Review Article

Optimizing the Management of High-Risk, Localized Prostate Cancer

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Prostate cancer has a high prevalence and a rising incidence in many parts of the world. Although many screen-detected prostate cancers may be indolent, prostate cancer remains a major contributor to mortality in men. Therefore, the appropriate diagnosis and treatment of localized prostate cancer with lethal potential are of great importance. High-risk, localized prostate cancer has multiple definitions. Treatment options that should be individualized to each patient include observation, radical prostatectomy, external beam radiotherapy, brachytherapy, androgen deprivation, and combined modality treatment. Specific outcomes of radical prostatectomy and combined modality treatment for high-risk prostate cancer are reviewed. The rationale for extended pelvic lymphadenectomy at the time of surgery is discussed, as is the role for surgery in the setting of node-positive, high-risk disease. There is not yet a biomarker that accurately identifies lethal prostate cancer, but rigorous clinical studies have identified methods of optimizing oncologic outcomes in high-risk men.

Key Words: *Prostate-specific antigen; Prostatectomy; Prostatic neoplasms; Radiotherapy*

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INTRODUCTION

Worldwide, prostate cancer is the most prevalent malignancy in men, with a tendency to cluster in regions that are more highly developed [1]. Prostate cancer mortality rates are relatively low, however, because many indolent cancers are detected by serum prostate-specific antigen (PSA) screening [2,3]. However, deaths from prostate cancer are a significant problem owing to the high overall prevalence of the disease: mortality ranges from 2 to 40 per 100,000 [4]. Even though prostate cancer deaths have declined in some countries that have adopted PSA screening, mortality rates have been increasing in most parts of the world [2]. In Korea, prostate cancer incidence is rising [5]. In addition, there are suggestions in retrospective screening [6] and surgical [7] cohorts that the population of Korean men with prostate cancer may be enriched for high-grade (Gleason score 8−10) disease. Thus, the paramount challenges to reduce the burden of prostate cancer deaths are 1) to correctly identify men with lethal disease while it is still curable and 2) to effectively treat this high-risk group to optimize oncologic and survival outcomes. This review addresses the definition of high-risk, localized prostate cancer; treatment options; surgical and comparative outcomes; the role of pelvic lymphadenectomy (PLND); and the benefit of radical prostatectomy (RP) in the setting of lymph node metastasis.

DEFINITION OF HIGH-RISK PROSTATE CANCER

There are multiple definitions of high-risk prostate cancer. One of the goals of risk stratification at the time of the initial diagnosis should be to identify the subset of men with lethal prostate cancers with the most pressing need for local or systemic treatment.

The most widely used high-risk definition is the D'Amico

classification. Introduced in 1998, D'Amico high-risk prostate cancer is defined by clinical stage ≥T2c, serum PSA >20 ng/ml, or biopsy Gleason sum of 8–10 [8]. This system has also been adopted by the American Urological Association (AUA) [9]. The National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) define high-risk prostate cancer similarly, by clinical stage ≥T3a, serum PSA >20 ng/ml, or biopsy Gleason sum of 8–10 [10,11]. Table 1 summarizes the criteria that are used to define high-risk prostate cancer according to the different classification schemes. In their original report, D'Amico et al. [8] found that freedom from biochemical recurrence after various local therapies varied according to preoperative risk classification, with high-risk men having a shorter time to biochemical recurrence when treated with brachytherapy instead of external beam radiotherapy or RP.

Prostate cancer risk can also be classified according to the chance of adverse pathologic findings or biochemical recurrence. In the Partin tables, a combination of validated preoperative variables (clinical stage, serum PSA, biopsy Gleason score) can predict the likelihood of extraprostatic disease, seminal vesicle invasion, and lymph node metastasis [12]. An alternative risk classification is the Cancer of the Prostate Risk Assessment (CAPRA) score, which uses the same preoperative variables as the D'Amico/ NCCN/EAU risk strata and the Partin tables but also incorporates patient age and the proportion of positive biopsy cores, resulting in a numerical score of 0–10. In this classification, high-risk prostate cancer is conventionally defined as CAPRA 6–10, which correlates with adverse pathologic features and biochemical recurrence [13]. Several nomograms predict the risk of biochemical recurrence after RP or radiotherapy [14-16]. The advantage of these nomograms in prostate cancer is their precision and resulting utility in decision making when taking into account individual patient attitudes toward risk. The disadvantage of nomogram-defined risk is that the result is within a continuum that lacks easily-identified risk categories, which are helpful in guiding management decisions.

