



Current Status of Radical Prostatectomy for High-Risk Prostate Cancer

Ho Won Kang¹, Joo Yong Lee¹, Jong Kyou Kwon¹, Seong Uk Jeh¹, Hae Do Jung¹, Young Deuk Choi^{1,2}

¹Department of Urology, Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, Seoul,
²Robot and Minimal Invasive Surgery Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Despite the wide application of prostate-specific antigen-based screening leading to a profound stage migration in prostate cancer (PC), a significant percentage of men are still being diagnosed with clinically high-risk disease that requires aggressive treatment. Optimal management in these patients remains challenging, and strong advocates for radical prostatectomy (RP), radiotherapy, androgen deprivation therapy, and, increasingly, a multimodal approach abound. Currently, surgery for high-risk PC is frequently applied. RP offers an attractive opportunity for tumor excision either as a definitive management or as a first step in multimodal therapy. Nevertheless, this approach is still controversial. In this review, we discuss the current evidence for the role of RP in this clinical setting, including surgical considerations and outcomes. The role of robot-assisted RP, which is increasingly utilized in Korea in this clinical scenario, is discussed.

Keywords: Prostatectomy; Prostatic neoplasms; Survival; Treatment outcome

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Corresponding Author:

Young Deuk Choi
Department of Urology,
Urological Science Institute and
Clinical Trial Center for Medical
Devices, Severance Hospital,
Yonsei University College of
Medicine, 50 Yonsei-ro,
Seodaemun-gu, Seoul 120-752,
Korea
TEL: +82-2-2228-2317
FAX: +82-2-312-2538
E-mail: youngd74@yuhs.ac

INTRODUCTION

Approximately 15% to 26% of patients with prostate cancer (PC) will present with high-risk disease despite prostate-specific antigen (PSA) screening [1,2]. High-risk disease is understood to be a significant predictor of progressive, symptomatic disease or death from PC [3]. The widely accepted definition of high-risk PC was first proposed by D'Amico on the basis of a pretreatment Gleason score of 8, a clinical stage of at least T2c, or a presenting PSA level of 20 ng/mL [4].

The optimal management of patients with high-risk PC remains controversial [5-7]. Available therapeutic options include monotherapy by radical prostatectomy (RP) or combined modality approaches that include local treatments such as radiotherapy (RT) along with androgen deprivation therapy (ADT) or chemotherapy. High-risk PC patients are at increased risk of locally advanced or micrometastatic disease; therefore, it is reasonable to employ a more aggressive treatment plan targeting the local as well as the systemic components of the disease [8,9]. Considerations

for surgical management were often discarded in such individuals owing to the increased risk of biochemical recurrence (BCR), systemic progression, and worse oncologic outcomes [10,11].

Currently, several studies have shown comparable oncologic outcomes for RP relative to RT or ADT in the context of high-risk disease [12-15]. Zelefsky et al. [16] showed that RP was associated with a nearly 10% lower risk of progression to metastasis and a lower cancer-specific mortality (CSM) compared with high-dose RT in patients with high-risk PC. The 10-year outcomes from the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database for men with high-risk PC treated with RP showed 90% local recurrence-free survival, 89% systemic progression-free survival (PFS), 95% cancer-specific survival (CSS), and 80% overall survival (OS) [17]. Even in the very-high-risk category using the Cancer of the Prostate Risk Assessment (CAPRA) score, approximately 20% of men will be cured with RP alone [2,18].

High-risk PC patients treated with RP have variable survival outcomes, according to different high-risk definitions.

Nevertheless, independent of the definition, highly convincing, long-term CSS rates have been described. Frequent downgrading and downstaging, and a possible therapeutic role of local tumor debulking, support RP and extended pelvic lymph node dissection (e-PLND) as primary management strategies during multimodality treatment [19]. However, many guidelines are reluctant to endorse RP as an equivalent treatment to RT and ADT [18].

The aim of this review was to define high-risk PC and to elaborate on the emerging evidence to support the role of RP as both a monotherapy and as part of a collaborative, multimodal approach in high-risk localized PC. The role of robot-assisted RP (RARP), which is increasingly being utilized in Korea for the surgical treatment of PC in this clinical scenario, is discussed.

WHAT IS HIGH-RISK PROSTATE CANCER?

