Oncologic Outcome of Radical Prostatectomy as Monotherapy for Men with High-risk Prostate Cancer

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Key Words

High-risk prostate cancer • Radical prostatectomy • Biochemical recurrence

Abstract

Background: The objective of this study was to review our experience with radical prostatectomy (RP) as monotherapy for men with high-risk prostate cancer (PCa). **Patients and Methods:** This study included 382 consecutive patients who were diagnosed with high-risk PCa according to the D'Amico definition and subsequently underwent RP without neoadjuvant therapy. Biochemical recurrence (BR) was defined as a serum prostate-specific antigen (PSA) level ≥ 0.2 ng/ml on two consecutive measurements, and none of the patients received any adjuvant therapies until their serum PSA levels reached ≥ 0.4 ng/ml. **Results:** The median preoperative serum PSA level in these 382 patients was 15.9 ng/ml. Pathological stages $\geq$ pT2c and Gleason scores ≥ 8 were observed in 288 and 194 patients, respectively. During the observation period (median, 48.0 months), BR occurred in 134 patients, and the 5-year BR-free survival rate was 60.1%; however, no patient died of cancer progression. Multivariate analysis identified capsular invasion, seminal vesicle invasion, and surgical margin status as independent predictors of BR. **Con-**

clusions: Comparatively favorable cancer control could be achieved using RP as monotherapy for men with high-risk PCa; however, RP alone may be insufficient for patients with capsular invasion, seminal vesicle invasion, and/or surgical margin positivity.

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Introduction

Prostate cancer (PCa) is the most common malignancy and the second leading cause of cancer-related death in men in Western industrialized countries [1]. Despite the widespread use of prostate-specific antigen (PSA) screening, approximately 15–25% of PCa patients are still diagnosed with locally advanced disease [2]. In 1998, D'Amico et al. [3] proposed a useful risk classification using pretreatment clinicopathological parameters, which remains the most widely accepted and validated system in a number of reports [4, 5]. In this system, patients with a serum PSA level > 20 ng/ml, Gleason score of 8–10, and/or clinical stage $\geq$ T2c are categorized as a high-risk group [3].

Table 1. Patient characteristics

Patient demography	Value
Age, years (range)	67.8 (50–79)
Prostate-specific antigen, ng/mL (range)	15.9 (2.9–65.4)
Clinical stage	
T1c	69 (18.1%)
T2a	89 (23.3%)
T2b	59 (15.5%)
T2c	109 (28.5%)
T3	56 (14.6%)
Biopsy Gleason score	
≤ 6	75 (19.6%)
7	113 (29.6%)
≥ 8	194 (50.8%)
Pathological stage	
pT2a	36 (9.4%)
pT2b	58 (15.2%)
pT2c	133 (34.8%)
pT3a	94 (24.6%)
pT3b	61 (16.0%)
Gleason score	
≤ 6	40 (10.5%)
7	228 (59.7%)
≥ 8	114 (29.8%)
Extracapsular extension	
Negative	235 (61.5%)
Positive	147 (38.5%)
Seminal vesicle invasion	
Negative	321 (84.0%)
Positive	61 (16.0%)
Perineural invasion	
Negative	113 (29.6%)
Positive	269 (70.4%)
Lymphovascular invasion	
Negative	233 (61.0%)
Positive	149 (39.0%)
Lymph node status	
pN0	361 (94.5%)
pN1	21 (5.5%)
Surgical margin status	
Negative	201 (52.6%)
Positive	181 (47.4%)

Of the 2 major recommended options, external beam radiotherapy (EBRT) rather than radical prostatectomy (RP) is likely to be selected as the primary treatment for patients with localized high-risk PCa, due to the significant morbidity associated with the low probability of a complete cure by surgery alone in this cohort of patients [6, 7]. To date, however, a reliable randomized trial comparing RP and EBRT has not been conducted in men with high-risk PCa. Several retrospective studies on clinically localized PCa have favored RP [8–10], whereas others have favored EBRT [11, 12]; therefore, the optimal treatment for men with high-risk PCa remains controversial.

