (*i.e.*, 1% vs. 4%), TUR tumor volume, or TUR Gleason grade (*i.e.*, Gleason score 2 vs. 6).

In summary, most authorities recommend a conservative approach in the management of older men with stage A1 disease. However, the definition of older men is controversial and ranges from between 60 to 65 years of age. This conservative approach is related to the high incidence of incidental cancer found at autopsy and the increased likelihood of death from other causes versus the risk of progressing with prostate cancer. The management of younger men with stage A1 tumor is controversial. One option is also a conservative approach with follow-up until progression. Arguments in favor of this approach are: (1) most radical prostatectomies done for stage A1 disease show minimal tumor; (2) follow-up with a combination of digital rectal examination, serum PSA levels, and transrectal ultrasound will identify progression of some stage A1 patients at a time when they are still curable; and (3) progression, if it occurs, may be many years following diagnosis.

The other option for the management of young men with stage A1 disease is aggressive therapy such as radical prostatectomy. Arguments in support of this approach are: (1) These men have a longer life expectancy with a relatively high risk of prostate cancer progression. With studies having an eight to ten year follow-up demonstrating approximately a 16–20% risk of progression, younger men can be expected to have a higher risk of progression during their lifetime. (2) As discussed earlier, there is a lack of means of ensuring detection at a curable stage with conservative follow-up. Whether following serial serum PSA levels will provide us with this ability remains unproven. (3) About 20% of radical prostatectomies done for stage A1 disease show significant tumor, and radical prostatectomy provides a cure in almost all patients with low morbidity.

As with the aggressive treatment of all early carcinomas, the decision becomes potential over-treatment of the majority of patients while guaranteeing their cure, or potential under-treatment of the minority of patients who may go on to progress and die of their disease.

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