Table 1 summarizes the contemporary and most widely used definitions of high-risk PC. The exact definition of high-risk PC is unclear, and a consensus has not yet been reached. This lack of consensus on a definition of high-risk disease represents a critical barrier for patient counseling, comparative assessment of treatment outcomes, and the design of randomized trials. High-risk, clinically localized disease was classically defined by D'Amico et al. [4] as any combination of the following factors: a PSA greater than 20 ng/mL, a Gleason score of 8 to 10, or a clinical stage of T2c or higher. The American Urological Association (AUA) has endorsed these D'Amico high-risk criteria [20]. More recently, the National Comprehensive Cancer Network (NCCN) and the European Association of Urology (EAU) modified this definition to include any combination of a clinical T3 stage, a PSA score greater than 20 ng/mL, or a Gleason score of 8 to 10 [21,22]. The Radiation Therapy Oncology Group also described a classification system to predict overall and cause-specific survival [23]. However, an estimation of patients' risk of progression with this definition is far from perfect, because these criteria encompass a heterogeneous group of patients.

Clinical stage is often inaccurate in localized PC. Digital

rectal exams fail to detect extracapsular extension in 30% to 50% of patients. The role of clinical stage remains controversial, because it does not necessarily add information and displays interobserver variability [5,24,25]. In a recent review of the CaPSURE database, an inaccurate clinical stage was assigned to 35.4% of patients [24,26]. Pretreatment PSA can reflect not only cancer, but benign prostatic hyperplasia or chronic inflammation [27]. Finally, biopsy downgrading after the final pathological assessment is a common phenomenon, occurring in up to 45% of cases [28,29].

Because of these limitations, several multivariate risk assessment tools have been developed. The Kattan preoperative nomogram uses a multivariate model that combines stage, PSA, and additional prostate biopsy information to generate an estimate of the risk of treatment failure following RP [30]. Recently, Cooperberg et al. [31] developed another high-risk PC definition: the CAPRA score. They added secondary parameters, including prostate biopsy profiles (biopsy Gleason score and percentage of positive biopsy cores) and patient age to the existing basic parameters. The CAPRA score ranges from 0 to 10, and a CAPRA score of 6 to 10 represents high-risk PC. This tool was recently updated, because both the CAPRA post-surgical score (CAPSA-S) and postoperative pathologic results can be used to predict BCR after RP on a continuous scale. Additional variables such as extent of cancer in needle biopsy, pretreatment PSA velocity, PSA doubling time, or the presence of a tertiary Gleason pattern have been suggested to optimize risk stratification [32].

To be clinically useful, criteria defining high-risk PC should reliably distinguish patients whose cancer is amenable to cure with local therapy alone from those who may require additional systemic therapy. Novel molecular markers that can both significantly enhance the prediction of relapse following therapy and identify locally advanced and occult metastatic disease are needed. Incorporating several known risk factors together with endorectal magnetic resonance imaging findings, pretreatment PSA velocity, and additional data from prostate biopsies may produce a more precise, high-risk disease definition.

TABLE 1. Definition of high-risk prostate cancer

Definition	Source or Utilized by
PSA \geq 20 ng/mL or GS 8-10 or clinical stage \geq T2c	D'Amico et al. [4] American Urological Association [20]
PSA \geq 20 ng/mL or GS 8-10 or clinical stage \geq T3a	European Association of Urology [21] UK National Institute for Health and Clinical Excellence [62]
PSA \geq 20 ng/mL or GS 8-10 or clinical stage \geq T3a or Any two of the following: T2b/c, GS 7, PSA 10-20 ng/mL	National Comprehensive Cancer Network [22]
PSA 20-100 ng/mL, biopsy GS 8-10, and any clinical T stage or PSA < 100 ng/mL, GS 8-10, and clinical stage \geq T2c	The Radiation Therapy Oncology Group [23]
Combination of age, PSA value, clinical stage, biopsy GS, and percentage of positive biopsy cores	The Cancer of the Prostate Risk Assessment score [31]

