

Incidental Prostatic Adenocarcinoma in Patients with PSA Less than 4 ng/mL Undergoing Radical Cystoprostatectomy for Bladder Cancer in Iranian Men

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ABSTRACT

Objective: To assess the incidence of prostate adenocarcinoma in patients undergoing radical cystoprostatectomy due to bladder cancer in Iranian men.

Materials and Methods: Fifty cystoprostatectomy specimens removed due to bladder malignancy (2004-2005) at two referral centers (Shaheed Modarress and Shaheed Labbafinejad Hospitals, Tehran, Iran) were examined for the coincidental finding of prostate cancer (PCa). At the time of surgery the patient's serum PSA was less than 4 ng/mL and there were no suspicious lesions by digital rectal examination. Pathologic grade, stage, morphometric volume, number of tumor foci and association with areas of high grade prostatic intraepithelial neoplasia (HGPIN) were assessed by light microscopy. All specimens were totally embedded and whole-mounted. Clinically significant cancers were defined as tumors with ≥ 0.5 mL volume, Gleason pattern 4 or 5, pT3, positive surgical margin, and multifocality > 3 .

Results: Incidentally detected cancer was found in 7 (14%) of cystoprostatectomy specimens. HGPIN was present in 1 (14.3%) of the cystoprostatectomies with incidentally detected prostate cancer. None of cystoprostatectomies without prostate cancer had HGPIN. Four (57%) of the detected cancers were significant.

Conclusion: We conclude that incidentally detected prostate cancer in Iran is lower than the rates reported in other countries. Further studies are warranted for better declaration of variability of prostate cancer between different ethnic groups.

Key words: Incidental cancer, prostate cancer, bladder cancer, cystoprostatectomy

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INTRODUCTION

The distribution of cancer varies significantly from country to country all over the world. The latest estimates of global cancer incidence show that prostate cancer has become the third most common

cancer in men, with half a million new cases every year, almost 10% of all cancers in men (1-3). The lifetime risk of clinically detected prostate cancer is 9.5%, and the probability of dying from prostate cancer is 3%. The frequency of incidentally detected cancer is approximately 42% in men older than 50 years of

age; the frequency of autopsy-detected cancer is similar or higher (4). In no other malignancy, there is such a vast reservoir of undetected cases that may never be clinically significant or cause death (4). Prostate cancer incidence is characterized by a very large geographical variability. Asian countries present much lower rates of occurrence of the disease when compared to North American, North and Western European countries, with Southern European and South American countries displaying an intermediate incidence rate (5). The incidence of clinical prostate cancer in Black men is greater than in any other ethnic group. Japanese and Chinese men are less likely to develop prostate cancer (6). The incidence of prostate cancer is considerably low in Orientals. Such differences seem to be linked to ethnic characteristics.

Because Iranian men are ethnically and racially different from most of Asian countries' men (e.g. Japanese, Chinese, and Arabic men) the prevalence of prostate cancer should be different. We conducted a prospective study in Iranian men undergoing cystoprostatectomy to study this issue.

MATERIALS AND METHODS

Between 2004 and September 2005, fifty men with bladder cancer underwent radical cystoprostatectomy at Shaheed Modarress and Shaheed Labbafinejad Hospitals, Tehran Iran. Mean age of patients was 62.5 ± 10.56 years, with age limits ranging between 44 and 82 years. The inclusion criteria comprised a serum PSA level < 4 ng/mL and normal digital rectal examination. Patients with a history of radiotherapy, chemotherapy, previous prostate surgery and any medical therapy for benign prostatic hyperplasia (BPH) were also excluded from the study. The product from the radical cystoprostatectomies was fixed in 10% formalin solution and processed according to the usual standards for fixation and inclusion routinely employed in pathology services. After receiving the specimens, they were measured and weighed, the outer surface of the specimen was inked and they were opened totally and fixed in buffered formalin for 24 hours. After fixation, the prostate including prostatic urethra

