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Original Article

Incidental prostate cancer in transurethral resection of prostate specimens in men aged up to 65 years

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ABSTRACT

Background: The identification of prostate cancer (PC) is important in men aged ≤ 65 years. We examined complete transurethral resection of prostate (TURP) specimens to quantify the incidence and nature of PC in men aged ≤ 65 years.
Methods: A prospective multi-institutional database included TURP specimens. The cohort was stratified into two groups according to age. For men aged ≤ 65 years, the entire specimen was submitted for histological analysis, while the TURP specimens from men aged > 65 years were sampled following standard guidelines.
Results: A total of 923 men were included, with 224 in the younger group. PC was identified in 13.4% in men aged ≤ 65 years, compared with 28.7% the older group. The younger group had a lower proportion of Gleason score ≥ 7 (30% compared with 40%) and higher rates of pT1a (57% compared with 43%). In men aged ≤ 65 years with cancer, tumor was identified in one block in 15 of 30 cases (50%). Following diagnosis, 4/30 underwent radical prostatectomy, 5/30 underwent curative radiotherapy, 10/30 androgen deprivation, and 1/30 received palliative radiotherapy.
Conclusion: Incidental PC in men aged ≤ 65 years is not uncommon. Our results suggest that TURP specimens in men aged ≤ 65 years should be completely assessed. Underidentification of cancer may occur as a result of increasing use of laser prostatectomy and the consequent loss of tissue for pathological examination.

1. Introduction

Prostate cancer is common, presenting clinically in 8% of men. On autopsy, up to 60% of 70-year-olds and 80% of 80-year-olds are found to have latent prostate cancer.[1] The landmark study by Bill-Axelson et al[2] in 2011, confirmed early prostatectomy was significantly associated with reduced mortality when compared with watchful waiting. At 23-year follow up, men aged ≤ 65 years experienced the greatest oncological benefit, with a reduction in overall mortality of 25.5% and a prostate cancer death reduction of 15.8% following prostatectomy.[3] Furthermore, this study reported that in men aged ≤ 65 years, the number needed to treat to avert one death was only four. These findings suggest that early prostate cancer diagnosis and management is critical in this younger population.

Transurethral resection of the prostate (TURP) targets the transitional zone of the prostate. Prostate cancer isolated exclusively in the transitional zone (TZ) is uncommon, accounting for only 2–7% of all prostate cancers.[4–6] Several recent studies have reported that cancer arising from the TZ have a more favorable prognosis than tumors that arise in the peripheral zone (PZ).[4,7] As a result, several groups argue that the TURP specimen may hold limited diagnostic value.[8] In the postprostate-specific antigen (PSA) testing era, incidental prostate cancer (ICP) on TURP remains common, occurring in 4.1–16.7% of TURP specimens.[9,10] Despite

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this prevalence, oncological outcomes have been poorly studied, with small series suggesting favorable survival.[11]

Unfortunately, there is no consensus on pathological assessment of TURP specimens. *Standard handling* of these specimens includes embedding and analyzing only part of larger specimen. The College of American Pathologists (CAP) recommend that specimens weighing ≤ 12 g should be examined in entirety. For specimens weighing > 12 g, the initial 12 g should be assessed with the addition of 2 g of tissue for every 10 g of specimen.[12–14] Intuitively, embedding the entire TURP specimen for histological examination will lead to a higher rate of identification of prostate cancer.[15] Despite this, literature suggests that partial assessment detects up to 90–100% of incidental cancer on TURP specimens.[16,17]

Given the importance of diagnosis in men aged ≤ 65 years as outlined, there is an argument for assessment of the entire specimen in men of this age group. In the current study, we aimed to determine the frequency of incidental cancer on TURP accurately in men aged ≤ 65 years by completely assessing pathological specimens. Outcomes produced by Bill-Axelson et al[2] are not directly comparable with the incidental PC and thus we further aimed to establish the prostate cancer outcomes in these young patients following diagnosis. This information is of interest in the climate of laser prostatectomy, which is characterized by the absence of pathological specimens for analysis.

2. Materials and methods

2.1. Patients

Following Human Research and Ethic Committee (HREC) approval, a multisurgeon, multicentre database was prospectively collected and utilized for analysis. All consecutive TURP specimens collected between January 2010 and December 2013 were recruited for the study. Pathological assessment was conducted by a single-specialist uropathologist at a high-volume uropathology service. The cohort was subdivided into two discrete groups based on age; Group A represented men aged ≤ 65 years and Group B represented patients aged > 65 years.

