Incidental prostate cancer in patients with muscle-invasive bladder cancer who underwent radical cystoprostatectomy

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Abstract

Objectives: The aim of this study was to analyze the features of incidentally detected prostate cancer (PCa) in radical cystoprostatectomy (RCP) specimens to determine their pathological characteristics and clinical significance.

Methods: In this retrospective study, we reviewed the clinical and pathological records of 431 consecutive patients with muscle-invasive bladder cancer who underwent RCP at Hirosaki University. Of these, we focused on 237 male patients with prostate-specific antigen (PSA) measurements and digital rectal examinations (DRE) that were recorded prior to the RCP. Significant PCa was defined as a tumor with a Gleason 4 or 5 pattern, pathological T3 or higher stage, lymph node involvement or three or more multifocal lesions within the prostate specimen. We compared clinically significant and insignificant PCa.

Results: In this study, a total of 43 patients (18.1%) were diagnosed with incidental PCa via RCP specimens. Age, preoperative PSA levels and pathological T stage in patients with clinically significant PCa were considerably higher than in those with insignificant cancer. Apical involvement was found in 16 patients, including 11 of those with clinically significant PCa. By the end of the follow-up period, none of the enrolled patients had a biochemical recurrence after surgery or died from PCa.

Conclusion: According to our findings, preoperative risk factors were not reliable enough to accurately predict clinically significant PCa. Although there was no biochemical relapse or clinical recurrence of PCa in this study, the potential oncologic risk of prostate-sparing RCP must be considered.

Key words: incidental prostate cancer, muscle-invasive bladder cancer, cystoprostatectomy, prostate-sparing surgery

Introduction

Radical cystoprostatectomy (RCP) with bilateral pelvic lymphadenectomy is the standard treatment in patients with muscle-invasive bladder cancer (MIBC), or any high-risk, recurrent and noninvasive disease according to the European Association of Urology guidelines (1). Recently, the development of orthotopic neobladder reconstruction and nerve-sparing techniques provides a further benefit in patients with MIBC. Several investigators have reported the use of prostate...
apex or capsule-sparing techniques to improve voiding and sexual functions after surgery (2,3). However, such ‘prostate-sparing’ techniques present the inherent risks of either prostate involvement in urothelial carcinoma (UC) or the existence of prostate cancer (PCa) as a second malignancy (3–5). Therefore, ‘prostate-sparing’ cystectomy is currently recognized as a treatment option for carefully selected patients with MIBC without primary involvement of the prostatic urethra or known PCa (4).

Incidental PCa occurs in ~30% of 50-year-old men, with the rate gradually increasing to as high as 70% in 80-year-old men (6). The PCa is usually small, well or moderately differentiated and localized within the prostate (4). Many patients with insignificant PCa will never present clinically during their lifetime (7). The majority of incidental PCa in RCP specimens is small, organ confined and generally considered clinically insignificant (8).

The aim of this study was to analyze features of incidentally detected PCa in RCP specimens to determine their pathological characteristics and clinical significance.

Methods
Study population
The present study was conducted at the Hirosaki University Graduate School of Medicine in Japan. In this retrospective study, we reviewed the clinical and pathological records of 431 consecutive patients with MIBC who underwent RCP and bilateral pelvic lymphadenectomy (PLND) between May 1994 and July 2016 at Hirosaki University. Of these, we focused on 237 male patients whose prostate-specific antigen (PSA) levels and digital rectal examinations (DRE) were measured and recorded prior to the RCP. The enrolled patients had histologically confirmed Stage T2–T4a cancer of the bladder (9). Patients who had previously undergone RT for the prostate or pelvis or had received androgen deprivation therapy (ADT) for PCa were excluded. Patients who received finasteride or dutasteride before the surgery were also excluded.

The study protocol and informed consent documents were reviewed and approved by the Hirosaki University institutional review board.

Treatment
Of the 237 included patients, 115 patients received neoadjuvant gemcitabine and carboplatin or cisplatin (10), 15 received neoadjuvant cisplatin and doxorubicin arterial infusion (BOAI) and 107 underwent RCP alone. All patients with MIBC at our institution received neoadjuvant therapy from 2005 onward (10–12). Patients with BOAI received two cycles of 70 mg/m² cisplatin and 30 mg/m² doxorubicin. Our RCP and PLND surgical techniques have been previously described in detail (13–15). The choice of urinary diversion was determined according to the surgeon’s discretion and/or the patient’s preference. PLND, including removal of the hypogastic, external iliac, obturator and common iliac lymph nodes up to the aortic bifurcation, was routinely performed.

