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Seminar article

Radical prostatectomy in high-risk and locally advanced prostate cancer: Mayo Clinic perspective

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Abstract

Purpose: Men diagnosed with high-risk prostate cancer represent the cohort of prostate cancer patients at greatest risk for subsequent disease-specific mortality. Unfortunately, however, the classification of high-risk tumors remains imprecise and heterogeneous. There has been a historical reluctance to offer such patients aggressive local treatment, and considerable debate exists regarding the optimal management in this setting.

Methods: We present here our institutional experience, as well as data from several other centers, with radical prostatectomy for high-risk tumors.

Results: We discuss that surgery affords accurate pathological staging, thereby improving the identification of patients for secondary therapies. Moreover, prostatectomy not only provides durable local disease control but in addition numerous contemporary surgical series in high-risk patients have shown radical prostatectomy to be associated with excellent long-term cancer-specific survival. Further, although studies comparing surgical and radiotherapy modalities in high-risk prostate patients have been wrought with methodological challenges, consistently these observational studies have found equivalent to improved oncologic outcomes when surgery is utilized as the primary treatment.

Conclusions: Herein, we review the advantages, long-term outcomes, and technique of surgery for high-risk prostate cancer.

Keywords: Prostate cancer; Prostatectomy; High risk; Treatment

Introduction

Despite the stage migration in prostate cancer (PC), which has been noted over the course of the prostate-specific antigen (PSA) era, between 14% and 24% of men with newly diagnosed disease continue to be classified as high risk based on clinicopathological tumor features [1]. Notably, the designation of high risk represents a term that has been applied to heterogeneous cohorts of patients, including the classifications proposed by D'Amico et al. [2], now used as the definition by the American Urological Association [3], the National Comprehensive Cancer Center (NCCN) [4], and the University of California San Francisco [5]. Nevertheless, regardless of classification system, high-risk patients harbor the greatest risk of death owing to PC. Unfortunately, however, the optimal management of these men continues to be debated, as no accepted standardized treatment paradigm currently exists for such patients.

Historically, men with high-risk PC have been managed most often with external beam radiation therapy (RT) or androgen-deprivation therapy (ADT) or both [1,6]. In fact, the practice of combining these modalities for high-risk patients has become recommended following randomized clinical trials, which demonstrated a survival benefit to long-term ADT with RT for men with locally advanced PC [7,8]. By contrast, surgical therapy (i.e., radical prostatectomy [RP]) has previously been discouraged in the setting of high-risk tumors, secondary to concerns regarding increased side effects, positive surgical margins, and inadequate disease control [9].

The lack of a standardized method of incorporation of surgery into the multimodal approach for patients with high-risk PC represents a stark contrast to the typical

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management algorithms used, for example, in breast [10,11] and colorectal cancers [12]. That is, for these malignancies, multimodal treatment for advanced tumors has shown superior efficacy compared with a single-treatment approach [13–15]. Importantly, however, a role for RP in high-risk PC has not been rigorously tested in randomized clinical trials, and thus the quality of evidence to support its use is limited. Nevertheless, increasing data suggest a variety of benefits afforded by the inclusion of surgery as part of the treatment paradigm for men with high-risk tumors, and in fact, surgery has been considered the treatment of choice for these patients at our institution. Herein, we review our experience and data from other centers regarding surgery for men with high-risk PC. Particular focus is given to presenting long-term outcomes and comparative results vs. RT as well as to providing technical aspects of the procedure to facilitate the integration of surgery into a multimodal treatment approach.

Advantages of surgery in high-risk PC

Accurate pathological staging

A continued challenge to establishing an optimal management paradigm for patients with high-risk PC has been the lack of a consensus definition for high-risk disease, that is, patients who have met any of a variety of criteria involving pretreatment PSA or PSA kinetics or both, clinical stage, and biopsy Gleason score have historically been classified as high risk [16]. This heterogeneity in high-risk PC classifications in turn creates difficulties for individualized patient counseling, for defining clinical trial enrollment criteria, and for interpreting comparative outcome assessments between treatment modalities and even between surgical series. Indeed, widely disparate clinicopathological outcomes have been noted when various high-risk definitions were applied among men undergoing RP [16].