The prevalence of D'Amico high-risk prostate cancer ranges from 20 to 35% [17]. With the widespread adoption of PSA screening for prostate cancer (1992 onward), the characteristics of men with high-risk features have evolved. For example, compared to the pre-PSA era, contemporary high-risk men are more likely to be high risk by a biopsy Gleason sum of 8–10 but to present with lower PSA and lower clinical stage [18].

TABLE 1. Definitions of high-risk prostate cancer: tumor profile must fulfill at least one criterion

	Gleason sum	PSA (ng/ml)	Clinical stage	Other
NCCN	8–10	>20	≥T3a	
EAU	8–10	>20	≥T3a	
D'Amico	8–10	>20	≥T2c	
AUA	8–10	>20	≥T2c	
CAPRA				Total score ≥6

NCCN, National Comprehensive Cancer Network; EAU, European Association of Urology; AUA, American Urological Association; CAPRA, Cancer of the Prostate Risk Assessment (incorporates clinical stage, serum prostate-specific antigen [PSA], biopsy Gleason score, patient age, and percent positive biopsy cores; total score range, 0–10).

TREATMENT OPTIONS

Common treatment options for high-risk, localized prostate cancer include RP with bilateral pelvic lymph node dissection; observation; monotherapy with external beam radiation, androgen deprivation therapy, or brachytherapy; and combined modalities. Table 2 summarizes society-specific guidelines from the AUA, NCCN, and EAU for the treatment of high-risk prostate cancer.

TABLE 2. Recommended treatment options for high-risk prostate cancer: society-specific guidelines

AUA [9]	Active treatment is preferred over observation. For high-risk patients, there are survival benefits associated with RP when compared with watchful waiting and with combined modality radiotherapy with androgen deprivation when compared to radiotherapy alone.
NCCN [10]	Active treatment at the time of diagnosis is preferred if life expectancy exceeds 5 years. The preferred treatment is combined modality radiotherapy with androgen deprivation. In the setting of no fixation to adjacent organs, RP is an option. In the setting of node-positive disease at RP, adjuvant androgen deprivation therapy or observation is recommended. In the setting of other adverse features at or after RP (seminal vesicle invasion, positive surgical margins, extracapsular extension, or detectable PSA), recommendations include adjuvant radiotherapy or observation.
EAU [11]	RP is a reasonable first step in selected patients who are high risk by Gleason 8–10 or PSA>20 ng/ml and for patients whose tumor volume is low. For patients who are high risk by clinical stage ≥T3a (locally advanced), increased consideration should be given to combined modality radiotherapy with androgen deprivation, though RP can have significant oncologic benefit if nomograms, imaging, or directed biopsies indicate negative seminal vesicles and lymph nodes preoperatively. Management should proceed after discussion of options with a multidisciplinary team (urology, radiation oncology, medical oncology, radiology).

AUA, American Urological Association; NCCN, National Comprehensive Cancer Network; EAU, European Association of Urology; RP, radical prostatectomy; PSA, prostate-specific antigen.

In their seminal randomized prospective trial of RP versus watchful waiting in localized prostate cancer, Bill-Axelson et al. [19] reported 13-year follow-up results, which demonstrated a significant overall survival benefit to RP, even in the subgroup of men with high-risk disease.

Combined modality treatment entails external beam radiotherapy (up to 81 Gray) with long term (2 to 3 years) androgen deprivation therapy (the "preferred" high-risk treatment according to the NCCN) or external beam radiotherapy with brachytherapy with short-term (4 to 6 months) androgen deprivation [9]. In a randomized trial in which 74% of men had intermediate- or high-risk prostate cancer, D'Amico et al. [20] found that 6 months of androgen deprivation therapy was associated with a significant benefit in overall survival when compared with 70 Grays of external beam radiation alone. In a prior randomized trial of men with high-risk and locally advanced prostate cancer, Bolla et al. [21] demonstrated significantly improved overall survival when 3 years of androgen deprivation was added to 70 Grays of external beam radiation alone.