Patient evaluation
The following baseline information was obtained for each patient: complete history and physical examination findings, Eastern Cooperative Oncology Group performance status, abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI) and chest radiography or CT.

The diagnosis of MIBC was confirmed by a single pathologist at our institution by reviewing the results of transurethral resection and the baseline MRI findings.

Specimens obtained during the cystoprostatectomy were extensively examined to determine the presence of MIBC. We performed a pathological examination of complete transmural sections of the bladder wall to accurately determine the pathological stage of the tumor. In addition, histological examination of several sections from various sites within the bladder, including the dome, anterior wall, lateral walls, posterior wall, trigone and both ureters, was performed to identify superficial disease or a second primary tumor. The prostate specimens were processed according to our whole mount protocol and were evaluated according to the 2005 International Society of Urological Pathology guidelines (16). The apex of the prostate was shaved perpendicular to the prostatic urethra. The bladder neck margin was coned from the specimen and sectioned perpendicularly. The remaining prostate tissue was completely sectioned on 3-mm intervals along a plane perpendicular to the urethral axis.

Tumor staging was performed according to the staging system defined in the American Joint Committee on Cancer Staging Manual (9,17). Clinically significant PCa was defined as a tumor with a Gleason 4 or 5 pattern, pathological T3 or higher stage, lymph node involvement, or three or more multifocal lesions within the prostate specimen (3,18).

Follow-up schedule
Each patient was evaluated every 3 months using ultrasonography (to check for hydronephrosis), urine cytology, and renal and liver function tests. CT of the chest to the pelvis was performed every 6 months for 5 years and annually thereafter.

The patients with incidental PCa were assessed according to their serum PSA at 3-month intervals. The date of clinical recurrence or BCR was defined as the date when the serum PSA level exceeded 0.2 ng/ml. If the PSA level did not decrease to <0.2 ng/ml after surgery, the date of the RCP was defined as the disease recurrence.

Statistical analysis
Data were analyzed using IBM SPSS Statistics 24 (IBM Corp., Armonk, NY, USA). Clinicopathological factors were analyzed using the chi-square test, unpaired t-test or Mann–Whitney U test. All P values were two-sided, and the significance level was set at P < 0.05.

Results
Clinicopathological outcomes
The clinical chart in patients who had incidental PCa in RCP specimens is shown in Fig. 1. In this study, a total of 43 patients (18.1%) were diagnosed with incidental PCa via RCP specimens. A total of seven patients (20.6%) with preoperative PSA levels >4 ng/ml and 36 (17.6%) with PSA levels ≤4 ng/ml were incidentally diagnosed as having PCa via RCP specimens (P = 0.435). Among nine patients with preoperative PSA levels >4 ng/ml and palpable induration on DRE, one patient (11.1%) was diagnosed with incidental PCa after surgery. Meanwhile, among 184 patients with PSA levels ≤4 ng/ml before RCP who had no induration on DRE, 26 patients (14.1%) were diagnosed with incidental PCa after RCP.
Incidental prostate cancer

The clinicopathological characteristics of patients with incidental PCa in the RCP specimens are listed in Table 1. Age, preoperative PSA levels and pathological T stage in patients with clinically significant PCa were significantly higher compared with those of patients with insignificant cancer. Apical involvement was observed in 16 patients (37.2%), including 11 of those with clinically significant PCa (P = 0.024). None of the enrolled patients had metastatic lymph node disease from PCa or seminal vesicle involvement.

Table 2 shows preoperative PSA levels in patients with or without PCa. There were no significant differences between the patients with or without incidental PCa.

Table 3. Published data on incidentally detected prostate cancer in radical cystoprostatectomy specimens

<table>
<thead>
<tr>
<th>References</th>
<th>Number of patients</th>
<th>Mean age (year)</th>
<th>Number of prostate cancer (%)</th>
<th>Number of significant cancer (%)</th>
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<tr>
<td>(3)</td>
<td>95</td>
<td>70.2</td>
<td>26 (27)</td>
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<td>(4)</td>
<td>251</td>
<td>65.3</td>
<td>31 (12)</td>
<td>9 (29)</td>
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<tr>
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<td>217</td>
<td>67</td>
<td>58 (27)</td>
<td>18 (31)</td>
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</tr>
<tr>
<td>(26)</td>
<td>63</td>
<td>67</td>
<td>34 (54)</td>
<td>7 (20)</td>
</tr>
</tbody>
</table>