2.2. Specimen handling

All specimens were weighed. To assess incidental cancer in Group A accurately, the complete resected specimen was embedded and submitted for histopathological analysis. In Group B, *standard handling* was performed on the specimen. For specimens weighing ≤ 10 g, the entire specimen was processed and examined histologically. For specimens weighing > 10 g, the first 10 g were processed with an additional 2 g for every 10 g of tissue resected. Thus, any specimen weight that exceeded 12 g marked the point at which a limited specimen would be assessed as per the *standard handling* protocol as outlined by CAP.[14]

The specimens were fixed in 10% neutral buffered formalin with overnight processing. A single hematoxylin and eosin-stained section was cut from each block and examined histologically. All foci were outlined on the glass slides and an estimate of tumor volume as a visual estimate of the percentage of surface area of tumor to the entire specimen determined. Gleason scoring was based on the 2005 International Society of Urological Pathology (ISUP) consensus guidelines. Small malignant foci were confirmed with immunoperoxidase stains using a cocktail of p504S (Dako, Carpinteria, CA, USA. Clone 13H4 dilution 1:50), 34BE12 (Dako, Carpinteria, CA, USA. Clone 34BE12 dilution 1:50) and p63 (Leica, Buffalo Grove, IL, USA. Clone 7JUL dilution 1:25), using the Ventana Ultra automated immunoperoxidase stainer, Roche, Switzerland).

Reporting of incidental cancer on TURP aligned with the CAP recommendations.[14] pT1a disease was defined as incidental tumor in ≤ 5% of TURP specimens. pT1b disease was defined as incidental tumor in > 5% of TURP specimens.

2.3. Data collection and analysis

Limited preoperative and postoperative data were collected from medical records. Such data included patient demographics. Follow-up data were collected prospectively in a similar method, variables collected included: subsequent transrectal ultrasonography (TRUS) biopsy, prostatectomy, radiotherapy, androgen deprivation, or chemotherapy.

Data were collated on an Excel 2003 database (Microsoft Corp., Redmond, WA, USA). Statistical analysis was completed on SPSS statistical package v20 (SPSS Inc, Chicago, IL, USA). Groups were classed based on the aforementioned age criterion. Chi-square *t* test was used to assess categorical data where possible. Two-sided $P < 0.05$ was considered statistically significant.

3. Results

A total of 923 patients were recruited into the study, 224 in Group A and 699 in Group B. The patient demographics and cancer detection rates are outlined in Table 1. On histopathological assessment of the TURP specimen, prostate cancer was diagnosed in 13.4% of the younger group and 28.7% in the older group. The younger group had a higher proportion of low-volume disease (pT1a). Of the diagnosed prostate cancers, the 92.2% were of acinar adenocarcinoma subtype, with similar proportions between subgroups. Within the younger group, a significantly higher rate of low-grade prostate cancer was diagnosed (Gleason score ≤ 6).

Each group was further subdivided into categories based on specimen weight. Within the younger group, 57% of the patients diagnosed with cancer had a specimen weight > 12 g. In the younger group, the median number of blocks embedded for analysis was seven (range, 1–27) and the median number of positive blocks with cancer was one (range, 1–5). In the younger group, 15/30 cancers diagnosed had cancer in only one block. These results are summarized in Table 2.

Following TURP, of the men in Group A diagnosed with cancer, 6/30 underwent TRUS biopsy. The results are shown in Table 3.

Table 1
Patient Demographics and Cancer Detection Rates in Each Group.

	Group A (age ≤ 65 y)	Group B (age > 65 y)	*P*
n	224	699	
Specimen weight (g)	14.0 (2–65)	11.0 (0.1–74)	0.33
Prostate cancer	30 (13.4%)	213 (28.7%)	< 0.001
pT1a	17	92	
pT1b	13	115	
Acinar	27	197	0.50
Ductal	3	12	
Urothelial	0	4	
HGPIN	8 (3.6%)	24 (3.1%)	0.9

HGPIN, High-grade Prostatic Intraepithelial Neoplasia.

Table 2
Proportion of Patients in Each Group Categorized by Diagnosis and Specimen Weight.

