

ORIGINAL ARTICLE

Probability of finding T1a and T1b (Incidental) prostate cancer during TURP has decreased in the PSA era

JS Jones¹, HW Follis¹ and JR Johnson^{1,2}

¹Department of Regional Urology, Cleveland Clinic, Glickman Urological Institute, Lerner College of Medicine, Case Western Reserve University, Cleveland, OH, USA

The purpose of this study is to assess the likelihood of detecting stage T1a and T1b cancer in transurethral prostatectomy specimens during the PSA era. Comparison was made of transurethral resection of prostate (TURP) cohorts in the pre-PSA era (1986–1987) and the PSA era (1994–2000), excluding patients with known PCa. A total of 228 men without a known history of prostate cancer underwent TURP during the pre-PSA era time frame and 501 underwent the procedure during the PSA era time frame. Malignancy diagnosed at the time of TURP decreased from 14.9 to 5.2% of patients in the pre-PSA and PSA eras, respectively. Stage T1a decreased from 4.4 to 2.4% and Stage T1b decreased from 10.5 to 2.8% of patients in the pre-PSA and PSA eras, respectively ($P < 0.001$, Fisher's exact test). Prostate cancer newly identified during TURP has decreased significantly in the era of PSA screening in our study population, with the most significant drop being in clinically significant stage T1b. The decrease in TURP rates reduces the overall incidence of T1a/b cancer but cannot explain the lower risk of detecting previously unsuspected cancer at the time of any given TURP. Identification of many men with occult prostate cancer before TURP through screening and early detection is the most likely cause of this finding. These data suggest that men considering surgical or medical management of benign prostatic hyperplasia may be informed that it should be infrequent that men properly evaluated for prostate cancer will harbor clinically significant undetected malignancy.

Prostate Cancer and Prostatic Diseases (2009) 12, 57–60; doi:10.1038/pcan.2008.14; published online 1 April 2008

Keywords: screening; transurethral prostatectomy; prostate-specific antigen; incidental

Introduction

The majority of cases of localized prostate cancer (PCa) were diagnosed as an incidental finding during examination of transurethral prostatectomy (TURP) specimens before the introduction of prostate-specific antigen (PSA) screening,¹ but this is an uncommon presentation in recent series.² This change could be due to either a decrease in the frequency of TURP or a decreased likelihood that any given TURP specimen would contain previously unrecognized adenocarcinoma in the era of contemporary PCa screening or both.

With the success of medical therapy for benign prostatic obstruction, the incidence of TURP has fallen dramatically. Moreover, those men who do fail to respond to or forego medical therapy increasingly undergo energy-based treatments, such as laser or microwave

therapy. These procedures preclude pathologic examination of resected tissue, so the potential incidence of clinical stages T1a (formerly A1 under the Whitmore–Jewett staging system) and T1b (formerly A2) in these patients remains unknown.

Historically, resected prostatic tissue was found to harbor previously unsuspected or occult malignancy in approximately 10–31% of cases.^{3,4} This concept is theoretically part of advising patients on informed consent for TURP, but the literature has not clearly addressed the risk of finding stages T1a and T1b in the modern era. In addition, knowing whether the men currently treated with TURP alternatives have that same substantial risk of occult PCa is important in considering the implications of treating such men without submitting tissue for pathological interpretation. We reviewed matched cohorts undergoing TURP in the PSA and pre-PSA eras to determine if the likelihood of previously unrecognized cancer being identified during any given TURP has decreased in men undergoing surgical treatment for presumed benign prostatic obstruction in the PSA era.

Materials and methods

Pathology reports were retrospectively reviewed on all patients who underwent TURP in a large tertiary-care

Correspondence: Dr JS Jones, Glickman Urological Institute, Cleveland Clinic, 9500 Euclid Avenue Street A100, Cleveland, OH 44195, USA.

E-mail: jonesS7@ccf.org

¹Current address: 1001 E. Primrose, Springfield, MO 65804, USA.

