MANAGEMENT OF PROSTATE CANCER IN CHINA: A MULTICENTER REPORT OF 6 INSTITUTIONS

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ABSTRACT

Purpose: In China the incidence of prostate cancer (PCa) is low and sparse data are available regarding its management. We analyzed the management of PCa at 6 Chinese urological institutions.

Materials and Methods: A retrospective analysis was performed of 431 consecutive patients treated for PCa at 6 Chinese institutions, including 5 in the divisions of Shanghai and 1 in the province of Chongqing, between January 2000 and December 2004. Tumor characteristics, therapeutic options and patient outcomes were recorded.

Results: At diagnosis median patient age was 72 years and median prostate specific antigen was 46.1 ng/ml. Most PCa cases were revealed by urinary symptoms (75.9%) or bone pain (12.8%). PCa was palpable on digital rectal examination in 74% of cases. At least 44 patients (10.2%) had metastases to lymph nodes at diagnosis and 112 (26%) had bone metastases. A total of 236 patients underwent bilateral orchiectomy and 100 received medical hormone therapy, which in 75% consisted of antiandrogen alone. At a median followup of 16.8 months 60% of these patients experienced biological recurrence. Radical prostatectomy was performed in 24 patients as monotherapy or in combination with bilateral orchiectomy. No patient with clinically localized PCa experienced biological recurrence after radical prostatectomy.

Conclusions: The management of PCa in China differs from that in Western countries. To date surgical castration represents standard treatment. Screening detection of PCa could help detect earlier stage tumors and improve the outcome in patients.

Key Words: prostate, prostatic neoplasms, prostatectomy, castration, China

Prostate cancer (PCa) is 1 of the most common malignancies in Western countries but it is relatively rare in Asia. In an epidemiological study Yu et al compared the incidence rates of PCa among native Chinese, Chinese-American and American populations. They reported a 26-fold higher rate of PCa in American than in Chinese men with an intermediate rate in Chinese-American men. Such differences may be due to genetic and/or environmental factors. Cook et al analyzed the incidence of PCa in Chinese, Japanese and Filipino immigrants to the United States and in their descendants. In 45 to 69-year-old Asian-American men the annual rate per 100,000 in native Chinese, Japanese and Filipino men (24.0, 29.6 and 56.8) was approximately half that in United States born Chinese, Japanese and Filipino men (44.4, 42.2 and 111.3, respectively). In United States residents the annual incidence in all generations of Asian-American men was half that in white men born in the United States. These results suggest that Asian-American men retain some genetic or life-style factors that decrease their risk of PCa compared with that in white residents of the United States.

Although PCa is uncommon in China, some recent reports indicate that its incidence is increasing rapidly. Gu evaluated the incidence of benign prostatic hyperplasia and PCa at 187 hospitals based in 26 Chinese provinces. Overall the incidence rates of benign prostatic hyperplasia and PCa in 1997 were 16.1% (15,459/95,749 men) and 1.5% (1,389/95,749), respectively. Between 1951 and 1960 the incidence rate of PCa at the Institute of Urology, Beijing University was 0.6%. From 1991 to 1997 this rate increased to 3.4%.

Because there is no screening for PCa in China, only sparse information is available regarding the incidence and management of PCa in this country. In a collaborative study among groups at Cochin Hospital, Paris, France and Shanghai-East Hospital, Shanghai, China a retrospective analysis of 431 consecutive patients treated for PCa in China was performed. We analyzed tumor characteristics as well as therapeutic options and patient outcomes.

MATERIALS AND METHODS

All cases of PCa diagnosed at 6 Chinese urological institutions between January 2000 and December 2004 were retrospectively collected. These institutions included 5 departments of urology in Shanghai (Shanghai-East, Renji, Huadong, Changzheng and Chang Hai Hospitals) and the department of urology at Daping Hospital, province of Chongqing. All of these institutions are related to a medical university. The hospitals in Changzheng, Chang Hai and Daping are military hospitals.