Diagnosis	Group A (age ≤ 65 y)		Group B (age > 65 y)	
Specimen weight (g)	< 12	> 12	< 12	> 12
Benign	91 (48.9)	95 (51.1)	290 (55.7)	231 (44.3)
Malignant	13 (43.3)	17 (56.6)	113 (53.1)	100 (46.9)

Data are presented as *n* (%).

Table 3
Transrectal Ultrasonography (TRUS) and Prostatectomy Findings in Men in GROUP A (Age ≤ 65 y).

	PSA	TURP Gleason	TURP stage	TRUS Gleason	TRUS + cores	RP Gleason	RP stage, tumor volume
Case 1	26.9	4 + 5 = 9	pT1b	5 + 5 = 10	12/12 cores	NP	NP
Case 2	5.5	3 + 3 = 6	pT1a	3 + 3 = 6	1/12 cores	G3 + 3 = 7	pT2c, 0.2cc
Case 3	0.69	3 + 3 = 6	pT1a	Benign	NP	NP	NP
Case 4	2.7	3 + 3 = 6	pT1a	3 + 4 = 7	6/12 cores	NP	NP
Case 5	30.7	4 + 3 = 7	pT1a	4 + 5 = 9	11/12 cores	G4 + 5 = 9	pT3a, 5.0cc
Case 6	4.5	3 + 3 = 6	pT1b	NP	NP	G3 + 3 = 6	pT2c, 0.5cc
Case 7	3.7	3 + 3 = 6	pT1b	NP	NP	G4 + 5 = 9	pT2a, NR

NP, not performed; PSA, prostate specific antigen; RP, radical prostatectomy; TURP, transurethral resection of prostate.

Table 4
Management Outcomes for Men in GROUP A Diagnosed with Cancer.

	Group A: age ≤ 65 y
Active surveillance	19 (63.3)
Radical prostatectomy	4 (13.3)
RP only	3
RP + RTx	1
RTx only	4 (13.3)
Curative	3
Palliative	1
RTx + ADT	2 (6.6)
ADT only	1 (3.3)

Data are presented as *n* (%).
ADT, androgen deprivation therapy; RP, radical prostatectomy; RTx, radiotherapy.

Further, 10/30 of these patients underwent some form of further treatment for a new diagnosis of prostate cancer including: prostatectomy, androgen deprivation or radiotherapy. One patient received palliative radiotherapy (Table 4). Of the seven patients that underwent either TRUS biopsy or prostatectomy, three experienced upstaging to disease grade on subsequent pathological data (Cases 2, 5, and 7). The pathological findings for patients in Group A that underwent TRUS biopsy or prostatectomy are summarized in Table 3.

4. Discussion

The importance of diagnosis of prostate cancer in younger males is well established in contemporary urological practice. The current study confirms that ICP in younger men is common, having significant implication on further oncological management.

The histopathological significance of TURP specimens has been questioned following the introduction of PSA. Most prostate cancers arise from the PZ of the prostate, with recent studies suggesting that isolated TZ tumors occur in only 2–7% of cancers.[4–6] In addition, TZ tumors tend to correspond with a more favorable oncological outcome, including lower Gleason scores, rates of Extra-prostatic extension (EPE), and risk of biochemical recurrence.[5] Intuitively, TURP tends to result in the resection of the TZ, while the PZ is sampled the least with this treatment. Given this, many suggest that concerns regarding missed ICP may not be clinically significant. In the current study, ICP on TURP specimens remains common, occurring in up to 26% of patients. This figure remained significant on subgroup analysis in men aged ≤ 65 years at 13.4%. These figures of ICP on all TURP specimens are higher when compared with previous literature, with reported rates of 4.1–16.7%,[5,10,18–22] summarized in Table 5. When patients with suspicious rectal examination, high PSA, or previous positive biopsy are excluded, ICP occurs less frequently at 1.8–5.5%.[23–26]

The relatively high rates of ICP may be the result of pathologist opinion or methodology of specimen processing. Specimens in Group A underwent extended assessment, including histological assessment of the entire specimen, regardless of specimen weight. In this group, 57% of cancers diagnosed had a specimen weight > 12 g. In laboratories that perform standard handling as suggested by CAP, the potential for a missed diagnosis becomes apparent. Further, of the cancers diagnosed in the younger group, 50% of cases had cancer in only one block. These findings suggest embedding and assessment of complete specimens should occur to maintain diagnostic accuracy. The cost implications of such practice must be considered and represents scope for further research.