²Current address: 1965 S. Fremont, Springfield, MO 65804, USA.

Received 14 January 2008; revised 7 February 2008; accepted 7 February 2008; published online 1 April 2008

hospital between 1986–1987 and 1994–2000. These periods were chosen to compare patients with TURP during the era before the use of PSA screening to those with TURP after PSA screening for PCa became widespread. To assure adequate power to determine if the observations were statistically significant, a larger cohort was reviewed during the PSA period based on the observation that occult PCa was not being commonly observed during the current era.

The primary research question was to determine the likelihood that TURP would identify cancer that was previously unknown and to determine the risk that a patient should be quoted during informed consent for surgical intervention. Therefore, patients who had undergone negative evaluation for malignancy, including biopsy, were included. Patients with known PCa were excluded to identify only previously unrecognized malignancy.

The target population came from a group of 7 urologists in the pre-PSA era and 10 urologists in the latter era. Six of the original seven were still actively performing TURP in the PSA era. The same pathology group interpreted the specimens with primarily the same pathologists, using standard tissue-sampling techniques in both eras.⁵

Records were reviewed to assure that the patient had no known previous diagnosis of PCa and to determine preoperative evaluation (PSA, previous biopsy results). Resected volume, age and TURP pathology results were obtained from the pathology reports without slide repeat review and tabulated. Patients were categorized as stage T1a and T1b based on the 1997 AJCC staging system. A designation of stage T1a was limited to those with a reading of low grade or Gleason 3 + 3 = 6 cancer in less than 5% of chips on the pathology report. All others were categorized as stage T1b.

Results

A total of 228 men without a known history of PCa underwent TURP during the pre-PSA era time frame, and 501 underwent the procedure during the PSA era time frame. Average age at time of operation was 72.6 years in the pre-PSA era and 72.9 years in the PSA era. Average specimen weight was 28.1 g in the pre-PSA era and 25.8 g in the PSA era (not significant).

Indications for surgery in both groups were similar. Over 90% in each group were operated for partial or total urinary retention. The remaining patients underwent surgery for bladder calculi, failure to respond to medical therapy or with a desire for surgical instead of medical therapy to avoid chronic medications, with no significant difference of indications between the two groups.

Previously unrecognized malignancy was identified in 34 (14.9%) and 26 (5.2%) patients in the pre-PSA and PSA eras, respectively. Stage T1a cancer was identified in 10 (4.4%) and 12 (2.4%) patients in the pre-PSA and PSA eras, respectively. Stage T1b cancer was identified in 24 (10.5%) and 14 (2.8%) patients in the pre-PSA and PSA eras, respectively. On the basis of a two-sided Fisher's exact test, there is evidence of a statistically significant decrease in the proportion of patients with stages T1a, T1b and overall (combined T1a and T1b) PCa newly diagnosed during TURP in the study populations in the PSA era ($P < 0.001$).

Transrectal ultrasound and biopsy were not in use during the time frame of the pre-PSA era. In contrast, 399/501 patients in the PSA era had a PSA level obtained preoperatively, and 95 of these were biopsied before TURP. Elevated PSA using the cutoff of 4.0 ng/ml per was observed in 90 men and was the most common indication for biopsy. Ten men had undergone two or more biopsies. However, it is notable that eight patients with elevated PSA who were found to have previously unrecognized PCa had not undergone biopsy. Advanced age was the reason for foregoing biopsy in most of these men, as all but two were over 70 years old. The three men with elevated PSA who had not undergone biopsy but were found to have T1b cancer had undergone relatively urgent TURP for complete urinary retention. Of 95 men who had previously undergone biopsy, 5 (5.3%) were found to have unrecognized cancer in the TURP specimen, which is the same rate as was found in the entire population (5.2%). Moreover, 6 of 102 (5.9%) patients in the PSA era who had not undergone PSA screening were found to have cancer during TURP. Only one of these had undergone biopsy for a nodule. The remainder were all 76 years or older and had not been screened before TURP.