Every man with high-risk prostate cancer is not a candidate for treatment, however. Although observation and expectant management are extolled more for very low-risk disease, an asymptomatic man with high-risk prostate cancer may have advanced age or be significantly frail due to comorbidities. However, it should be noted that high-risk prostate cancer can be quite lethal even in the elderly. For example, in a population-based (SEER) study of men ≥ 80 years old with a Gleason sum of 8–10 who were diagnosed in the PSA era but were managed *without* surgery or radiation, a significant proportion (16 to 29%) died of prostate cancer, whereas rates of death from competing causes ranged from 44 to 52% [22].

TREATMENT OUTCOMES

After RP for high-risk disease, 10-year outcomes reported by Loeb et al. [23] include a 32% rate of biochemical recurrence, 16% rate of metastasis, and 8% rate of prostate cancer-specific death. Oncologic outcomes after RP vary according to several factors. Biochemical recurrence after RP is associated with preoperative PSA and biopsy Gleason score [18]. In men who have only one high-risk feature, those who are high-risk by PSA >20 ng/ml have a 5-year actuarial biochemical recurrence risk of 55%, whereas high-risk patients by a Gleason sum of 8–10 have a 62% risk [18]. Patients who are at high risk by clinical stage $\geq$T2c experience biochemical recurrence at a rate even lower than that of intermediate-risk patients [24]. In men who have already experienced biochemical recurrence after RP, independent predictors of shorter metastasis-free survival are faster PSA doubling time and high pathologic Gleason sum [25].

Given these outcomes, it is essential to determine which patients should be selected for definitive local therapy. Patient selection is critical because adverse pathologic

findings at RP may commit the patient to undergoing additional therapy. For example, men with only one high-risk feature (compared with 2 or 3 features) have less biochemical recurrence, metastasis, and cancer-specific mortality, and a Gleason sum of 8–10 is the most adversely prognostic high-risk feature [23]. In addition, in men with high-risk prostate cancer according to a high Gleason score only (8–10) who underwent RP, the independent predictors of unfavorable pathology (seminal vesicle invasion or lymph node metastases) were a Gleason sum of 9–10, an increasing number of cores with a Gleason sum of 8–10, PSA >10 ng/ml, clinical stage $\geq$pT2b, and $>50\%$ core involvement [26]. Therefore, preoperative predictors can help to select the high-risk prostate cancer patients who are most likely to benefit from RP.

There is not yet a detailed standard indication of adjuvant radiotherapy following RP. The NCCN guidelines recommend adjuvant radiotherapy for PSA recurrence or adverse pathologic features (extracapsular extension, positive surgical margin, or seminal vesicle invasion) as long as there is no evidence of disseminated disease (Table 2) [10].

COMPARATIVE OUTCOMES

No prospective randomized studies have compared RP with combined modality radiotherapy and androgen deprivation in prostate cancer. There is limited retrospective evidence to suggest that RP may have superior oncologic outcomes in high-risk disease. Zelefsky et al. [27] reported on a multicenter cohort of 2,400 men with high-risk prostate cancer that the 8-year unadjusted actuarial probability of death was 3.8% with RP and 9.5% with external beam radiotherapy. The 8-year rate of absolute metastasis-free survival was 7.8% higher in the RP cohort as well. Note that whereas men in the radiation cohort often received more than 81 Gray, only 56% received androgen deprivation therapy, which was short-course instead of long-term [27]. Others have shown RP to be associated with less cancer-specific mortality in high-risk disease than radiotherapy with or without androgen deprivation, with a suggestion that the benefit to surgery may be limited to men <70 years old [28,29]. However, another retrospective analysis showed that in patients with a Gleason sum of 8–10, RP has no benefit over combined modality treatment in a multivariate analysis [30]. In light of these limited data, proper patient selection for RP is paramount and should take into account patient age, preoperative stage and grade, and patient attitudes toward treatment-specific side-effects.