Within the younger cohort (Group A), a significant proportion diagnosed with cancer on TURP underwent further oncological management. Of these men 10/30 (33%) underwent some form of treatment with a curative intent including prostatectomy, radiotherapy, or androgen deprivation. Interestingly, staging on TURP tends to predict the stage of subsequent specimens obtained from transrectal biopsies and prostatectomy. However, anecdotally, this is not entirely reliable, as seen in Case 6 in the TRUS specimens (Table 3). Furthermore, several cases were significantly upstaged on subsequent pathological assessment (Cases 2, 5, and 7). Due to this, we recommend that all patients diagnosed with cancer on TURP should undergo further pathological testing to clarify the extent of the local disease. In particular, patients being considered for active surveillance following low-grade prostate cancer on TURP should

Table 5
Previous Series Outlining Diagnosis of Incidental Prostate Cancers.

Author, yr	Location	Clinically benign	Negative TRUS	Mean age (y)	Number TURP	Number cancer
Yoo et al[23]	Korea	Yes	Yes	71	1,613 (included RP)	78 (4.8)
Voigt et al[18]	Dresden, Germany	NA, all cases	NA, all cases	69	1,000	111 (11.1)
Bright et al[19]	Leicester, UK	NA, all cases	NA, all cases	72	476	47 (9.9)
Jones et al[24]	Cleveland, USA	Yes	Yes	nr	501	26 (5.2)
Biers et al[5]	Winchester, UK	NA, all cases	NA, all cases	77	680	23 (4.1)
Trpkov et al[20]	Alberta, Canada	NA, all cases	NA, all cases		747	126 (16.7)
Antunes et al[25]	Sao Paulo, Brazil	Yes	Yes	68	168	3 (1.8)
Di Silvero et al[8]	Rome, Italy	Yes	Yes	69	3942	217 (5.5)
Zigeuner et al[10]	Graz, Austria	NA, all cases	NA, all cases	72	2422	314 (13)
Merrill and Wiggins[9]	Utah, USA	NA, all cases	NA, all cases	nr	6,426	675 (10.5)
Mai et al[22]	Ontario, Canada	NA, all cases	NA, all cases	nr	449	36 (8.0)

Data are presented as *n* (%).
NA, not applicable; nr, not reported; RP, radical prostatectomy; TRUS, transrectal ultrasound biopsy of prostate; TURP, transurethral resection of prostate.

undergo further assessment to exclude high grade disease in the peripheral zone.

The current study suggests that detection of ICP on TURP may be clinically significant, even in a younger cohort. The introduction of nonablative therapies, such as laser prostatectomy or urolift, pose the difficult issue of a lack of prostatic specimen for histopathological analysis, potentially leading to diagnostic compromise. This situation poses the question—should we be performing transrectal biopsies targeting the transitional zone prior to, or during, laser prostatectomy to exclude prostate cancer? Alternatively, is monitoring the trend in PSA following the establishment of a new baseline sufficient?

Several limitations were identified within the current study. Histopathological analysis was performed by a single uropathologist and may account for a high rate of prostate cancer through overdiagnosis. To address this concern, all small foci were confirmed with PIN4 immunoperoxidase stains. The cohort examined in the study represents patients from the private sector within Australian practice, potentially introducing selection bias. This cohort may have also been exposed to a more aggressive treatment protocol. While this study identifies the importance of diagnosis of ICP in younger males, a larger, more comprehensive study is required to ascertain rates in the larger population and clinical significance. Crucial clinical details were not available for analysis including PSA, digital rectal examination findings, and previous medical history.

The current study shows that prostate cancer is not uncommon in TURP specimens in men up to age 65 years. Many of these cancers are clinically significant, requiring further oncological management. Despite thorough histopathological assessment, 50% of cases had tumor in only one block. These findings suggest that all of the TURP specimens in men up to 65 years should be submitted for pathological examination. These findings are also of importance given the increasing use of laser prostatectomy and the consequent loss of tissue for pathological examination. This may lead to an underidentification of cancer in these men.

Conflicts of interest

The authors have no conflicts of interest to declare.

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