Patient medical charts were collected by the chief of department at each institution. Only patients with newly diagnosed PCa were included in the study. Those with a history of PCa who were treated for another condition were excluded from study. After the medical charts were collected we ana-
lyzed the characteristics of each PCa case using prostate specific antigen (PSA) and biopsy findings. We also analyzed management and outcome.

RESULTS

Clinical findings. During the 5-year study period the diagnosis of PCa was established in 431 patients. At diagnosis median patient age was 72 years (range 49 to 92). Table 1 lists the presenting symptoms of PCa. Most cases of PCa were revealed by such symptoms with urinary symptoms in 75.9% and bone pain in 12.8% being the most common ones. The diagnosis of PCa was suspected based on increased PSA without symptoms in only 27 patients (6.2%). In those patients median PSA was 40.9 ng/ml (range 9 to 117).

For all except 21 patients a serum PSA measurement was available. Overall median serum PSA was 46.1 ng/ml (range 0.15 to 500). Digital rectal examination (DRE) was considered normal in 112 patients (26%). DRE raised suspicion of stage T2 PCa in 153 patients (35.5%), stage T3 PCa in 42 (9.7%) and stage T4 PCa in 103 (23.9%).

Cancer diagnosis and staging. The diagnosis of PCa was established by prostate biopsy in 293 patients (68%). Prostate biopsy was performed transrectally under ultrasonographic guidance on an outpatient basis. The prostate biopsy protocol varied among institutions, in that the number of biopsy cores was between 3 and 10, although in the majority of cases 9 or 10 were obtained. The diagnosis of PCa was established by transurethral resection of the prostate in 23 patients and by open prostatectomy in 4. The remaining 111 patients underwent neither prostate biopsies nor prostatectomy intervention and, therefore, they had no pathological evidence of PCa available. However, these patients had clinical evidence of advanced PCa on DRE and high biological suspicion for PCa. Gleason score, which was analyzed in only 84 patients, was less than 6 in 44%, 6 in 22.6% and more than 6 in 33.4% (table 2).

For PCa staging abdominal computerized tomography was performed in 209 patients, which showed retroperitoneal lymph nodes in 44. Additionally, bone scintigraphy was performed in 154 patients, which revealed bone metastases in 112.

Table 3 lists clinical tumor stages according to the current TNM classification. Distinctions between T2a and T2b, and T3a and T3b were not available. Median PSA for T1 to T4 tumors was 46.7, 31.5, 64.0 and 81.3 ng/ml, respectively.

Treatment and outcome. A total of 236 patients underwent bilateral orchiectomy, which was done as monotherapy in 98 and in association with antiandrogen in 133. Antiandrogen always consisted of 750 mg flutamide daily. In 1 case orchiectomy was performed in association with estrogen therapy. Moreover, 4 patients with metastatic PCa underwent orchiectomy and pelvic external beam radiation therapy (60 to 70 Gy). In the group of patients treated with bilateral orchiectomy complete followup data were available on 120 and median followup was 16.8 months (range 3 to 92). Of the 120 patients 80 (66.7%) experienced biological recurrence during followup at a median of 13 months. Moreover, 13 patients (10.8%) experienced disease progression, defined as new metastases. Two of these patients died of metastatic PCa.

Table 1. Presenting symptoms in 431 Chinese patients with PCa

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. Pts (%)</th>
</tr>
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<tbody>
<tr>
<td>Urinary symptoms (dysuria + frequency)</td>
<td>327 (75.9)</td>
</tr>
<tr>
<td>Bone pain</td>
<td>55 (12.8)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>11 (2.6)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Acute retention</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Lower limb edema</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Increased PSA, no symptoms</td>
<td>27 (6.2)</td>
</tr>
<tr>
<td>Not available</td>
<td>7 (1.6)</td>
</tr>
</tbody>
</table>