Table 2. Uni- and multivariate analyses of several pathological factors for predicting biochemical recurrence-free survival

Variables	Univariate analysis		Univariate analysis	
	Hazard ratio	p	Hazard ratio	p
Gleason score (< 8 vs. 8)	1.43	< 0.0001	1.32	0.0021
Extracapsular extension (negative vs. positive)	3.16	< 0.0001	1.55	0.0439
Seminal vesicle invasion (negative vs. positive)	4.42	< 0.0001	2.47	< 0.0001
Lymphovascular invasion (negative vs. positive)	1.96	< 0.0001	1.10	0.4882
Perineural invasion (negative vs. positive)	2.69	< 0.0001	1.46	0.2136
Lymph node status (pN0 vs. pN1)	4.13	< 0.0001	1.49	0.1869
Surgical margin status (negative vs. positive)	2.83	< 0.0001	1.84	0.0059

RP has been shown to provide excellent local control, accurately stage the disease, and remove benign sources of PSA, which makes it possible to promptly identify biochemical recurrence (BR) and initiate subsequent treatment in an optimal time frame [13]. Several previous studies suggested that these advantages of RP could be applied to patients with high-risk PCa as well, resulting in the achievement of favorable cancer control by combining other therapeutic modalities [6, 7, 13–18]. For example, Meng et al. [14] reported the 10-year outcomes from the CaPSURE database for men with high-risk PCa treated with RP, showing 95% cancer-specific survival and 80% overall survival. However, the significance of RP as monotherapy for high-risk PCa has not been well characterized. Accordingly, we retrospectively assessed the clinical outcomes in a total of 382 consecutive patients with high-risk PCa who underwent RP without neoadjuvant therapy and received no postoperative adjuvant therapies until their serum PSA levels reached ≥ 0.4 ng/ml.

Patients and Methods

Informed consent for conducting this study was obtained from each patient, and the study design was approved by the Research Ethics Committee of our institutions. This study included a total of 382 consecutive patients who were diagnosed with clinically localized high-risk PCa, and subsequently underwent RP and pelvic lymphadenectomy without any neoadjuvant therapies at our institutions between January 2004 and December 2013. High-risk PCa was defined as those with a serum PSA level > 20 ng/

Fig. 1. Biochemical recurrence-free survival of 382 patients with high-grade prostate cancer who underwent radical prostatectomy.

ml, Gleason score of 8–10, and/or clinical stage $\geq$ T2c according to the D'Amico criteria [3]. Prior to RP, PCa was diagnosed histopathologically using specimens obtained from systematic transrectal ultrasound-guided needle biopsy and/or transurethral resection of the prostate. The staging procedures included digital rectal examination, transrectal ultrasonography, serum PSA assay, computed tomography, magnetic resonance imaging, and/or bone scan.

In this series, RP was performed based on the procedure described by Walsh in combination with modifications by others [19, 20]. As a rule, the anatomical extent of bilateral lymphadenectomy was the obturator fossa and external iliac region, and the median number of lymph nodes resected per patient was 16.5 (range 5–26). All pathological examinations were generally performed under the guidance of a single pathologist based on the 2010 TNM classification system. The surface of the resected specimen was inked, fixed, and whole-mount step sections were cut transversely at 3-mm intervals from the apex of the prostate to the tips of the seminal vesicles. A positive surgical margin was defined by the presence of cancer cells at the inked margin. As for the Gleason grading for both biopsy and radical prostatectomy specimens, the modified International Society of Urological Pathology 2005 Gleason grading system was used [21].

After RP, patients were followed by periodic measurement of the serum PSA value at least every 3 months for the first 2 years, and every 6 months thereafter. BR was defined as a PSA level ≥ 0.2 ng/ml on 2 consecutive measurements. Irrespective of the pathological findings suggesting a poor prognosis, none of the patients were treated with any postoperative adjuvant therapies until their serum PSA levels reached ≥ 0.4 ng/ml.

In this study, all statistical analyses were performed using Statview 5.0 software (Abacus Concepts, Inc., Berkeley, CA, USA), and *p* values < 0.05 were considered significant. The BR-free survival rates of the included patients were calculated employing the Kaplan-Meier method, and the differences were determined

by the log-rank test. The prognostic significance of certain factors was assessed using the Cox proportional hazards regression model.