was sectioned in quadrants. Sections from transitional and peripheral zones of the prostate and from apical, middle and basal regions in both lobes were included, resulting, in average, in 6 blocks per case. The margin of prostatic urethra was represented separately. The blocks were sectioned in slices with 3- to 5-micrometers in thickness and the resultant histological slides were stained by hematoxylin-eosin. If adenocarcinoma was discovered, then tumor location and Gleason score was determined and involvement of the margins or seminal vesicle extension was evaluated. If there was HGPIN, it was also mentioned. Cancer location and extent were determined and mapped in each section. The presence of tumor cells at the inked margin of resection (defined as the presence of ink on neoplastic cells) was considered to present a positive surgical margin. A positive surgical margin in an area where no capsule was identified was referred to as pT2+ and was thought to indicate where the plane of dissection entered the prostatic capsule or otherwise where no capsule was present, i.e. apex and anteriorly (7). A single pathologist reviewed all tumors for tumor stage (1997 AJCC TNM classification) (8), grade (Gleason scoring system) (9), and surgical margin status. Cancer volume was calculated from histological tissue sections using the grid method (10). All disease-containing areas were outlined in each prostatectomy specimens section. Tumor area was measured using a 1 mm grid, and aggregate tumor volume was estimated by multiplying the sum of tumor areas in consecutive sections by the section thickness. To calculate the tumor volume it was multiplied by a factor of 1.25 to correct the shrinkage that occurs during fixation. The volume of the single largest cancer focus was the incident tumor for investigation. The number of PCa foci within the prostate, the presence and volume of prostate HGPIN, and the proximity of HGPIN to PCa were also gauged for each specimen. Criteria for defining HGPIN included (1) intraluminal proliferation of the secretory cells in the prostate duct-acinar system, forming pseudostratified layers, (2) large nuclei of relatively uniform size, an increased chromatin content, which may be irregularly distributed, and (3) multiple prominent nucleoli (11,12). High-grade PIN was classified as "low volume" if there were three or fewer

separate foci/acini of high-grade PIN, and as “high volume” if there were more than three foci/acini of high-grade PIN on different sections.

Extraprostatic extension was defined as seminal vesicle involvement, malignant cells outside the prostatic capsule, or lymph node metastases. Seminal vesicle invasion was diagnosed when tumor penetrated the muscular coat of the seminal vesicles. Prostate cancers with one of the following characteristics were regarded as clinically significant: an estimated tumor volume ≥ 0.50 mL, contains a component of Gleason histologic pattern 4 or 5, exhibits extraprostatic extension (pT3), has a positive surgical margin, or is recognized in more than three separate areas of the prostate (multifocal).

Clinical features were summarized with mean and ranges or as percentages. Linear regression to complete a bivariate fit of the number of cancer foci by the number of HGPIN foci was done using the computer statistical package SPSS/10.0 (SPSS, Chicago, IL).

RESULTS

The mean age was 62.5 ± 10.56 years (range 44-82 years). This was 57.35 ± 9.75 and 63.19 ± 10.5 years for patients with and without prostate cancer, respectively. Of fifty patients, 7 (14%) had the incidental finding of PCa within the radical cystoprostatectomy specimen. The mean serum PSA

level was 1.89 ± 1.32 and 1.33 ± 1.095 ng/mL in patients with and without prostate cancer, respectively. Table-1 details the patient characteristics and associated pathologic findings. The majority (57%) was pT2a and 28.6% pT2b, with lower frequency in other pT categories (14.3% pT3a, 0% pT3b, and 0% pT4). In 14.3%, 28.6 and 14.3% of cases, Gleason scores were 5, 6, and 7 respectively. The most prevalent (28.6 %) Gleason histological pattern was 3+3=6. One patient (14.3%) demonstrated a focus of Gleason pattern 4 carcinoma. All patients were pN0 for prostate cancer and one (14.3%) had positive surgical margin. High-grade PIN was present in 14.3% of incidentally detected prostate cancer. None of the cystoprostatectomies without prostate cancer had HGPIN. A single patient had a 0.15 mL volume, Gleason score 7 cancer with clear extraprostatic extension (pT3a) at the prostatic base. More than half of the patients (4/7) had ≥ 3 separate foci of PCa identified. The largest tumor volume exceeded 0.5 mL in 4 patients (57%).