The median PSA of patients who were found to have cancer during the PSA era was 6.9 for those with stage T1a and 4.7 for those for stage T1b ($P = 0.79$).

Discussion

Although urologists recognize that PCa identified during TURP is an uncommon presentation in the current era, the literature has not thoroughly considered the reason for this finding. Its clinical importance lies in two areas. First, it is appropriate to explain to patients during informed consent the risk that cancer will be identified by pathologic examination of the resected specimen. This risk depends on whether the individual has undergone screening and/or biopsy or not. In addition, patients considering newer Benign prostatic hyperplasia (BPH) treatment using techniques that fail to provide tissue for histological diagnosis also have potentially unrecognized cancer. Most men with obstructive symptoms are currently treated with medications or minimally invasive alternatives to TURP, such as microwave or laser therapy.⁶ The number of TURPs has decreased dramatically in the past two decades, presumably owing to the increased success of these alternatives.⁷ Because T1a and T1b cancers are defined as being identified during TURP, the reduction in the numbers of TURP procedures limits the potential for such diagnoses by definition.

Some reports have suggested that the frequency of T1a and T1b cancer has decreased but that the likelihood of finding the condition at the time of any given TURP may not have done so during the PSA era.^{8–13} However, we believe that most men with occult PCa who would have fit stages T1a and T1b cancers in the past would be identified before TURP through PSA screening in the current era. This should lead to fewer men reaching the operating room before PCa is recognized; with these men removed from the pool of men without a known diagnosis of PCa who undergo TURP, it is logical that the actual percentage of men whose cancer is unrecognized until TURP should decrease. Contrary to our

theory, the urological literature has not clearly supported this. Fowler⁸ concluded that the decreased utilization of TURP explained the drop in the rate of T1a and T1b cancers and that the incidence of occult malignancy identified as a percentage of men actually undergoing TURP had not changed appreciably. Merrill⁷ reviewed results from the Surveillance, Epidemiology and End Results (SEER) program, determining that TURP explained much of the observed increase in overall PCa incidences between 1973 and 1986 and that possibly all of it in men over the age of 70 and the decrease in T1a and T1b after that was primarily due to decreased utilization of TURP. They acknowledged the impact of PSA testing and early diagnosis, but found that this had proportionately little impact on the incidental finding of PCa at the time of TURP compared to the decrease in TURP surgical volume.

Other studies have shown little decrease in stage T1a and T1b cancer, including a Japanese report, which found that PSA and PSA density were helpful in their population to determine before TURP which patients would be found to have T1b cancers, but they did not help with identifying T1a.⁹ A Spanish study similarly found an inability to differentiate between candidates for TURP who had impalpable and unrecognized cancer from those who were found to have no cancer at TURP.¹⁰ The screening project in Tyrol, Austria found little decrease in either T1a or T1b, although the rate of incidental cancer in their experience was only 5–6% in both the pre-PSA and PSA eras, which is significantly less than the baseline found in the vast majority of other studies.¹¹ A study from the Mayo Clinic early in the PSA era, with methodology similar to the present report, found no change in the incidence of previously unrecognized tumors, although there was a slight trend towards a lower incidence of T1b, which was not statistically significant.¹² Finally, the Washington University group reported that even in men who had undergone screening and one or more biopsies, the rate of incidental PCa was >15%, the same as it was in men who had not undergone biopsies.¹³

The use of TURP has fallen more drastically in the United States than in many other countries as a result of readily available medical therapy and minimally invasive procedures.⁷ Nevertheless, only studies from outside North America have suggested a clear decreased risk of finding previously unrecognized PCa during TURP in the modern era. An Austrian report found a 6.4% risk of T1a and T1b PCa in the PSA era, but their conclusions were based only on comparisons to historical series from other centers and not to its own control group, so the actual change in their population was only speculated.¹⁴ Thus, in contrast to methodologically limited reports comparing case series to uncontrolled and unmatched historical published series, this is, to our knowledge, the first report that shows a statistically significant decrease in the rate of T1a and T1b PCa in the PSA era using a control population.

