Pathological and Oncological Outcomes of Elderly Men with Clinically Localized Prostate Cancer

Koji Mitsuzuka1,2,*, Takuya Koie2,3, Shintaro Narita2,4, Yasuhiro Kaiho1,2, Takahiro Yoneyama2,3, Norihiko Tsuchiya2,4, Narihiko Kakoi2,5, Sadafumi Kawamura2,5, Tatsuo Tochigi2,5, Chikara Ohyama2,3, Tomonori Habuchi2,4 and Yoichi Arai1,2

1Department of Urology, Tohoku University Graduate School of Medicine, Sendai, 2Michinoku Japan Urological Cancer Study Group, Sendai, 3Department of Urology, Hirosaki University Graduate School of Medicine, Hirosaki, 4Department of Urology, Akita University Graduate School of Medicine, Akita and 5Department of Urology, Miyagi Cancer Center, Natori, Japan

*For reprints and all correspondence: Koji Mitsuzuka, Department of Urology, Tohoku University School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980-8574, Japan E-mail: mitsuzuka@uro.med.tohoku.ac.jp

Received May 2, 2013; accepted August 26, 2013

Objective: The aim of the study was to characterize pathological and oncological outcomes of elderly men with clinically localized prostate cancer treated with radical prostatectomy.

Methods: Data from 1268 patients undergoing radical prostatectomy between 2000 and 2009 were retrospectively reviewed. Patients were classified according to whether they were of age ≥70 or <70 years at radical prostatectomy. Patient characteristics, pathological and oncologic outcomes were compared among the groups.

Results: Of the total population, 31.4% (398 of 1268) of patients were ≥70 years of age. The median age in patients ≥70 years and <70 years of age was 64 (45–69) and 72 (70–83) years. The proportion of low-risk disease was significantly lower among those ≥70 years of age than in those <70 years, while the proportion of high-risk disease was significantly higher among those ≥70 years of age than in those <70 years (P < 0.001). The proportions of pathological high-risk disease (≥T3b, GS >8, positive surgical margin or lymph node invasion) in patients <70 and ≥70 years of age were 42.0 and 50.0%, respectively (P = 0.008). The proportions of organ-confined disease in patients <70 and ≥70 years of age were 69.9 and 65.1%, respectively (P = 0.09). With a median follow-up of 50 months, 5-year biochemical recurrence-free and cancer-specific survival rates were not significantly different among the groups.

Conclusions: Radical prostatectomy was more likely to be performed in those with higher-risk disease among patients ≥70 years of age. About half of the patients ≥70 years of age had pathological, high-risk disease. Radical prostatectomy could be considered for patients with expected long-term life expectancy, even in the setting of advanced age.

Key words: radical prostatectomy – elderly – oncological outcome – age

INTRODUCTION

The newly diagnosed prostate cancer is the sixth most common form of cancer in Japanese males in 2005 and is predicted to be the second most common cancer by 2020 (1). At least, some portion of this increase is attributed to a widespread use of prostate-specific antigen (PSA) screening and the general aging of the population. Prostate cancer arises mainly in elderly men, and a substantial portion of men who undergo radical prostatectomy (RP) are elderly. However, the use of RP in elderly patients remains controversial. Recently, the Scandinavian Prostate Cancer Group Number 4 examined...
the benefit of RP when compared with watchful waiting and concluded that RP did not produce a survival benefit in men >65 years (2). Moreover, the Prostate Intervention Versus Observation Trial (PIVOT) Study Group recently reported that RP did not significantly reduce all-cause or prostate-cancer mortality when compared with observation alone through at least 12 years of follow-up (3). On the other hand, the life expectancy for Japanese men who are 65 years old is 18.9 years, which is longer than that in the USA (17.7 years) and most European countries (Germany, 17.8 years; the Netherlands, 17.9 years; Spain, 18.6 years; the UK, 18.3 years (4). Although age at RP is an important factor when considering the indications for RP, data from one geographic region cannot necessarily be generalized to another geographic region. The present study examined the results of RP performed in men of age ≥70 years in Japan to help refine the indications for RP in elderly patients with clinically localized prostate cancer.

PATIENTS AND METHODS

This study was approved by the institutional review boards at each participating site, and institutional data-sharing agreements were established before initiation of the study. Between January 2000 and December 2009, 1268 consecutive patients with clinically localized prostate cancer underwent RP at Tohoku University, Hirosaki University, Akita University and Miyagi Cancer Center. None of the patients had a prior history of prostate surgery, nor did they undergo neoadjuvant hormonal or radiation therapy. RP was achieved in an open retropubic manner in all cases. The surgical specimen containing the prostate gland with seminal vesicles attached was serially sectioned perpendicular to the long axis of the gland. Pathological evaluation of biopsy and surgical specimens was performed at each institution by a dedicated genitourinary pathologist according to the Gleason grading system and pathological stage based on the 2002 TNM classification. The total tumor volume was measured at Tohoku and Hirosaki Universities using computer-assisted image analysis (NIH Image, developed and maintained by the National Institutes of Health, Bethesda, MD, USA) and defined as the sum of the volumes of individual cancer foci (5).

