

The role of radical prostatectomy in high-risk prostate cancer

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Because of the increase in prostate cancer patients, urologists can detect more clinically localized prostate cancer in patients before the disease has progressed to advanced stages. Nevertheless, some patients are still diagnosed with high-risk prostate cancer. Even though several treatment options are available for high-risk prostate cancer patients, including radical prostatectomy, radiotherapy, and hormone therapy, used alone or in combination, the recurrence rate is high regardless of the type of treatment. Nevertheless, in the experience of many urologists, a substantial proportion of high-risk prostate cancer patients are cured by local definite therapy or multimodality treatment. Thus, several treatment combinations have been attempted as treatments in these patients. Among them, radical prostatectomy is regarded as the first step in high-risk prostate cancer patients, on a selective basis. In some high-risk prostate cancer patients, surgery is a one-step modality in treatment and has an excellent oncological prognosis. However, because of the lack of evidence and well-controlled comparative prospective studies, the best course of treatment can be unclear, and oncological outcomes often appear heterogeneous. We therefore review the current literature on clinical outcomes in high-risk prostate cancer.

Keywords: High-risk prostate cancer, Radical prostatectomy, Radiotherapy, Hormone therapy

INTRODUCTION

Prostate cancer is the most common cancer among men in Western countries [1-3]. In Asia, a recent rapid increase in the incidence and detection of prostate cancer has been observed. Environmental elements, such as increased average life expectancy, the change to Western dietary habits, and the medical development of laboratory diagnosis and prostate-specific antigen (PSA) screening campaigns [4] are believed to be causal factors in the increased incidence of prostate cancer. Because of PSA screening, urologists can detect clinically localized prostate cancer in patients before the disease has progressed to advanced stages. Because many indolent cancers can be detected, prostate cancer mortality rates declined significantly between 1990 and 2005 [5]. Nevertheless, some prostate cancer patients still die because the disease

progresses [6]. Prostate cancer patients who have a higher likelihood of disease progression despite definite therapy, including radical prostatectomy (RP) and radiotherapy (RT), are classified by urologists as high-risk prostate cancer patients [7], and they are acknowledged to be at a higher risk for prostate-related death [8,9].

In high-risk prostate cancer patients, the best course of treatment is often unclear, and the oncological outcomes appear heterogeneous. Even though several treatment options, including RP, RT, and hormone therapy (HT) alone or in combination, are available for high-risk prostate cancer patients, the recurrence rate is high regardless of the type of treatment [10,11]. Despite the lack of high-level evidence of treatment benefits for these patients, the high-risk of disease progression and death from the disease may result in making active treatment, including RP, a preferred option. The aim of this

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Table 1. Definition of high-risk prostate cancer

Investigator	Definition
D'Amico et al. [12]	PSA \geq 20 ng/mL or GS 8–10 or clinical stage \geq T2c
American Urologic Association [2]	PSA \geq 20 ng/mL or GS 8–10 or clinical stage \geq T2c
European Association of Urology [1]	PSA \geq 20 ng/mL or GS 8–10 or clinical stage \geq T3a
National Comprehensive Cancer Network [13]	PSA \geq 20 ng/mL or GS 8–10 or clinical stage \geq T33 or any two of following criteria: T2b/c, GS 7, PSA 10–20 ng/mL
Radiation Therapy Oncology Group [14]	PSA 20–100 ng/mL, GS 8–10, and any clinical stage or clinical stage \geq T2c or PSA < 100 ng/mL and GS 8–10

PSA, prostate-specific antigen; GS, Gleason score.

article is to define high-risk prostate cancer and to review the various outcomes after RP.

DEFINITION OF HIGH-RISK PROSTATE CANCER

The definition of high-risk prostate cancer varies according to clinical stratification systems (Table 1) [1,2,12–14]. Using these classification systems, urologists can predict the biochemical recurrence (BCR) after definitive therapy. The most commonly used model was developed by D'Amico et al. [12]. This model is based on the preoperative PSA, the preoperative Gleason score, and the clinical stage of the disease. High-risk prostate cancer was defined as preoperative PSA > 20 ng/mL and/or preoperative Gleason score of 8–10 and/or clinical stage \geq T2c. In The National Comprehensive Cancer Network [13] and European Association of Urology [1], the definition of high-risk prostate cancer varied in D'Amico et al. as preoperative PSA > 20 ng/mL and/or preoperative Gleason score of 8–10 and/or clinical stage \geq T3a. In addition, other investigators have developed definitions of high-risk prostate cancer, which differ slightly. In other words, the exact definition of high-risk prostate cancer is unclear and a consensus has not yet been reached.

