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Original Article

Prevalence of incidental prostate cancer in patients undergoing radical cystoprostatectomy: data from China and other Asian countries

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Abstract

The purpose of this study is to investigate the frequency of prostate cancer (Pca) discovered incidentally in radical cystoprostatectomy specimens in Asia and to determine the feasibility of prostate-sparing cystectomy (PSC) for Asian patients. Ninety-two male bladder cancer patients who underwent radical cystoprostatectomy at our center between January 2003 and January 2008 were included in this study. The mean age of patients was 67.1 years (range: 32–75 years). Prostate-specific antigen (PSA) levels and digital rectal examination (DRE) results before surgery were obtained retrospectively. Prostates of all patients were embedded and sectioned at 5-mm intervals. The same pathologist examined the prostatic tissues from radical cystoprostatectomy specimens. Finally, a structured literature review was performed using MEDLINE and PUBMED to estimate the occurrence of incidental Pca in Asia. Of the 92 patients, 3 (3.3%) were found to have Pca; in one out of three (33.3%) patients the disease was clinically significant due to a Gleason grade 4 carcinoma. Eight articles were included in our review. The overall incidence of Pca discovered incidentally in radical cystoprostatectomy specimens in Asia was 9.9% (64/642). When age was restricted to < 60 years, only 7 out of 222 (3.2%) patients were found to have synchronous Pca, and none of the cases was clinically significant. The occurrence of Pca in radical cystoprostatectomy specimens in Asia is much lower than that in Western countries. PSC might be feasible for Asian patients under a strict preoperative selection.

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Keywords: bladder cancer, cystoprostatectomy, incidental, prostate cancer, prostate-sparing cystectomy

1 Introduction

Radical cystoprostatectomy (RCP) combined with bilateral pelvic lymphadenectomy remains the standard treatment for muscle-invasive and refractory superficial bladder cancer. However, because of the high levels of complications associated with this procedure, alternative techniques have recently been suggested for younger patients, in whom the prostate apex, prostate capsule or even the whole prostate is preserved, with the aim of improving urinary continence and erectile function. However, these techniques have raised some concerns, essentially because of two risks: concurrent prostate neoplasm and prostatic involvement with transitional cell carcinoma (TCC).

The incidence of prostate cancer (PCa) varies significantly among different ethnic groups and populations. In Asia, the lowest incidence rate was found in Shanghai, China (1.6/100 000), and the highest rate was in the Phili-

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ppines (18.6/100 000) [1]. Although recent data from Asia have shown a general trend toward an increasing occurrence of PCa, especially in some low-risk regions, such as Japan, China and Singapore, the PCa incidence is still much lower than that in the USA (124.8/100 000) and many European countries [2]. In autopsy studies, the prevalence of PCa in America was 33% in men aged 60–69 years and 46% in men aged 71–80 years [3]. Autopsy studies conducted in China revealed that the rate of incidental PCa in men who were 51–69 years of age was only 9.3% and that for men who were > 70 years of age was 25% [4]. Therefore, the incidence of PCa in RCP specimens in Asia is also probably much lower than that in the Western countries. If this is true, prostate-sparing cystectomy (PSC) might be more appropriate for Asian patients because there would be a lower chance of residual cancer in the preserved glands.

However, until now, there have been few reports about incidental PCa in RCP specimens from entirely Asian populations. Therefore, we collected the data from RCPs performed in our department over the past 5 years and reviewed the literature to investigate the relevant features of incidentally discovered PCa in Asia. We also discuss whether PSC is feasible for Asian patients.

2 Materials and methods

Between January 2003 and January 2008, 96 men with bladder cancer underwent RCP at our hospital. Excluded from this study were four patients: three were diagnosed with PCa before RCP and the other had previously had prostate surgery for benign prostatic hyperplasia (BPH). The ages of the 92 patients included in the study ranged from 33 to 79 years (mean = 67.1 years). None of the patients had a known history of PCa before surgery, and none had a history of radiotherapy or chemotherapy. The preoperative evaluation consisted of digital rectal examination (DRE), intravenous pyelogram (IVP) and either computed tomography (CT) or magnetic resonance imaging (MRI). Prostate-specific angigen (PSA) was determined in 61 patients before surgery.

The entire circumference of the resected prostate gland was inked and fixed in 10% formalin solution for 24 h. Complete transverse sections of the prostate were obtained at 5-mm intervals from the apex to the base. Each slice was numbered consecutively, embedded in paraffin, and mounted on glass slides according to standard procedure. Hematoxylin and eosin stains were performed. To assist with the diagnosis of malignancy, immunohistochemical staining with monoclonal antibodies to P504s and P63 was used to confirm the status of basal layers on atypical lesions. Tissue samples of each cross-section were examined under a microscope. A single pathologist reviewed all specimens for tumor stage (2002 AJCC TNM classification), tumor grade (Gleason scoring system) and surgical margin status. The presence of tumor cells at the inked margin of specimens indicated a positive surgical margin. Cancer volume was calculated from histological tissue sections using the grid method [5], with a shrinkage factor of 1.5 to correct for the shrinkage that occurs during fixation. Clinically significant cancer was defined according to Abdelhady *et al*. [6] as cases with the following: a tumor volume ≥ 0.5 mL; Gleason grade ≥ 4; extracapsular extension; seminal vesicle invasion; lymph node metastasis; or positive surgical margins.