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

RATIONALE FOR SURGERY FOR HIGH-RISK PROSTATE CANCER

Traditionally, RP was not considered a viable treatment option for high-risk PC cases [33]. However, several recent studies of high-risk PC have presented another view (Table 2). In some high-risk PC patients, RP is a one-step modality for a cure, with excellent oncological prognosis. One of the most important benefits of RP compared with nonsurgical therapy is pathologic staging of both the primary cancer and regional lymph nodes. Although preoperative risk group stratification and nomograms may identify patients with adverse features, studies have established that pathologic variables, such as pathologic Gleason pattern and stage, more accurately predict who may benefit from additional therapy. In favorable situations, pathologic downgrading and downstaging at RP may potentially spare patients from receiving adjuvant therapy. In a review of the CaPSURE database, an inaccurate clinical stage was assigned to 35.4% of patients [24]. About one-third of high-grade (8-10) biopsy Gleason scores were subsequently downgraded at RP and 26% to 31% were shown to have organ- or specimen-confined disease [34,35]. A study by Abern et al. [36] on this issue of PC adds significantly to the literature by demonstrating that pathologic downstaging occurs more frequently than previously reported and that patients who were downstaged had survival outcomes that were similar to those of patients with intermediate- and low-risk PC.

Lymphadenectomy at the time of RP confers information about the level and extent of nodal involvement and may guide the initiation of earlier adjuvant ADT [37]. Multiple series suggest an approximately 10% to 20% 10-year disease-free recurrence without adjuvant therapy following lymph node dissection for men with lymph node metastases [38]. Another potential benefit of RP for high-risk disease is the possible posttreatment avoidance of additional therapy.

Approximately one-half of men with high-risk disease

will be cured with RP monotherapy and thus avoid any further treatment [9,39,40]. In one study, Yossepowitch et al. [41] found that 35% to 76% of high-risk patients avoided secondary therapy altogether 10 years after surgery. Joniau et al. [42] reported on a cohort of 51 men with very high-risk PC (cT3b-T4), in which 31.4% avoided ADT, and after a median follow-up of 9 years, the 10-year biochemical PFS (BPFS) rate was 45.8%. Using CaPSURE data, Meng et al. [17] showed that men receiving RT for high-risk PC are 3.5 times as likely to receive ADT as are patients treated with RP. Even if men ultimately require salvage ADT for disease control after RP, they may delay the time to initiation of ADT. In a study by the Mayo Clinic on patients with cT3 disease, the average duration of freedom from ADT after RP monotherapy was 4.0 years [43].

Another advantage of RP is the expectation and significance of nondetectable PSA. After RP in completely excised patients, serum PSA should decline to a non-detectable level. The sensitivity of post-RP PSA provides a prompt assessment of disease cure and control, allowing early recognition of recurrent disease and delivery of salvage RT if necessary. Primary treatment with RP allows for salvage RT with curative intent in the setting of a promptly recognized local recurrence. Even in patients with poorly differentiated disease and positive margins, recurrence after RP can be effectively treated with salvage radiation that may prevent metastatic progression. Adjuvant or salvage RT cures another 50% of recurrences, representing a three-fold reduction of death from PC after surgery with minimal additional morbidity [44].

ROLE OF SURGERY IN THE TREATMENT OF LOCALLY ADVANCED PROSTATE CANCER

Until recently, surgical treatment had not been used in locally advanced PC. The role of RP in patients with locally advanced PC has been debated, because the combination of RT and hormone therapy is coming to be used more frequently for locally advanced PC. Today, according to the

TABLE 2. Outcomes of radical prostatectomy as monotherapy in high-risk prostate cancer

Source	Cases	Definition	OCD (%)	Median follow-up	BCR-free survival	CSS	MFS	OS
Gerber et al. [63]	242	cT3	9	-	29% at 5 y	57% at 10 y	32% at 10 y	-
Yossepowitch et al. [64]	957	D'Amico	43	4.3 y	68% at 5 y, 59% at 10 y	-	-	-
Stephenson et al. [65]	1,962	D'Amico	-	48 mo	-	92% at 10 y, 81% at 15 y	-	-
Loeb et al. [39]	175	D'Amico	36	8 y	68% at 10 y	92% at 10 y	84% at 10 y	-
Walz et al. [11]	887	D'Amico	-	2.4 y	47.4% at 5 y, 35.7% at 10 y	-	-	-
van den Ouden et al. [66]	83	cT3	18	52 mo	29% at 5 y	85% at 5 y, 72% at 10 y	69% at 5 y, 50% at 10 y	75% at 5 y, 60% at 10 y

OCD, organ-confined disease; BCR, biochemical recurrence; CSS, cancer-specific survival; MFS, metastasis-free survival; OS, overall survival.