Results

Table 1 summarizes the clinicopathological characteristics of the 382 high-risk PCa patients included in this study. Of these 382, 116 (30.4%), 194 (50.8%), and 288 (75.4%) were judged to have a serum PSA level > 20 ng/ml, Gleason score of 8–10, and clinical stage $\geq$ T2c, respectively. During the observation period of this series (median 48.0 months; range 1–115 months), BR occurred in 134 of the 382 patients (35.1%), and the 1-, 3-, and 5-year BR-free survival rates were 79.2%, 68.4%, and 60.1%, respectively (fig. 1).

We then evaluated the impact of several pathological parameters on the prediction of BR-free survival in the 382 patients. As shown in Table 2, univariate analysis using the Cox proportional hazards regression model showed that the Gleason score, extracapsular extension, seminal vesicle invasion (SVI), lymphovascular invasion, perineural invasion, lymph node metastasis, and surgical margin status (SMS) were significant predictors for BR-free survival. Moreover, the Gleason score, extracapsular extension, SVI, and SMS appeared to be independently related to BR-free survival on multivariate analysis of these 8 significant parameters determined by univariate analysis. BR-free survival curves according to these 4 independent predictive factors for BR are shown in fig. 2, and significant differences in BR-free survival with respect to all of these 4 factors were noted.

To more precisely characterize the prognostic features in this cohort of patients, we classified patients into 3 groups according to the positive number of 4 independent risk factors for BR-free survival identified by multivariate analysis; that is, BR occurred in 16 of 112 patients who were negative for all risk factors (14.3%), 66 of 203 positive for 1 or 2 risk factors (32.6%), and 52 of 67 positive for 3 or 4 risk factors (77.7%). As shown in fig. 3, there were significant differences in BR-free survival among these 3 groups.

Discussion

Although an increasing proportion of men with high-risk PCa receive combined treatment with EBRT and hormonal therapy, the optimal management of high-risk PCa remains controversial. However, with a marked de-

Fig. 2. **a** Biochemical recurrence (BR)-free survival of patients with high-grade prostate cancer (PCa) who underwent radical prostatectomy (RP) according to the Gleason score. **b** BR-free survival of patients with high-grade PCa who underwent RP according to extracapsular extension. **c** BR-free survival of patients with high-grade PCa who underwent RP according to seminal vesicle invasion. **d** BR-free survival of patients with high-grade PCa who underwent RP according to the surgical margin status.

crease in the incidence of severe adverse events following RP due to recent advances in anatomical knowledge and improvements in surgical techniques [22], it has become common for PCa patients to choose avoiding the complications associated with hormonal therapy, which include hot flash, impotence, loss of libido, gynecomastia, osteopenia, and an increase in the risk of cardiovascular disease [23]. Accordingly, it has become attractive for patients with high-risk PCa, particularly younger men, to consider RP as an alternative option to EBRT combined with hormonal therapy. In fact, there have been several studies showing favorable cancer control by RP in men with high-risk PCa [6, 7, 13–18]; however, these studies included some patients, albeit a very small proportion, who received additional therapy as either neoadjuvant or

adjuvant setting. Considering these findings, in this study, we retrospectively assessed the prognostic outcomes in a total of 382 patients with high-risk PCa who underwent RP as monotherapy in order to address the significance of surgical treatment for patients with high-risk PCa.

In this series, < 60% of the included patients had pathologically organ-confined disease; however, BR was noted in 35.1% of the included patients, and there was no patient who died of PCa progression during the median observation period of 48.0 months. Despite being a comparatively shorter follow-up interval, these outcomes may be comparable to those in previous studies [5–7, 13–18]. For example, Loeb et al. [7] reported that at a median follow-up of 8 years in 175 high-risk PCa patients undergoing RP, BR, local recurrence, and metastatic dis-

Fig. 2. Biochemical recurrence (BR)-free survival of patients with high-grade prostate cancer who underwent radical prostatectomy according to the positive number of independent risk factors for postoperative BR, including the Gleason score, extracapsular extension, seminal vesicle invasion, and surgical margin status.

ease occurred in 29%, 3%, and 13%, respectively, and 6% died of PCa. Similarly, Boorjian et al. [5] assessed data on 1,513 men with high-risk PCa who received RP, and showed that the 10-year BR-free, systemic progression-free, and cancer-specific survival rates were 55%, 89% and 95%, respectively. Collectively, these findings suggest that a large proportion of patients with high-risk PCa could be cured by surgical therapy, irrespective of additional treatments.