We performed a literature review using databases including PUBMED and MEDLINE. Only full-length papers were included. We used terms such as 'PCa', 'Asia', 'concurrent', 'incidental' and 'cystoprostatectomy' in the search. Data were accumulated for analysis using the χ^2 test.

3 Results

In our series, 3 out of 92 patients (3.3%) who underwent RCP had incidentally diagnosed PCa. The mean ages were 69 and 66.9 years for patients with and without PCa, respectively ($P > 0.05$). The mean serum PSA levels were 2.16 and 1.66 ng mL^{-1} in patients with and without PCa, respectively ($P > 0.05$). Pathologic staging of the PCa revealed two (66.7%) cases of pT2aN0M0 and one (33.3%) case of pT2bN0M0. One patient (33.3%) had a Gleason grade 4 carcinoma, which was defined as clinically significant according to Abdelhady *et al*. [6]. None of the three patients had a tumor volume > 0.5 mL, and none of them had a positive surgical margin or positive regional lymph nodes. Table 1 details the patient characteristics and associated pathologic findings. In addition, we identified 9 (9.8%) patients with TCC involving the prostate. Of these

Table 1. Clinical and pathological findings of three incidental PCa patients.

Age (years)	PSA (ng mL^{-1})	Stage	Gleason score	Surgical margin	Volume (mL)	High-grade PIN	Clinical significance
67	2.99	T2a	8 (4+4)	Negative	< 0.5	Negative	Significant
71	2.11	T2b	5 (3+2)	Negative	< 0.5	Negative	Insignificant
69	1.39	T2a	4 (2+2)	Negative	< 0.5	Negative	Insignificant

Abbreviations: PCa, prostate cancer; PSA, prostate-specific antigen; PIN, prostatic intraepithelial neoplasia.

patients, three had carcinoma *in situ* (CIS) involving the prostatic urethra and six had TCC involving the prostate glands/parenchyma.

Our literature review identified eight articles from Korea, Japan, Iran, India, Taiwan, China and mainland China that we believe could represent the whole Asian population [7–14]. We combined our data with the data from the reviewed literature for analysis. Tables 2 and 3 detail the relevant features of incidentally discovered PCa in Asia.

4 Discussion

The incidence rate of PCa varies significantly among countries, and it is much lower in Asia than in the Western countries [15]. Incidental PCa is a common finding in RCP specimens in developed countries, according to a series of reports [16–23]. However, no studies have compared the prevalence of incidental PCa in RCP specimens in Asia with that in Western countries.

In this study, we found that the frequency of incidental PCa in China was 3.3%, similar to the frequency in Lee *et al.* [10] and Yumura *et al.* [7] studies (4% and 5.1%, respectively), but was much lower than the frequency in other series of RCP cases (14% to 60%) [19] and the age-adjusted frequency of autopsy-detected PCa in China [4]. In addition, according to our review, the overall prevalence of incidental PCa in Asia is only 9.9%, which is also much lower than that in Western countries (14% to 60%) [19]. The surprisingly low incidence of incidental PCa in Asia may be the result of genetic factors and certain protective lifestyles, dietary factors or environmental factors [15]. Another important bias may arise from the different techniques of anatomic and pathologic analysis of the specimens. Two important factors affecting pathologic analysis are the thickness of the slice and whether the prostate is totally embedded. In most Western series, prostate specimens were cut into slices of ≤ 3 mm, but three reports in our review did not show the pathologic technique in detail, and most of the studies in Asia still use a pathologic examination protocol with 5-mm sections. We believe that the Stanford technique, using slices taken every 2–3 mm, could result in the detection of a higher incidence of PCa. Furthermore, careful preoperative evaluation to diagnose concurrent PCa is very important. Three patients with concurrent PCa wer excluded from our study: two were diagnosed before RCP because of elevated PSA levels, and another was diagnosed as a result of a palpable nodule. This could also partially explain why the incidence rate in our study is lower than that in other studies.

Table 2. Prevalence of PCa in cystoprostatectomy specimens.

Nations/regions	Authors	Samples	Patients' mean age (years)	Section (mm)	PCa (%)	Clinical significance
Korea	Han *et al.* [9]	29	68	3	15 (51.7)	5
Iran	Hosseini *et al.* [8]	50	62.5 ± 10.5	3–5	7 (14)	4
Taiwan, China	Yang *et al.* [13]	49	67.8	3	16 (33)	0
Taiwan, China	Lee *et al.* [10]	248	63	5	10 (4)	2
India	Desai *et al.* [12]	44	54.7	NA	3 (6.8)	NA
Japan	Yumura *et al.* [7]	59	N/A	NA	3 (5.1)	NA
Mainland China	Xia [11]	22	67.1	4	3 (13.6)	0
Mainlan China	Liu *et al.* [14]	49	65.3	NA	4 (8.2)	1
Present study		92	67.1	5	3 (3.3)	1
Overall		642			64 (9.9)	

Abbreviations: PCa, prostate cancer; NA, not available.