As defined, clinically significant cancers were present in 57% of the studied patients having a mean age of 61 ± 6.5 years (range 49-72). The remainder 43% had insignificant prostate cancer.

COMMENTS

The incidence of prostate cancer varies considerably across populations. The highest reported

Table 1 – Pathological findings of incidental prostate cancers discovered in 7 men with a normal digital rectal examination and serum PSA < 4.0 ng/mL submitted to radical cystoprostatectomy.

Age (years)	PSA ng/mL	Stage	Gleason Score	Foci	Perineural Involvement	Surgical Margin	Volume (mL)	Clinical Significance	High Grade PIN
61	0.9	pT2b	4 “2+2”	Multifocal	Negative	Negative	>0.5	Significant	Negative
48	2.2	pT2a	3 “2+1”	Unifocal	Negative	Negative	<0.2	Insignificant	Negative
62	1.5	pT3a	7 “3+4”	Multifocal	Positive	Positive	>0.5	Significant	Negative
44	3.8	pT2a	5 “2+3”	Unifocal	Negative	Negative	<0.2	Insignificant	Negative
54	0.8	pT2a	3 “2+1”	Unifocal	Negative	Negative	<0.2	Insignificant	Negative
71	1.5	pT2a	6 “3+3”	Multifocal	Negative	Negative	>0.5	Significant	Positive
68	0.5	pT2b	6 “3+3”	Multifocal	Negative	Negative	>0.5	Significant	Negative

incidence of prostate cancer in the world is in Jamaica. The average age adjusted incidence of prostate cancer in Kingston, Jamaica is 304/100,000 men (13). In Asian countries, particularly in China, the incidence of PCa is low. According to Deng et al. in 1995 the incidence rate of PCa in Shanghai was only 2.4/100,000 men (14). It was reported in Los Angeles County, United States that the incidence rate was highest in African Americans (116/100,000 person-years) and lowest among Asians (Japanese, 39/100,000 person-years) and Chinese (28/100,000 person-years) (15). The significance of environmental factors in the development of prostate cancer is apparent from studies of migrants. Japanese men have a low incidence of prostate cancer in Japan. These rates are only one-fifteenth of those of white men in the United States, and they quadruple among first and second generation Japanese migrants to the United States (16). It remains to be determined whether similar environmental influences are responsible for the high incidence of prostate cancer in United States black men.

The frequency of incidentally detected cancer is approximately 42% in men older than 50 years of age; the frequency of autopsy-detected cancer is similar or higher (4). We found that 14% of cystoprostatectomy specimens in patients with bladder cancer also contained incidental prostate cancer. This result was much lower than overall mean frequency of incidentally detected prostate cancer in other series of cystoprostatectomy cases (range, 23%-68%) (4,17-23) and also much lower than the age-adjusted frequency of autopsy-detected prostate cancer (mean frequency, 40%; range, 36%-46% (24-27). Incidental prostate cancer in our cystoprostatectomy cases was usually stage pT2a or pT2b (57% and 28.6%, respectively). Of incidentally detected prostate cancer, 57% were low grade (Gleason scores 3, 4, and 5) and 43% were high grade (Gleason scores 6 and 7). In a study from Brazil, 28.3% of patients had prostate carcinoma in cystoprostatectomy specimens (28). Though the discrepancies between studies could be related to the method of pathologic evaluation employed, all indicate the presence of a significantly high incidence of prostate cancer.