Patients were classified according to age at RP (<70 or ≥70 years old), because the mean age of patients in this study was 68 years. Furthermore, 70 years was considered to be reasonable as the age cut-off for the purpose of analyses. Preoperative factors [PSA, body mass index (BMI), prostate volume, clinical stage, biopsy Gleason score (bGS) and risk group according to the D’Amico risk classification (6)], pathological findings [pathological stage, pathological Gleason score (pGS), tumor volume, organ-confined disease (OCD), positive resection margin (PSM), lymph node invasion (LNI)] and oncological outcomes [PSA recurrence-free (bFS), cancer-specific (CSS), overall survivals (OS)] were compared among the two subgroups. Insignificant cancer is defined as two cut-offs of tumor volume based on the Epstein criteria with pT2, pGS ≤6 and tumor volume <0.5 ml (7) and the recent European study of screening with pT2, pGS ≤6 and tumor volume <2.5 ml (8). Pathological high-risk cancer is defined as cancer that had at least one unfavorable pathological factor, including ≥pT3b, pGS ≥8, PSM or LNI (9–11)

The follow-up schedule after RP involved a PSA assay every 3 months for the first 2 years, every 6 months for the following 3 years and then annually thereafter. The date of disease recurrence or bFS is defined as the point at which the serum PSA level exceeded 0.2 ng/ml, when an RP was carried out if the PSA level did not decrease <0.2 ng/ml after surgery, or when adjuvant therapy was initiated even if the PSA level did not exceed 0.2 ng/ml.

All statistical analyses were performed using JMP 9.0.2 software (SAS Institute, Inc., Cary, NC, USA). Clinicopathological parameters were analyzed using the χ² test. bFS, CSS and OS were determined by the Kaplan–Meier method.

RESULTS

Of 1268 patients treated with RP, 31.4% (398 of 1268) were ≥70 years old. The median age at RP in those <70 years and those ≥70 years of age was 64 (45–69) and 72 (70–83) years, respectively. The total tumor volume was measured in 54.5% (474/870) of those <70 years of age and in 45.3% (179/398) of those ≥70 years of age.

Table 1 shows preoperative variables in the two age subgroups. BMI and prostate volume were significantly higher and larger, respectively, among those ≥70 years of age than in those <70 years of age. Clinical stage, bGS and number of biopsy-positive cores were also higher among those ≥70 years of age than in those <70 years of age. According to the D’Amico risk classification system, the proportion of low-risk group was lower and the proportion of high-risk group was higher among those ≥70 years of age than in those <70 years of age.

On pathological findings, high stage, high pGS, PSM, LNI and non-OCD were more likely to be seen in those ≥70 years of age than in those <70 years of age, although only pGS was significantly higher among those ≥70 years of age than in those <70 years (Table 2).

The proportions of insignificant cancer with tumor volume <0.5 ml in those <70 years of age and in those ≥70 years of age were 3.3 and 1.1%, respectively (P = 0.176), while the proportions of insignificant cancer with tumor volume <2.5 ml in those <70 years of age and in those ≥70 years of age were 6.8 and 2.8%, respectively (P = 0.025). The proportion of pathological high-risk cancer with at least one unfavorable pathological factor (e.g. pGS ≥8, ≥pT3b, PSM or LNI) was significantly higher among those ≥70 years of age (50.0%) than in those <70 years of age (42.0%) (P = 0.008) (Table 3).

With a median follow-up of 50 months, the 5-year bFS was 80.9% in those <70 years of age and was 77.4% among those
The 5-year CSS was 99.8% in those ≥70 years of age and was 99.5% among those <70 years of age (P = 0.692). The 5-year OS was significantly lower among those ≥70 years of age (95.8%) than in those <70 years of age (99.5%) (P = 0.011) (Fig. 1).

DISCUSSION

RP in elderly patients can sometimes represent a form of overtreatment and might result in undesired complications, functional impairment, decreased quality of life or excessive healthcare costs. Recent reports studying oncological outcomes of RP versus observation express some skepticism regarding the value of RP, especially in elderly patients (2,3).