Importantly, moreover, not only is PC risk classification heterogeneous, it is often imprecise as well. That is, the various criteria that are used to assign pretreatment disease risk have not infrequently been noted to inaccurately represent tumor pathology. For example, clinical staging, which relies on digital rectal examination, has been reported to be incorrectly assigned in 35.4% of men, with downstaging occurring more commonly than upstaging [17]. Indeed, 22% to 63% of men initially defined as high risk have been found to have pathologically organ-confined disease at RP [16]. Similarly, the designation of clinical T3–4 stage has been found to be inaccurate in up to 33% of cases [18]. Within our institution, downstaging to pathological T2 occurred in 26% of patients initially designated with clinical T3 PC [19,20]. Meanwhile, discrepancies in Gleason score have likewise been noted frequently between biopsy and RP, such that up to 51.3% of Gleason 8 tumors at biopsy have been found to have a lower score at RP, with 31.1% of Gleason 9 to 10 biopsies demonstrating an RP grade of 7 or less [21]. At the Mayo Clinic, discordance between biopsy and pathological Gleason scores, even in more contemporary years (1999–2003), occurred in 26.9% of patients [22]. Interestingly, we learned that these patients were more likely to harbor adverse pathological features at time of surgery, such as advanced tumor stage, lymph node metastasis, and positive surgical margins. Furthermore, increasing biopsy Gleason score was an independent predictor of biochemical recurrence and systemic progression and death due to PC in patients with pathological Gleason 3 + 4 [22]. Although the use of more sophisticated strategies such as diffusion-weighted magnetic resonance imaging (MRI) and magnetic resonance spectroscopy may improve our accuracy with clinical staging, currently their application is limited by their lack of widespread availability, standardization of technique, and cost [23–25].

An unfortunate potential consequence of the inaccuracies in risk assignment in PC is the implication for subsequent risk-based treatment. For example, patients assigned as high risk may be subjected to "therapeutic nihilism," that is, a clinicians' assessment of high-risk tumors as not surgically curable may lead to historical practice patterns of preferentially offering radiation or hormones or both rather than surgery [6]. As high-risk patients are recommended by guidelines to receive 24 to 36 months of ADT [4], some may be subject, unnecessarily, to the attendant side effects of ADT [26,27], if they actually harbor lower risk disease. In fact, an assessment of practice patterns within the Cancer of the Prostate Strategic Research Endeavor database illustrates that patients classified as having high-risk disease who undergo radiation are significantly more likely to receive ADT than those treated with surgery [6].

As such, one of the critical benefits of surgery for patients considered to harbor high-risk PC is the ability to obtain accurate pathological staging. Indeed, as noted previously, clinical stage or Gleason score or both may change in 30% to 50% of men undergoing RP, leading to a potential change in risk classification. Specifically, in our experience, the 57% of patients initially classified as D'Amico high risk were found to have organ-confined disease following RP [28]. Pathological staging through surgery thereby affords clinicians the ability to guide secondary therapy utilization based on more precise and individualized data than would be available from PSA, clinical stage, and biopsy parameters alone. Indeed, 3 randomized trials have demonstrated a benefit to adjuvant RT for men found to have locally advanced tumors at RP [7,29,30], whereas a separate randomized trial noted significantly increased survival with adjuvant ADT after surgery for men with lymph node–positive disease [31]. In a retrospective matched analysis of Mayo Clinic patients with pathological lymph node–positive disease, use of adjuvant ADT was found to improve cancer-specific survival (CSS) and systemic progression–free survival following prostatectomy. However, this benefit was lost when ADT was administered at time of PSA recurrence or systemic progression [32].