High-grade PIN was present in association with 70% of cases of incidentally detected prostate cancer and in 54% of cystoprostatectomies without prostate cancer (29,30). Interestingly in our series, only 14.3% of cystoprostatectomies with prostate cancer had HGPIN and none of the specimens without cancer had HGPIN. Arakawa et al. (29) found that PIN was present in association with 78% of cases of incidentally detected prostate cancer. Qian et al. (31) found PIN in 87% of radical prostatectomy specimens with localized cancer.

This percentage was higher in Iran, and it was lower than the percentages reported in the other Asian countries. Our finding may reflect a recent decrease in the incidence of prostate cancer in Iran. The incidence of prostate cancer varies considerably. Prostate cancer shows significant racial variation (32-34). The incidence and mortality rates for American black men are almost twice those for American white men (35). This increased incidence in black men cannot be ascribed to differences in socioeconomic status (36). Cancer registries are available in many countries but it is important to note that the degree of accuracy may vary. Possible explanations for low rates of cancer in some countries may be due to under-reporting (37).

The clinical incidence of adenocarcinoma of the prostate is 75.3 per 100,000 men (38). The life time risk of American men is calculated to be between 8 and 9.5% with a 2.9% risk of dying of prostate cancer (39). Mortality rates for black American men are the highest reported in the world until now. Even correcting for clinical stage at diagnosis, the mortality from prostate cancer in black men is 2 times higher than in white men (35). Prichett et al. (40) reviewed a 3-year experience and found 45 adenocarcinomas of the prostate in 165 male cystectomy patients with bladder cancers (27%). Patients with bladder neoplasia can present prostate neoplasia with a relative risk up to 19 times higher than what would be expected (41). However, incidental prostate tumors present characteristics that are similar to latent tumors found in autopsy series, some have a proven potential of progressive disease (42).

The objective of this work is to verify the incidence of incidental prostate adenocarcinoma in

patients who underwent radical cystoprostatectomy for bladder urothelial carcinoma.

Our study was limited by the moderate number of cases studied and potential bias in patient selection for surgery at our medical centers. We attempted to minimize biases by using totally embedded specimens and using a consecutive series of cases.

CONCLUSION

The present results indicate that the percentage of incidentally detected prostate cancer in cystoprostatectomies specimens in Iran is much lower than reported rates in the world until now. We therefore assumed regional differences in prostate cancer incidence rates to be related to environmental and racial factors. Still more epidemiologic research is essential to further understand the distribution as well as the prevalence and incidence of prostate cancer in certain ethnic groups.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Prostate cancer is unique among the potentially lethal human malignancies in the wide discrepancy between the high prevalence of histological (incidentally found) cancer and the much lower prevalence of the clinical disease. In 50 year-old men and with an expectancy of life more than 25 years, the risk for prostatic carcinoma is estimated to be 42% for histological (incidentally found) cancer, 9.5% for clinical cancer, and 2.9% for fatal cancer (1).

These epidemiological findings suggest the existence of latent or clinically unimportant cancers that should be distinguished from those that are clinically important by the larger volume, higher grade, and greater invasiveness. Unfortunately, when dealing with small volume cancers, there is no marker to predict whether a tumor will behave as latent or progress to clinical disease.

In spite of striking differences in the frequency of clinical carcinoma (in Asian countries being the lowest), the frequency of histological (incidentally found) carcinoma is fairly similar around the world. According to the theory of multistep events in carcinogenesis, molecular events (initiation) resulting

in histological prostate carcinoma probably occur equally around the world. For evolution to clinical carcinoma, further events related to race, food, environmental pollution, etc (promoting factors) must be implicated (2).

Incidentally found carcinoma can be studied in two ways: in autopsies and in cystoprostatectomies. The frequency of incidentally found cancer in both ways varies considerably and the main cause is the method of examination of the prostate. Baron & Angrist (3) compared the frequency of histological (incidentally found) cancer in autopsies conducted by two methods: examining routine fragments and step-sectioning the prostate. Using the first method the frequency was 9.9% and using the latter 46%.