Table 3. Incidental PCa of patients < 60 years of age.

Nations/regions	Authors	Samples (< 60 years)	PCa (%)	PCa < 60 years (%)	Clinical significance (< 60 years)
Iran	Hosseini *et al.* [8]	50 (9)	7 (14)	3 (33.3)	0
Taiwan, China	Yang *et al.* [13]	49 (25)	16 (33)	4 (16)	0
Taiwan, China	Lee *et al.* [10]	248 (124)	10 (4)	0	0
Mainland China	Xia [11]	22 (13)	3 (13.6)	0	0
Present study		92 (51)	3 (3.3)	0	0
Overall		461 (222)	39 (8.5)	7 (3.2)	0

Abbreviation: PCa, prostate cancer.

Although PSA is commonly used to screen for PCa, we did not find any difference in the PSA levels between patients with and without incidental PCa in the specimens, a result that has also been shown in several other studies [20, 24, 25]. We attributed this mainly to the low tumor volume and low Gleason score of incidentally detected PCa because in most cases of PCa, serum PSA levels correlate well with tumor volume and Gleason score [26, 27]. Similar to the results in the United States and western Europe, the diagnosed incidental PCa cases were primarily localized and well differentiated in our study [22, 28]. Therefore, PSA value was confirmed to be a poor screening tool for the detection of incidental PCa.

With regard to functional outcome, the overall post-operative potency preservation rates of the PSC series were 80%–94% and complete day-time and night-time urinary continence rates were close to 100% and 90%, respectively [29–33]. These rates are significantly superior to those described after standard cystoprostatectomy. Despite these promising functional results, concerns have been raised about leaving PCa or urothelial cancer in the prostate peripheral zone/capsule.

The possible presence of occult PCa remains the greatest criticism of the PSC technique. In the PSC series, although rigorous preoperative prostate investigations have been made, there was still a 6% risk of significant PCa in the residual tissue according to Hautmann *et al*. [34]. However, one point to be noted is that the PSC series reviewed by Hautmann *et al*. [34] were all performed in the Western countries, and the data from Asia have not been reported yet. According to our study, occult PCa was identified in only 3.2% of Asian patients who underwent RCP under the age of 60 years, which was the well-accepted age for PSC. What is more interesting is that none of the cases of occult PCa was clinically significant according to Abdelhady *et al*. [6]. Thus, we believe that under strict preoperative examination, almost all occult clinically significant PCa could be excluded for Asian patients who were prepared to receive PSC.

Another important consideration for PSC is TCC involving the prostate, the incidence of which ranges from 17% to 48% [22, 35, 36]. We found nine patients (9.8%) who had TCC involving the prostate in our series, which is lower than most reports. A tumor located at or distal to the trigone or CIS represents a high-risk factor for prostatic urothelial carcinoma (PUC). In their study of 70 patients, Kefer *et al*. [37] reported that no patient with a solitary bladder lesion located proximal to the bladder neck and without CIS was found to have associated PUC. Pettus *et al*. [35] found that only 1 of 35 (3%) patients who met these criteria had PUC. Nixon and coworkers [38] found that PUC was rare in patients without multifocal disease or CIS in a series of 192 patients. These findings have led us to conclude that the risk of PUC can be reduced greatly or eliminated if we exclude from treatment those patients suffering from multifocal bladder tumors and concomitant CIS and those with cancer located at the bladder neck and trigone.

Although our study cannot comment on the concern of local recurrence or metastatic disease in patients undergoing PSC, the effort towards selecting the appropriate patients for this procedure would ideally result in a reduction in excluding both residual cancer and the risk of recurrence. Taking together our data and the data from earlier studies, we believe the inclusion criteria for Asian patients preparing to receive PSC should comprise the following: young age (< 60 years) and socially active; normal erectile function [29]; normal DRE, PSA < 4 ng mL^{-1}, the ratio of free PSA in total PSA (f/tPSA) > 15% and a negative result of diffusion MRI followed by template/mapping biopsies of the prostate [33]; nonmuscle-invasive disease that cannot be treated conservatively, or solitary T2a patients; no tumor located at or distal to the trigone; and no CIS [39]. Although this subset of patients will comprise < 5% of the overall number of bladder cancer patients, a significantly low rate of PUC and incidental PCa can be found and a similarly low systemic recurrence rate compared with a classical RCP can be expected.

In conclusion, the percentage of incidentally detected PCa in RCP specimens in Asia is much lower than the reported rates in Western countries. We therefore assume that PSC might be more appropriate for Asian patients than for western patients under strict preoperative selection. Additional prospective studies in Asian patients are needed to evaluate the efficacy and efficiency of this procedure and the criteria for selecting the best candidates for PSC.

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