This situation has brought about difficulties in the comparison of oncological outcomes of high-risk prostate cancer, the clinical assessment of risk classification, etc. Moreover, there is a certain limitation in prostate cancer risk classification using the three basic parameters: the preoperative PSA, the preoperative Gleason score, and the clinical stage of the disease. In the case of PSA level, there are fluctuations according to the individual condition, which include benign prostatic hyperplasia, prostatitis, and other nonmalignant conditions. Clinical staging determination based on digital rectal examination is imprecise for the evaluation of extraprostatic disease. However, magnetic resonance imaging avoids inaccurate classifications of prostate cancer. Nevertheless, the accurate determination of clinical staging in the disease still has unresolved issues. In addition, the preoperative Gleason score

does not represent the postoperative Gleason score in the RP specimens.

Because of these limitations, several multivariate risk assessment tools have been developed. One well-known risk assessment tool is the Kattan nomogram [15]. This tool uses the PSA, Gleason score, clinical stage of the disease, and additional prostate biopsy information. Recently, Cooperberg et al. [16] developed another high-risk prostate cancer definition: the Cancer of the Prostate Risk Assessment (CAPRA) score. They added secondary parameters, including prostate biopsy profiles and age of the patient to the existing basic parameters. The CAPRA score ranges from 0 to 10, and a CAPRA score of 6–10 represents high-risk prostate cancer. This tool was recently updated because the CAPRA postsurgical score (CAPSA-S) and the postoperative pathologic results can be used to predict BCR after RP [17]. A consensus on the definition of high-risk prostate cancer as a worldwide standard is an urgent priority even though various tools based on clinicopathological information have been validated as useful in prostate cancer risk stratification.

RADICAL PROSTATECTOMY FOR HIGH-RISK PROSTATE CANCER

RP is considered the treatment of choice in low- and intermediate-risk prostate cancer patients. However, the role of RP in high-risk prostate cancer remains controversial. Not very long ago, many urologists agreed that RP was not a suitable treatment option for high-risk prostate cancer patients because they accepted that the BCR rate and systemic progression rate after RP was significantly higher than that in other risk prostate cancer patients [18]. However, several recent studies of high-risk prostate cancer have presented another view [19–24].

Recently, Johns Hopkins medical institutions reported their experiences of RP outcomes in high-risk prostate cancer patients. Loeb et al. [25] reported that a 10-year BCR rate was 32% with a 16% rate of metastasis and a 92% cancer specific survival (CSS) rate in high-risk prostate cancer patients who underwent RP. Spahn et al. [26] reported that the 5- and

10-year CSS was 89.8% and 84.5%, respectively, in 712 men with high-risk disease with preoperative PSA over 20 ng/mL. Zwergel et al. [27] also reported that the 5-, 10-, and 15-year CSS was 93%, 83%, and 71%, respectively, using 275 high-risk prostate cancer patients at a median of 42 months follow-up. They also used a cohort study with prostate cancer patients who had a preoperative PSA over 20 ng/mL. In cases of patients with prostate cancer in clinical stage T3a, Hsu et al. [28] reported the oncological outcomes of 200 men with initial clinical stage T3a disease who were treated by RP. At 10 years, the progression-free survival (PFS), CSS, and overall survival (OS) were 85.4%, 91.6%, and 77%, respectively. Long-term follow-up data was reported by Eggener et al. [29] for patients who had a high preoperative Gleason score between 8 and 10. They reported that the 10- and 15-year CSS was 72% and 89%, respectively. Boorjian et al. [30] reported that the 7-year CSS rate was 91% in a series of 584 men treated with RP with a Gleason score between 8 and 10.

Similarly, several studies supported the finding that RP could result in long term PFS and CSS despite the high rate of BCR in comparison with low- and intermediate-risk prostate cancer patients. RP had a potential role in men with high-risk prostate cancer. However, we should remember that these observations were influenced by pathological down staging and downgrading in comparison with clinical staging and grading [31-33]. Many patients who had clinically suspected high-risk prostate cancer were later revealed as pathologically favorable prostate cancer patients. According to several studies, about 20 to 30% of patients were pathologically down-staged to pT2 at the time of surgery. The proportion of patients who were cured by RP alone was quite low in comparison to low- and intermediate-risk prostate cancer patients. We found that many patients who showed long-term PFS and CSS received adjuvant therapy including RT and HT. Thus, no one can argue that patients who had pathologically unfavorable disease had a higher risk of BCR and disease progression in comparison with other patients.