It is of interest to identify factors associated with BR-free survival after RP in patients with high-risk PCa. In this series, of the several pathological parameters examined, the Gleason score, extracapsular extension, SVI, and SMS were identified as independent predictive factors of BR-free survival on multivariate analysis. The present outcomes are consistent with several previous studies [13–18]. For example, Ploussard et al. [15] reported that the Gleason score ≥ 8 , pathological stage $\geq$ pT3, positive SM, and lymph node involvement were independently associated with BR-free survival in 813 high-risk PCa patients who were treated with RP. These findings suggest the important role of conventional pathological factors in RP specimens in the prediction of biochemical outcomes in patients with high-risk PCa even after treatment with surgical monotherapy.

Another point of interest is to examine whether or not prognostic prediction could be refined by combining plural risk factors for BR simultaneously. In this series, based

on the outcomes achieved by multivariate analysis, the 382 patients were classified into the following 3 groups according to the positive number of independent risk factors for BR: negative for all risk factors, positive for 1 or 2 risk factors, and positive for 3 or 4 risk factors, and significant differences in BR-free survival among these 3 groups were noted. Abern et al. [18] reported that it was useful to classify high-risk PCa patients using the Gleason score, pathological T stage, and lymph nodal status into favorable and unfavorable prognostic groups, while Ploussard et al. [15] proposed a risk stratification system following RP for high-risk PCa based on extracapsular extension, SVI, and SMS. Taken together, a simultaneous consideration of the 4 major risk factors identified in this series (Gleason score, extracapsular extension, SVI, and SMS) may contribute to develop a novel predicting system that can be more closely related to BR after RP for men with high-risk PCa, and thus allow better individualization of the postoperative follow-up and management in this category of patients.

Here, we would like to describe the limitations of this study. Firstly, despite the comparatively larger number of patients included in this study, the observation period was not long enough to draw definitive conclusions, especially regarding those associated with prognostic issues. Thus, it will be necessary to confirm whether the findings of this study could be consistent with those obtained after extending the observation period. Secondly, the current cohort represents selected patients who were regarded as optimal candidates for surgery; therefore, the present findings could not be applied to all men with high-risk PCa. Thirdly, the D'Amico classification system is one of many criteria for the definition of high-risk PCa, and inconsistent outcomes were shown depending on the risk classification system [24]. Fourthly, a total of 17 surgeons were involved as operators in this series; and although they were all highly experienced, the oncological outcomes following RP could be influenced by differences in the surgical techniques of each surgeon, particularly those associated with local wide resection of tissues surround the prostate [25]. Finally, it should be carefully evaluated whether the strategy of additional postoperative therapy in this series negatively affect the prognostic outcomes, since the benefit of early introduction of adjuvant therapies in patients likely to develop disease recurrence, such as those with a positive surgical margin, is widely recognized.

In conclusion, to our knowledge, this is the first study to show that RP as monotherapy could provide encouraging mid-term oncological outcomes for the management

of high-risk PCa patients classified based on the D'Amico system, achieving a 60.1% BR-free survival rate at 5 years after surgery. These findings indicate that despite its utility, the D'Amico criteria define a heterogeneous cohort as a high-risk group; therefore, we developed a system to more precisely predict prognostic outcomes in high-risk PCa patients undergoing RP using a positive number of independent risk factors for BR, including the

Gleason score, extracapsular extension, SVI, and SMS. Collectively, these findings suggest that although some proportion of patients with high-risk PCa ultimately require a multimodal therapeutic approach following RP, it may still be suitable for this category of patients to be treated with surgical monotherapy considering the potential advantages in RP.

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