Table 2. Gleason score in 84 patients with PCa

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>No. Pts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>20 (23.8)</td>
</tr>
<tr>
<td>5</td>
<td>17 (20.2)</td>
</tr>
<tr>
<td>6</td>
<td>19 (22.6)</td>
</tr>
<tr>
<td>7</td>
<td>13 (15.5)</td>
</tr>
<tr>
<td>8</td>
<td>13 (15.5)</td>
</tr>
<tr>
<td>9</td>
<td>2 (2.4)</td>
</tr>
</tbody>
</table>

Of the 100 patients who received medical hormone therapy 75 received antiandrogen alone, 23 received complete androgen blockade consisting of antiandrogen plus luteinizing hormone-releasing hormone (LHRH) analogue, 1 received LHRH analogue alone and 1 received estrogen therapy. The antiandrogen was 750 mg flutamide daily and LHRH analogue consisted of a monthly implant of 3.75 mg leuprolide acetate. In this group complete followup data were available on 90 patients and median followup was 16.9 months (range 3 to 74). Of these 90 patients 46 (51.1%) experienced biological recurrence at a median of 14.1 months and 6 (6.7%) experienced disease progression. There was no specific mortality.

Retropubic radical prostatectomy (RP) was performed in 24 patients, that is as monotherapy in 16 and in combination with bilateral orchiectomy in 8. Table 4 lists the characteristics of patients who underwent RP. Complete followup data were available on only 8 patients who underwent RP as monotherapy for T1N0M0 PCa. In this group of patients no biological recurrence was noted at a median followup of 13 months. Pathological examination of the RP specimen showed a pT2 tumor in all cases. The final Gleason score was 5 in 2 cases, 6 in 4 cases and 7 in 2 cases. The functional results of RP were not available.

Four patients received pelvic external beam radiation for...
locally advanced PCa. Disease progressed rapidly and then they were lost to followup. Two patients underwent radical cystoprostatectomy with cutaneous ureterostomy for locally advanced PCa. These patients also experienced early recurrence. Finally, the remaining 65 patients did not receive any specific treatment for PCa. They refused orchectomy and hormone therapy, and most preferred traditional Chinese herbal medicine. These patients were lost to followup.

**DISCUSSION**

Only sparse information is available regarding the incidence and management of PCa in China. To our knowledge we report for the first time the management of this cancer at various Chinese medical universities.

One of the most important findings was the high rate of advanced tumors at diagnosis. We found that the majority of PCa cases were revealed by urinary symptoms (75.9%) or bone pain (12.8%). PCa was suspected because of increased PSA in only 6.2% of cases. Moreover, only 26% of patients had normal DRE. These results differ markedly from those in Western reports. Indeed, in the United States and Europe PCa is usually asymptomatic at diagnosis, DRE is normal and PCa is diagnosed on the sole basis of increased PSA in more than 60% of cases. These differences may be explained by the absence of screening for PCa in China. In Western countries PCa has emerged as 1 of the most common malignancies after age 50 years, it is the most frequently diagnosed cancer in men in the United States and its mortality rate is second to that of lung cancer. Therefore, in Western countries the early detection of PCa has become an important priority. The wide use of screening programs based on total and free PSA has led to the detection of asymptomatic and early stage PCa. Catalana et al recently compared screening results in 1,224 black men, 1,227 white men with a family history of PCa and 63 black men with a family history of PCa to those in 15,964 white men with no known family history of PCa. The PCa detection rate was 6.4% in controls vs 10.3%, 10.5% and 17.5% in the high risk groups. In this screening study 80% of the tumors detected were confined to the prostate. Conversely 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. It is reasonable to assume that PCa related mortality is only marginal in China and, therefore, in this country the early detection of PCa is not a critical issue. Screening for PCa using DRE and PSA is not done in routine practice, which may explain why most newly diagnosed PCa cases are symptomatic and late staged.