ADJUVANT RADIOTHERAPY IN HIGH-RISK PROSTATE CANCER PATIENTS

An important issue in treatment after RP is how to control the oncological outcomes of pathological high-risk prostate cancer patients. A high BCR rate after RP in high-risk prostate cancer was reported in several studies, especially in patients with positive surgical margins, extraprostatic extensions, and seminal vesicle invasion. In these patients, the issue was whether adjuvant radiotherapy (ART) could improve the on-

cological outcomes or not.

Recently, three randomized trials were reported [34-36]: the European Organisation for Research and Treatment of Cancer (EORTC) trial 22911, the Southwest Oncology Group (SWOG) trial 87-94, and the ARO 96-02/AUO AP 09/95. All three trials demonstrated improvement in BCR-free survival and excellent local control. However, only one trial, SWOG trial 87-94, noted a significant improvement in overall survival. The EORTC trial 22911 reported that ART improved BCR-free survival only. However, there were no benefits in PFS and overall survival reported in this trial [37]. Furthermore, patient selection bias was observed in these trials. Not all patients in the SWOG trial had a complete record of preoperative PSA. In addition, the effects of surgical margin status were not sufficient to explain the results of the SWOG trial. In the EORTC trial 22911 and the ARO trial, researchers analyzed the effects of surgical margin status and concluded that the benefit of BCR-free survival may be limited to patients with positive surgical margins. Therefore, ART after RP in pathological high-risk prostate cancer patients is not an accepted treatment despite these excellent trial findings. Swindle et al. [38] concluded that ART might be over-treated in 50% of patients who could have been cured by RP alone. Most importantly, high-risk prostate cancer patients with pathologically localized disease and positive surgical margins might be cured with RP alone and thus not require ART. However, patients with negative surgical margins could have a poor outcome in high-risk prostate cancer. In other words, the prediction of oncological outcomes after RP in high-risk prostate cancer patients is difficult. Therefore, close surveillance is required for these patients if the urologist selects RP as the initial modality for prostate cancer treatment.

ADJUVANT HORMONE THERAPY IN HIGH-RISK PROSTATE CANCER PATIENTS

HT has also been investigated as an adjuvant therapy to RP in high-risk prostate cancer patients even though few randomized trials are available. Messing et al. [39] showed a potential benefit to early hormonal therapy following RP. At a follow-up of 11 years, a significant improvement was exhibited in OS, CSS, and PFS in the adjuvant HT group. However, these results were observed in a small trial of patients who were positive for lymph node. In cases of patients with negative lymph node, this advantage was not demonstrated. In a randomized study with flutamide in 309 patients, Wirth et al. [40] also reported an improvement in PFS with immediate androgen

deprivation therapy (ADT). Adjuvant flutamide treatment delayed biochemical progression significantly; however, no difference was found in OS or CSS at a follow-up period of 6.1 years. However, in a randomized clinical trial McLeod et al. [41] concluded that patients with high-risk locally advanced disease might benefit from adjuvant ADT. Unfortunately, at a follow-up of 6 years, no improvement in OS was reported for the pT3. Recently, Siddiqui et al. [42] analyzed 191 patients with seminal vesicle invasion who received adjuvant HT. At a follow-up of 10 years, they experienced an improvement in BCR-free survival and CSS in comparison to patients who did not receive adjuvant HT. However, they also did not show a significant improvement in OS. Therefore, the advantages of adjuvant hormonal therapy after RP are debatable. The results of the aforementioned studies indicated that except for patients with positive lymph nodes, the role of adjuvant HT after RP remains unclear and is not recommended. Definitive results from a large randomized trial are warranted in order to define the role of adjuvant HT in high-risk prostate cancer.

RADICAL PROSTATECTOMY AND RADIOTHERAPY: WHICH IS THE SUPERIOR TREATMENT?