EAU and AUA guidelines, RP is a reasonable treatment option for selected PC patients with cT3a disease, a Gleason score of 8 to 10, or PSA>20 [21]. Moreover, surgery is considered by the NCCN to be an acceptable primary treatment option for selected patients with low-volume, high-risk PC and a limited number of adverse prognostic factors [45]. In a series from the Memorial Sloan-Kettering Center, of 176 men with cT3 over a 20-year period, the role and effectiveness of RP were reviewed. Within this cohort, only 64 men received neoadjuvant hormone therapy. Fifty-three patients were downstaged to organ-confined disease after pathological evaluation, and more than one-half (52%) of patients remained free of disease recurrence following RP [46]. In a Mayo Clinic study of men undergoing RP, cT3 was found in 841 of the 5,662 patients (15%) studied. Of these 841, 661 men (79%) did not receive neoadjuvant hormone therapy. After a pathological review of these patients, 223 (27%) were found to be overstaged, and in fact had organ-confined disease [35]. It is important to note that surgery can identify a substantial subset of men with favorable features in whom additional therapy is not indicated. Another feature to attribute a very high-risk stratification is the presence of positive regional lymph nodes [19]. Recently, Engel et al. [47] found a doubled risk of overall mortality when RP was abandoned compared with completed RP for patients in whom positive lymph nodes were found at the time of surgery. They concluded that RP may have a survival benefit, and the abandonment of RP in node-positive cases may not be justified. A systematic review by Verhagen et al. [48] concluded that there was a clinically important survival benefit in men with node-positive disease who received ADT when local control of the primary tumor is achieved.

ROBOTIC PROSTATECTOMY FOR HIGH-RISK PROSTATE CANCER

Traditionally, RP in high-risk PC is performed by use of an open approach. During the last several years, however, an increasing number of publications have discussed the use of minimally invasive techniques, particularly RARP [42]. The increasing availability of robotic technology to urologists has expanded the roles and indications for RARP, including recent reports of this approach in a high-risk setting. A recent retrospective analysis studied 913 patients with high-risk PC treated with open RP or minimally invasive RP with e-PLND and aimed to compare the pathological and short-term BCR-free survival outcomes for different therapeutic approaches. Of all patients, 81.4% underwent open RP, 11.5% underwent RARP, and 7.1% underwent laparoscopic RP (LRP). The authors demonstrated BCR-free survival rates of 56.3%, 67.8%, and 41.1%, respectively, and positive surgical margin (PSM) rates of 29.4%, 34.3%, and 27.7% for open retropubic RP, RARP, and LRP, respectively. An e-PLND was performed, and 10.8% of positive nodes were found in the open retropubic RP group compared with 3.5% in the minimally in-

vasive RP group. The authors concluded that equivalent rates of PSM and short-term BPFs between open RP and minimally invasive RP were observed [49]. However, major limitations were differences in the cumulative number of high-risk factors, short follow-up, nonstandardized e-PLND, and nerve-sparing indications.

Punnen et al. [50] compared outcomes of 233 high-risk RARP cases with 177 high-risk RRP cases from a single institution. RARP patients had less blood loss and similar pathological outcomes compared to RRP patients. Overall PSM rates were 29% and 23%, respectively, and RFS rates at 4 years were 66% and 79% for RARP and RRP, respectively. Similarly, Busch et al. [51] noted that RARP demonstrated similar oncologic outcomes compared to RRP and LRP in a propensity-score-matched cohort of patients with high-risk PC.

Strong debate surrounds the feasibility and role of robotic surgery in performing e-PLND. A recent series of 143 robotic e-PLND patients with intermediate or high-risk PC according to the D'Amico classification showed a median number of 20 (range, 9-65) excised nodes with positive node rates of 13% and without Clavien-Dindo complications in 82% of cases, thus confirming the technical feasibility of the procedure with minimally invasive surgery [52]. These promising results must be confirmed by randomized clinical trials, which will be vital to achieve optimal oncological, functional, and sexual outcomes, bearing in mind the high risk of cancer progression in this group of patients.