Another interesting point is the Gleason score analysis. At all institutions Gleason score was rarely reported. Overall it was assessed in only 84 patients. Surprisingly the majority of tumors were low grade. These findings may be explained by 2 factors, namely the lack of pathologist training and the high rate of metastatic tumors. Indeed, although Gleason score has a real prognostic impact in patients with confined tumors, its impact in metastatic disease is limited. Gleason score is a predictor of biological recurrence after curative treatment and, therefore, it is used as a criterion when considering different therapeutic options for a clinically localized tumor. On the other hand, patients with metastatic disease require hormone therapy regardless of Gleason score. In the current series Gleason score was not assessed in routine practice but it was analyzed in some select patients, mainly those who had no metastases at presentation. Therefore, inaccurate Gleason scoring and the high rate of metastatic tumors may explain why we observed a high rate of low grade tumors.

It is noteworthy that most patients were treated with bilateral orchietomy. That surgical castration is the standard treatment of PCa in China may be partly due to social and economic factors. Indeed, many Chinese individuals do not have easy access to medical care and, moreover, they are often reluctant to receive medication. Subsequently many patients are lost to followup after the first hospitalization. Therefore, bilateral castration is a simple and safe method to ensure that hormone deprivation is maintained. Another crucial point is that medical hormone therapy, such as that with antiandrogens and LHRH analogues, is much more expensive than orchietomy.

Of the patients treated with surgical or medical castration 60% experienced biological recurrence at a median followup of 18.5 months. These findings corroborate those in previous series. Kwak et al recently reported the results of hormone therapy in 177 patients with metastatic PCa. In their series 77.5% of patients had progression to hormone refractory PCa at a median followup of 39 months. Median time until nadir PSA was 8.1 months and median time until PCa became hormone refractory was 24 months. In our study we could analyze neither the interval when nadir PSA was achieved nor the time to hormone refractory cancer because the majority of patients underwent only 1 PSA measurement during followup.

In the current series 2 patients died of PCa. Although the reported specific mortality rate was particularly low, it was probably underestimated because of the large number of patients lost to followup. Moreover, chemotherapy is not commonly used for hormone refractory PCa in China. None of the patients who experienced biological recurrence in our series received chemotherapy. Therefore, the real rate of specific deaths is likely to be higher than that reported.

Finally, radical prostatectomy was performed in 8 patients with clinically localized tumors, of whom none experienced biological recurrence at a median followup of 13 months. Although our data are limited, they indicate that, as in Western countries, curative treatments such as RP may be effective for early stage tumors. Therefore, detecting organ confined PCa in China could dramatically improve the patient outcome. On the other hand, screening for PCa in China would raise the question of which optimal PSA cutoff could enhance cancer detection. In a study of He et al 1,096 healthy Chinese men underwent serum PSA determination. Median serum PSA was 0.82 ng/ml in 50 to 59-year-old men, 0.93 ng/ml in those 60 to 69 years old and 1.17 ng/ml in those 70 years or older. Compared with other populations median and 95th percentile serum PSA values in Chinese men after age 50 years were significantly lower than those in other races and even in other Asian men.

To our knowledge only 1 study of mass screening for PCa in Chinese men has been published. In this study 2,212 Japanese men from Natori and 3,566 Chinese men from Changchun were mass evaluated by PSA measurement. Prostate
biopsies were performed in those in whom the PSA cutoff was 4.1 ng/ml. PSA positive (PSA 4.1 ng/ml or greater) and cancer detection rates in the Japanese and Chinese men were 8.5% and 5.2% (p <0.0005) and 2.1% and 0.8% (p <0.0001), respectively. These findings suggested that the PCa incidence was lower in Changchun, China than in Natori, Japan. Since only limited data are available in the literature, further studies are mandatory to confirm these findings. A prospective study to establish optimal PSA screening criteria in Chang Hai Hospital is ongoing.

CONCLUSIONS

Only sparse information is available regarding the incidence and management of PCa in China. To date hormone therapy represents standard treatment due to the high incidence rate of metastatic tumors at diagnosis. Surgical castration is commonly done for socioeconomic reasons. Screening for PCa could help detect earlier stage tumors and improve the outcome in patients.

REFERENCES