MANAGEMENT OF PELVIC LYMPH NODES

PLND during RP is recommended when the nomogram-predicted probability of lymph node metastasis $\geq$ 2% [10]. PLND improves staging and guides the use of adjuvant treatment. The rates of lymph node metastasis

range from 39 to 55% in men with PSA >20 ng/ml and range from 55 to 80% in men with a Gleason sum of 8‒10 [31]. The extent of PLND can be standard (removal of obturator and external iliac nodal packets, proceeding distally to the femoral outlet), extended (also involving the removal of internal and common iliac nodes up to the level of the iliac bifurcation proximally), or "super-extended" (involving presacral and retroperitoneal dissection as well) [32,33].

The morbidity of PLND is directly related to its extent. Symptomatic lymphoceles are rare (2 to 4%) and are more frequent as more nodes are removed [31,32,34]. In a robotic RP series, extended PLND with a yield of ≥20 nodes was associated with worse continence and higher erectile dysfunction at 6 months [35]. In patients undergoing super-extended lymphadenectomy, the perioperative complication rate is reported to be up to 26% and includes prolonged lymphorrhea and wound dehiscence [33].

Evidence suggests that extended PLND has a therapeutic effect and associated oncologic benefit. This is especially important given the high rate of lymph node metastasis in high-risk prostate cancer. In a retrospective study seeking to define the natural history of men found to have lymph node metastasis at RP, rates of freedom from biochemical recurrence at a median follow-up of 45 months ranged from 10 to 39% and rates of asymptomatic biochemical recurrence ranged from 18 to 30%, with better oncologic outcomes for men with only a single nodal metastasis as opposed to multiple [36]. Others have shown improved recurrence-free survival when PLND reveals only a single positive node [37]. Allaf et al. [37] found that men undergoing extended PLND, compared to limited PLND, have significantly improved recurrence-free survival in the subset of men with a positive node density <15%. Therefore, in high-risk prostate cancer, given the prevalence of occult nodal metastasis and encouraging freedom from recurrence of symptoms in pathologic N1 disease, extended PLND is indicated at the time of RP.

Some men with high-risk prostate cancer who are potential surgical candidates may benefit from a staging PLND. If the cancer is localized (clinical stage T2a or T2b) but the biopsy Gleason sum is 8‒10, PLND can be useful insofar as positive nodes (on routine histological section after staging PLND) in this scenario would portend a poor oncologic prognosis (85% or greater progression to clinically detectable metastases within 5 years), thus minimizing the benefit of subsequent RP [38].

RP IN THE SETTING OF LYMPH NODE METASTASIS

Nevertheless, RP may have an oncologic benefit in the setting of lymph node metastasis. This was suggested by Cadeddu et al. [39], who retrospectively compared men who had RP with PLND compared with staging PLND alone. Among men with clinical stage pN1 and matching patients for metastatic tumor burden, 10-year actuarial survival was 61% in men who underwent RP compared with 45% in

those who underwent staging PLND only [39]. Similarly, in a series of men found to have nodal metastasis by intraoperative frozen sections, undergoing completion RP was an independent predictor of improved cancer-specific survival in a multivariate analysis [40].

Thus, extended PLND is indicated when RP is the treatment modality for high-risk prostate cancer given the high rate of lymph node metastasis. Conversely, RP appears to have a survival benefit even in the setting of pathologic nodal metastasis by routine or frozen histological sections.

CONCLUSIONS

Due to high worldwide prevalence, prostate cancer deaths comprise a significant health burden despite relatively low overall mortality rates. Strategies to reduce prostate cancer deaths, therefore, must focus on correctly identifying men with lethal, high-risk profiles of disease, and once diagnosed, treating these men effectively. Clinical definitions of high-risk prostate cancer vary, and a definite biological marker of lethal prostate cancer phenotypes is not yet available. Nevertheless, studying the commonly used D'Amico-NCCN high-risk definition, physicians have identified patient and preoperative tumor factors that can guide treatment decisions (surgery versus combined modality radiotherapy with androgen deprivation) to optimize oncologic outcomes.

CONFLICTS OF INTEREST
The authors have nothing to disclose.

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