THE SURGICAL APPROACH AS PART OF MULTIMODAL THERAPY

With respect to the treatment of high- and very-high-risk PC in general, the failure of RRP or RT alone (monotherapy) is well recognized, and multimodal therapy may be needed. In well-selected patients, RP combined with adjuvant or salvage treatment when needed may result in better outcomes than RT alone, similar to the combination of RT plus hormone therapy [9]. Definitive therapy for high-risk PC, often requiring a multimodal approach, appears to provide the greatest long-term survival benefit. According to the recent EAU guidelines, patients must be informed about the possible need for a multimodal approach because neoadjuvant hormone therapy has not been shown to increase BPFs and OS and is not recommended in these guidelines [6,53,54].

Although hormone therapy may decrease the size of the tumor and prostate overall, hormone therapy can induce a mild-to-moderate desmoplastic reaction around the prostate, obscuring tissue planes around the periprostatic fascia. In a minority of patients, dissection of the prerectal planes is difficult, and the rectum can be adherent to the posterior prostate. In addition, RP in an extremely small prostate after hormone therapy can be slightly more challenging. This added challenge is mostly due to the desmoplastic reaction as well as to difficulty in identifying the contours of the prostate and the normal tissue planes for

neurovascular preservation [25].

Adjuvant hormone therapy has a definite role in the management of high-risk patients after RP. Adjuvant hormone therapy has its most relevant clinical utility after RP in node-positive patients. However, the effect of adjuvant ADT on OS remains unclear, and it appears to be influenced by the individual risk profile. The classic study of Messing et al. [37,55] demonstrated improvement in PSA- and cancer-free survival and OS for hormone therapy immediately following RP for node-positive PC. More recently, Boorjian et al. [56] analyzed data for 507 patients with node-positive PC following RP. In this trial, patients with immediate ADT had a statistically significantly decreased risk of biochemical and local recurrence. There was no statistically significant difference, however, in the rate of systemic progression or CSS between the two groups. Therefore, the advantages of adjuvant hormone therapy after RP are debatable.

Recently, Lee et al. [57] evaluated the competing risks of CSM after initial therapy with RP versus RT in men with clinically localized high-risk PC. Their study had several differences compared with previous reports: (1) relatively long follow-up periods; (2) RP performed by a single surgeon; and (3) the first data in an Asian population. They demonstrated that 5-year estimates of CSS rates for men treated with RP and RT were 96.5% (95% confidence interval [CI], 94.2–98.9) and 88.3% (95% CI, 82.8–94.3), respectively. Cumulative incidence estimates for CSM using competing risks were statistically lower in men receiving RP versus RT ($p=0.002$). They summarized that initial treatment with RP versus RT was associated with a decreased risk of CSM in men with clinically localized high-risk PC.

Definitive results from a large randomized trial are warranted to define the role of adjuvant hormone therapy in high-risk PC. Hormone therapy has also been investigated as an adjuvant therapy to RP in high-risk PC patients, even though few randomized trials are available. Postoperative adjuvant RT after RP for high-risk PC also remains controversial. The results of three randomized trials of postoperative adjuvant RT in high-risk patients, typically categorized by adverse pathology, such as pathologic stage T3-4N0 with PSM, extracapsular extension of disease, or seminal vesicle invasion, have been reported. All detected improvements in BPFs were in association with acceptable rates of toxicity [58-60]. However, only one trial, a secondary analysis of the Southwest Oncology Group 8794 trial, noted marked improvement in OS following postoperative adjuvant RT [61].

CONCLUSIONS

Currently, surgery for high-risk PC is applied frequently. Nevertheless, this approach is still controversial. Because there is no standard definition of high-risk PC, outcome comparisons between series and treatment approaches are hampered. However, RP can provide durable local control,

long-term CSS, and accurate pathologic staging and may guide further individualized treatment. RP with extended pelvic lymphadenectomy delivers very good cancer-related outcomes in high- and very-high-risk PC, often within a multimodal approach. Definitive results from a large randomized trial are warranted to define the role of adjuvant hormone therapy and RT in high-risk PC. Minimally invasive surgery is showing promising results, but further studies are needed to support its role compared to open RP and e-PLND as the gold standard.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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