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Table 2. PSA values before radical cystoprostatectomy

<table>
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<tr>
<th>Number of</th>
<th>Preoperative PSA</th>
<th>P</th>
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<tbody>
<tr>
<td>Significant prostate cancer</td>
<td>20 (8.4)</td>
<td>2.61 (1.23–3.74)</td>
</tr>
<tr>
<td>Insignificant prostate cancer</td>
<td>23 (9.7)</td>
<td>2.27 (1.42–3.50)</td>
</tr>
<tr>
<td>No prostate cancer</td>
<td>194 (81.9)</td>
<td>1.40 (0.82–2.62)</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; IQR, interquartile range.

Discussion

Incidental PCa is a relatively common finding in RCP specimens, and it varies greatly among ethnic groups (19). The frequency of incidental PCa is extremely variable, ranging from less than 10 to nearly 60% (3–5, 19, 20). The outcomes of previous studies are summarized in Table 3 (4, 21). In this study, the rate of incidental PCa was 18.1%, which was remarkably low compared with those in previous studies from Western countries (4). The proportion of incidental PCa in Western countries appears to be 28% (4). Pettus et al. demonstrated a significant association between age and concomitant PCa in 235 RCP specimens with a multivariable odds ratio of 1.3 per 10 years increase in age (22). In addition, Buse et al. quantified the increase in the odds ratio of PCa at 2.8% per year in these patients (23). In this study, the median age of the enrolled patients was 68 years. Therefore, the proportion of incidental PCa in RCP specimens may be relatively low in patients who underwent RCP compared with that of latent PCa.

In this study, no significant differences in preoperative PSA levels were found between the patients with or without incidental PCa in RCP specimens. PSA value alone is a poor screening tool for the detection of incidental PCa due to the low tumor volume and low Gleason score (3, 7, 20). Nakagawa et al. reported that increasing patient age and PSA values were associated with a high incidence of significant PCa (21). Damiano et al. recommended that patients who receive prostate (apex)-sparing radical cystectomy should undergo routine evaluation with transurethral biopsies of the prostatic urethra and transrectal biopsies of the prostate prior to surgery (19). However, the predictive value of preoperative biopsies for the prostate remains unclear. Intraoperative frozen sections of the apical
margin were false-negative in up to 45% of patients who underwent radical prostatectomy for localized PCa (27). Currently, no reliable preoperative factors to precisely detect incidental PCa have been established (19).

Several authors have suggested that preserving apical tissue and/or the prostatic capsule may improve urinary continence and sexual function in patients who undergo orthotopic neobladder reconstruction (8,28). However, apex-sparing surgery presents an oncological risk in patients with residual carcinoma in the prostate apex. In the present study, the rate of incidental PCa in RCP specimens was 18.1%. Among them, apical involvement of the incidental PCa was only 6.8%. In addition, the incidence of apical involvement in patients with clinically significant incidental PCa was significantly higher compared with those with insignificant PCa. Therefore, prostate-sparing surgery may be appropriate for carefully selected patients with MIBC in whom underlying malignancy within the prostate has been ruled out.

Long-term oncological outcomes of incidental PCa in RCP specimens have been rarely reported. Abdenlhady et al. reported that 3.4% of patients who underwent RCP had local and distant recurrence from PCa at a mean follow-up period of 47 months (8). Wolters et al. reported that incidental PCa in RCP specimens showed less aggressive features than screen-detected PCa treated with radical prostatectomy (29). In this study, no biochemical relapse or clinical recurrence of PCa occurred. PSA surveillance should be ongoing after RCP in patients with incidental PCa. However, the overall or cancer-specific survival after RCP mainly depends on the stage or lymph node involvement of the primary bladder cancer (3). Therefore, the follow-up regimen for the incidental PCa may be adopted based on its particular grade or stage (30).

The present study has several limitations. First, because this was a retrospective study, there is an inherent potential for bias. Second, a relatively small number of patients were enrolled in the present study and the follow-up period was relatively short. Based on the findings of this study, preoperative risk factors are not reliable enough to accurately predict clinically significant PCa, as the rate of incidentally detected PCa in RCP specimens was relatively low. Although there was no biochemical relapse or clinical recurrence of PCa in this study, the potential oncologic risk of prostate-sparing RCP must be considered.

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Conflict of interest statement
None declared.

References
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