In the present study, RP was more likely to be performed in patients with higher PSA, bGS and clinical stage among those ≥70 years of age, which resulted in a lower proportion of low-risk disease and a higher proportion of high-risk disease in those ≥70 years of age when compared with those <70 years of age. Kunz et al. reported that those ≥70 years of age presented with a higher proportion of high-risk disease when compared with those younger than 70 years of age among their 1636 patients undergoing RP (12). This may be because less aggressive treatment modalities, such as active surveillance, brachytherapy or external beam radiotherapy, are preferred in elderly patients (13). These unfavorable characteristics like higher PSA, bGS and clinical stage at the time of RP among those ≥70 years of age would have led to a higher proportion of pathological high-risk cancer (e.g. pGS ≥8, pT3b, seminal vesicle invasion or LNI) and a lower proportion of insignificant cancer, with only 2.8% of those ≥70 years of age satisfying the insignificant cancer definition (i.e. pT2, GS <6 and tumor volume <2.5 ml). On the other hand, bFS or CSS was not different when comparing the two age subgroups. The follow-up period in this study might have been relatively short to estimate the influence of advanced age on oncological outcomes. Albertsen et al. (9) reported that men with high-grade prostate cancers have a high probability of dying from prostate cancer within 10 years of diagnosis. Therefore, longer follow-up might have resulted in the detection of significant difference in bFS or CSS in the present study.
Data from the present study indicated that unfavorable characteristics like higher PSA, bGS and clinical stage at the time of RP resulted in adverse pathological outcomes among those ≥70 years of age, while several studies have reported that prostate cancer tends to have more aggressive features in elderly patients than in non-elderly patients. For example, Ko et al. reported that prostate cancer in mean >70 years of age commonly had adverse pathological features, and that the treatment failure rate was significantly higher in older patients than in matched younger patients (14). Kunz et al. reported that patients ≥70 years of age had biologically more aggressive and locally advanced tumors when compared with those <70 years of age, although age itself was not an independent predictor of survival after RP with a median follow-up of 4 years (12). Nakagawa et al. (15) showed that the incidence of significant prostate cancer increased with patient age, based on the study of their cystoprostatectomy specimens. These results support the use of RP in elderly patients and argue against the use of conservative treatment.

Life expectancy is another important factor when considering the indication for RP in elderly patients. In the PIVOT study, 47.0% of patients (median age, 67 years) who underwent RP died during a median follow-up of 10 years. In the present study, the 5-year OS rate was 95.8% with the median age of 72 years among those ≥70 years of age, which was much better than that reported in the previous studies (3,12). Life expectancy in Japanese men is longer than that for men in other countries (4), and men under healthy conditions and less comorbidities would have undergone RP in our study. These factors might produce a large difference in OS when comparing the present study with other studies.

Complications related to RP are also essential when considering the use of RP. Trinh et al. (16) reported that the use of RP among older patients (≥75 years) was associated with increased homologous blood transfusion rates, intraoperative and postoperative complication rates, and mortality rate. Agarwal et al. (17) reported that age was predictive of surgical complications when assessing the safety profile of robot-assisted RP. On the other hand, Alibhai et al. reported that comorbidity is a stronger predictor of early complication than age (18). Further, they concluded that the risk of postoperative mortality after RP is relatively low in otherwise healthy older men ≤79 years of age. Thus, while age could be a predictor of complications after RP, comorbidities or health status seems to be much better predictors of complications than age.

Urinary incontinence or erectile dysfunction is a major concern after RP, even in elderly patients. Ficarra et al. (19,20) recently conducted a systematic review and meta-analysis of urinary continence and potency after robot-assisted RP and revealed that age is a predictor of urinary continence or recovery after RP. On the other hand, the prostate volume was significantly larger among those ≥70 years old than in those <70 years. A larger prostate volume often causes lower urinary tract symptoms (21), and RP might be beneficial to relieve these symptoms. We previously reported that urinary function was significantly lower in elderly patients than in younger patients after RP, but that both younger and older groups had a similar recovery by the end of Year 2, despite a consistently lower level of sexual function both before and after RP in elderly patients (22).

Determination of the optimal indications for RP in elderly patients with clinically localized prostate cancer is difficult, because comprehensive assessment is needed, including an assessment of age, comorbidities, life expectancy, oncological outcomes, function and quality of life. However, selected patients with few comorbidities and/or intermediate- or high-risk disease might be candidates for RP and benefit from RP, even in the setting of advanced age (i.e. ≥70 years). Long-term follow-up and accumulation of data in Japanese elderly patients are needed to select patients appropriately for RP, because health status and life expectancy may differ according to the specific geographic location.

This study has several limitations. First, a median follow-up time of 50 months might be relatively short to determine the oncological outcomes of RP. Second, this study did not address health status or comorbidities in patients treated with RP and did not study complications or function after RP. These factors are likely significant when considering the use of RP in elderly patients. Third, patients ≥70 years of age in this study might not be representative of all Japanese elderly men or elderly patients with prostate cancer, because well-selected patients who were healthy and who have less morbidities tended to select RP (13,23). Fourth, this study focused only on RP, and radiation therapy either with or without

Figure 1. Probability of (A) biochemical recurrence-free survival, (B) cancer-specific survival and (C) overall survival among those <70 years of age and among those ≥70 years of age.
androgen deprivation represents an alternative to RP, especially in elderly patients. Despite these limitations, the present data provide clinically relevant information for the consideration of indications for RP in elderly patients with clinically localized prostate cancer.

Conflict of interest statement
None declared.

References
7. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 1994;271:368–74.