Bean et al. (4) found a frequency of 6.6% in routine processing and 27.2% in step-sectioning. The same applies to the examination of cystoprostatectomy specimens. The number of fragments processed is critical for properly evaluating the frequency of a lesion. In a series of 265 consecutive radical prostatectomies in our Institution with step-sectioning of the surgical specimen, the mean number of blocks examined

(excluding blocks from the seminal vesicles, vas deferens and cone amputated base and apex of the prostate) was 31 with a minimum of 10 and a maximum of 56.

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EDITORIAL COMMENT

In recent years, incidentally detected prostate carcinoma (PCa) in patients undergoing radical cystoprostatectomy has become a concern for practicing urologists because of the suggestion of prostate sparing cystoprostatectomy by several authors (1). To our opinion, the major questions that merit comment about this issue are the following. 1) Should all patients undergoing radical cystoprostatectomy be screened for the coexistence of PCa? 2) Does PCa coexist with bladder cancer? 3) Is prostate sparing cystoprostatectomy established in terms of oncological principles? The current opinions of the authors about these questions are as follows.

1) Screening of patients who are candidates for radical cystoprostatectomy with serum PSA determination and digital rectal examination (DRE) have a risk of overdiagnosis for prostate cancer. Overdiagnosis is the diagnosis of cancers that for whatever reason do not threaten the health condition or the life of a given patient, which is the rationale for PSA determination to the patients with an estimate life expectancy over 10 years. For this reason, it is

logical for not to evaluate the patients with bladder cancer requiring cystoprostatectomy in terms of PCa. However, we recently reported that despite the vast majority of the patients had organ confined PCa (90.5%) after surgery, 9.5% of the patients had capsular extension and 4.75% were lymph node positive (2). Moreover, only 57.1% of the patients survived after a mean follow-up of 24.3 months. Similarly, Hosseini et al., in the present paper, reported that 14.3% of the patients had capsular extension and 14.3% had positive surgical margin. In patients without organ-confined disease, the extent of PCa may threaten the life of patient instead of bladder cancer, which is especially important for patients with clinically low stage (Ta, T1) cancer. For this reason, we believe that all patients undergoing radical surgery for bladder cancer should receive DRE and PSA testing. In addition, in the case of palpable prostatic abnormalities or elevated PSA levels, more accurate clinical staging (with transrectal ultrasound biopsy or sophisticated imaging modalities) should be attempted, especially in patients with clinically low stage disease.

2) Around 20% of prostate cancers detected during incidental autopsies are clinically significant PCa by the tumor volume criteria (> 0.5 mL). Hautmann et al. (3) reported that 44% of the patients had clinically significant PCa, which is significantly higher than the estimated percentage in autopsy studies. Meanwhile, this incidence is reported as 14% by Hosseini et al., in the present paper. It is hard to interpret the difference between this study and the former study and autopsy series. However, it may be attributed to the lower incidence of prostate cancer in particular countries. Furthermore, despite the lower rates of PCa, the rate of incidental prostate carcinoma is as high as western countries. This observation advocates that the data of the previous surveys suggesting a carcinogenic correlation between bladder and prostate cancer such that the incidence of PCa is 9 to 20.5 times greater following cystoprostatectomy (4-6).

3) Recently, oncological justification of the prostate sparing cystoprostatectomy was critically evaluated by Hautmann & Stein (7). Briefly, the authors noted that distant failure rate of patients with sexuality sparing surgery is at least twice as high as expected for superficial or organ-confined transitional cell carcinoma. Moreover, they addressed a 6% risk of leaving PCa in any residual tissue. For this reason, until long term data is available from the patients receiving prostate sparing cystoprostatectomy, we continue to perform a complete removal of the prostate during surgery in our clinical practice. On the other hand, it should be mentioned that prostate sparing cystoprostatectomy is an attractable option for a young

patient with superficial bladder cancer. However, before performing this surgery, urologists should discuss the risks of this “experimental” surgery with the patient.

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