The actual likelihood of men having occult PCa even after negative biopsy and/or TURP must be recognized. Autopsy studies have demonstrated that many men have PCa even at ages younger than typically considered its clinical age range. Men dying untimely traumatic death were found to have 31% prevalence of PCa identified at autopsy even in their 30s, rising well beyond that at

greater ages,¹⁵ and the Prostate Cancer Prevention Trial elucidated the finding that many men with completely normal PSA levels have PCa identified during biopsy performed without clinical indication.¹⁶ Multiple studies have demonstrated that the false-negative biopsy rate is in the range of 30% or higher.^{17,18} Therefore, identification of cancer and the presence of cancer are poorly correlated even if biopsy has been performed. Moreover, TURP classically removes only the adenomatous tissue of the transition zone. Whether the cancers that are identified through TURP overlap with those found on biopsies, which typically focus on the peripheral zone, remains unknown, but it is likely that many significant peripheral zone tumors are missed during TURP.

The limitations of this study include the retrospective nature of the review and the fact that we cannot quantify the number of men who were candidates for TURP but had a positive prostate biopsy before TURP. Similarly, we included men who had undergone biopsy in the past as long as their biopsy had identified no malignancy, based on the clinical focus of our report, to determine the risk of T1a and T1b PCa in the modern era. Nevertheless, the risk of PCa in these men who had undergone biopsy was similar to the risk in men who had not undergone biopsy, so the results appear similar whether biopsy had been performed previously or not. Thus, the suspicion of cancer based on elevated PSA did not increase the likelihood that subsequent TURP would identify cancer as long as biopsy was negative. Moreover, some of the men had not undergone screening or biopsy in the PSA era group for a variety of reasons, usually advanced age. Notably, the risk in this group appeared similar to the risk in the screened group (5.9 vs 5.2%).

Our clinical question regards the likelihood that a patient consenting to TURP will be found to have unrecognized PCa in the current era. This question is salient for informed consent regardless of whether the patient has undergone screening or not, but we found that the risk of finding a previously unrecognized cancer was similar in men whether screening and/or biopsy had occurred or not. This suggests that PSA screening not only identifies most men with significant cancer before TURP but also removes enough of these men from the population at risk for TURP such that the pool has an overall lower likelihood of having occult cancer. In addition, although it is possible that men treated with medical or minimally invasive energy-based therapies have a different risk of PCa, we believe this is unlikely. Without the ability to test this hypothesis through examining TURP chips for cancer in these patients who forego TURP, we believe it is reasonable that such men may be advised that these data suggest they have an approximately 5–6% chance of having undiagnosed PCa that will remain undiagnosed if they pursue their alternative treatment.

Conclusion

Prostate cancer newly identified during TURP has decreased significantly in the era of PSA screening in our study population, with the most significant drop being in clinically significant stage T1b. The decrease in TURP rates reduces the overall incidence of T1a/b cancer, but it cannot explain the lower risk of detecting

previously unsuspected cancer at the time of any given TURP. Identification of many men with occult PCa before TURP through screening and early detection is the most likely cause of this finding. These data suggest that men considering surgical or medical management of BPH may be informed that it should be infrequent that men properly evaluated for PCa will harbor clinically significant undetected malignancy.

Acknowledgements

We thank Denise Babineau, PhD, for her statistical assistance with this paper.