A comparison of RP and RT is difficult because there are no compared prospective trials and these two treatments have different PSA nadir standards. Almost all results were from large retrospective and case-matched studies. Cooperberg et al. [43] compared the risk-adjusted mortality in 7,538 men treated by RP, RT, or ADT. The study showed that higher-risk patients had better CSS following surgery in comparison with other treatments. In a retrospective observational study, Abdollah et al. [44] reviewed the comparative treatment outcomes of clinically localized prostate cancer. They found that disease-specific mortality was lower in men aged < 69 years with high-risk disease when they choose RP. However, there was no significant difference between RP and RT in patients over 70 years. Arcangeli et al. [45]'s retrospective study used a small cohort to analyze patients who underwent RP or RT. They showed a significantly better outcome after RT than after RP in patients with high-risk prostate cancer. Tewari et al. [46] compared 453 high-risk prostate cancer patients treated by RP, RT, or observation. They concluded that RP was superior to RT in OS, but it was not significant in CSS.

In contrast, Westover et al. [47] compared long-term survival in high-risk men treated by either RP or RT. They found that there was no significant difference in disease-specific mortality between the two treatment modalities. Boorjian et

al. [48] compared patients with high-risk prostate cancer undergoing RP (n = 1,238) or RT with ADT (n = 344) or without ADT (n = 265) from 1988 until 2004. They showed that the 10-year cancer-specific survival rates were 92%, 92%, and 88% after RP, RT plus ADT, and RT, respectively, and they were not significantly different. Systemic PFS also did not significantly differ between the treatment modalities. However, the OS was greater in men who underwent RP than those who had RT ± HT. Recently, Parikh and Sher [49] published an interesting article comparing the quality-adjusted life expectancy (QALE) between men with high-risk prostate cancer who received RT+HT versus RP+RT versus a hypothetical trimodality therapy (RP+RT+HT). They reported that RT+HT resulted in a higher QALE compared with RP+RT over a wide range of assumptions, which nearly always resulted in an increase of > 1 quality-adjusted life year with outcomes highly sensitive to the risk of increased all-cause mortality from HT; RP+RT+HT was typically superior to RT+HT. They concluded that high-risk prostate cancer patients who underwent RT+HT were superior to RP+RT, and the result was sensitive to the risk of all-cause mortality from HT. Moreover, trimodality therapy may offer local and distant control benefits that lead to optimal outcomes in a meaningful population of men.

The results shown in the relevant literature indicate that it is unclear whether RP or RT is superior for high-risk prostate cancer. Even though some oncological outcomes demonstrated the superiority of RP, it must be taken into account that several experienced urologists concluded that there were no significant differences in oncological outcomes between RP and RT. Although these large retrospective studies provided some information, for the ideal comparison of RP and RT in high-risk prostate cancer, we need more results from high-level studies in prospective randomized trial settings. Moreover, with regard to prospective randomized trials, a number of issues must be resolved when comparing RP and RT; the main problem is the "Will Rogers phenomenon." This term refers to the improvement in survival rates in stage-specific prognosis caused by changing the criteria for assigning patients to the various stages of a disease, even though the outcome of the individual patients does not change.

To compare the oncological outcomes between RP and RT in high-risk prostate cancer, we included patients in a cohort study using a clinical risk classification system. However, in patients who underwent RP, we identified their pathologic staging and determined whether the patient was overestimated or not in the risk assessment for prostate cancer. However, in high-risk prostate cancer patients who underwent RT, we could not ascertain the exact pathologic staging. Therefore,

it is impossible to identify the actual position of RT in these patients. It was difficult to compare patients who underwent RT with those who did not undergo RP, even in a prospective randomized trial. There was no way to identify accurately the pathologic status of patients who underwent RP. Consequently, we classified them as clinically high-risk prostate cancer in this study. However, in reality, these same patients would not be classified as having pathologically high-risk prostate cancer. Therefore, the question of which treatment is better for high-risk prostate cancer patients remains unresolved.

CONCLUSION

Presently, RP is regarded as the first step of treatment for high-risk prostate cancer patients, on a selective basis. In some high-risk prostate cancer patients, RP is a one-step modality for a cure, with excellent oncological prognosis. Nevertheless, a substantial proportion of prostate cancer patients need adjuvant therapy after RP. In these patients, urologists should utilize a tailored approach with RT or HT. Therefore, before utilizing RP, urologists should inform patients about the possibility of surgical complications caused by the wide excision created during surgery and the need of adjuvant therapy, including RT and HT. The main goal of treatment for high-risk prostate cancer is the improved CSS, not BCR. Therefore, in patients who are willing to undergo radical therapies in pursuit of a cure, I agree that RP could be an attractive therapeutic option for high-risk prostate cancer. However, further studies with randomized controlled trials comparing RP and RT are necessary for urologists and their patients to be better informed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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