References

- Murphy GP, Natarajan N, Pontes JE, Schmitz RL, Smart CR, Schmidt JD *et al*. The national survey of prostate cancer in the United States by the American College of Surgeons. *J Urol* 1982; **127**: 928–934.
- Endrizzi J, Optenberg S, Byers R, Thompson IM. Disappearance of well-differentiated carcinoma of the prostate: effect of transurethral resection of the prostate, prostate-specific antigen, and prostate biopsy. *Urology* 2001; **57**: 733–736.
- Ornstein DK, Rao GS, Smith DS, Andriole GL. The impact of systematic prostate biopsy on prostate cancer incidence in men with symptomatic benign prostatic hyperplasia undergoing transurethral resection of the prostate. *J Urol* 1997; **157**: 880–883.
- Argyropoulos A, Doumas K, Farmakis A, Aristas O, Kontogeorgos G, Lykourinas M. Characteristics of patients with stage T1b incidental prostate cancer. *Scand J Urol Nephrol* 2005; **39**: 289–293.
- Moore GH, Lawshe B, Murphy J. Diagnosis of adenocarcinoma in transurethral resectates of the prostate gland. *Am J Surg Pathol* 1986; **10**: 165–169.
- Harkaway RC, Issa MM. Medical and minimally invasive therapies for the treatment of benign prostatic hyperplasia. *Prostate Cancer Prostatic Dis* 2006; **9**: 204–214.
- Merrill RM, Feuer EJ, Warren JL, Schussler N, Stephenson RA. Role of transurethral resection of the prostate in population-based prostate cancer incidence rates. *Am J Epidemiol* 1999; **150**: 848–860.
- Fowler Jr JE, Pandey P, Bigler SA, Yee DT, Kolski JM. Trends in diagnosis of stage T1a-b prostate cancer. *J Urol* 1997; **158**: 1849–1852.
- Meguro N, Maeda O, Saiki S, Kinouchi T, Kuroda M, Usami M *et al*. Clinical significance of prostate specific antigen (PSA) and PSA density in the detection of T1a and T1b prostate cancer. *Hinyokika Kiyo* 1998; **44**: 639–643.
- Herranz Amo F, Verdu Tartajo F, Diez Cordero JM, Bueno Chomon G, Leal Hernandez F, Bielsa Carrillo A *et al*. Incidence of prostatic cancer in symptomatic patients with non-suspicious rectal palpation and PSA levels greater than 10 ng/ml. *Actas Urol Esp* 1999; **23**: 316–322.
- Horninger W, Reissigl A, Rogatsch H, Volgger H, Studen M, Klocker H *et al*. Prostate cancer screening in Tyrol, Austria: experience and results. *Eur Urol* 1999; **35**: 523–538.
- Monda JM, Barry MJ, Oesterling JE. Prostate specific antigen cannot distinguish stage T1a (A1) prostate cancer from benign prostatic hyperplasia. *J Urol* 1994; **151**: 1291–1295.
- Ornstein DK, Rao GS, Smith DS, Andriole GL. The impact of systematic prostate biopsy on prostate cancer incidence in men with symptomatic benign prostatic hyperplasia undergoing transurethral resection of the prostate. *J Urol* 1997; **157**: 880–883.
- Zigeuner RE, Lipsky K, Riedler I, Auprich M, Schips L, Salfellner M *et al*. Did the rate of incidental prostate cancer change in the era of PSA testing? A retrospective study of 1127 patients. *Urology* 2003; **62**: 451–455.
- Sakr WA, Grignon DJ, Haas GP, Heilbrun LK, Pontes JE, Crissman JD. Age and racial distribution of prostatic intra-epithelial neoplasia. *European Urology* 1996; **30**: 138–144.
- Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG *et al*. The influence of finasteride on the development of prostate cancer. *N Engl J Med* 2003; **349**: 215–224.
- Walz J, Graefen M, Chun FK, Erbersdobler A, Haese A, Steuber T *et al*. High incidence of prostate cancer detected by saturation biopsy after previous negative biopsy series. *Eur Urol* 2006; **50**: 498–505.
- Jones JS. Saturation biopsy for detecting and characterizing prostate cancer. *BJU Int* 2007; **99**: 1340–1344.