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The Surgical Management of Prostate Cancer

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ABSTRACT

Prostate cancer is a heterogeneous disease with a variable natural history. Therefore, optimal management remains challenging. While many men with newly diagnosed prostate cancer may be candidates for active surveillance, there are others who will benefit from aggressive local therapy. Radical prostatectomy is associated with improvements in cancer-specific mortality, metastasis-free survival, and need for palliative treatments when compared with observation in several randomized controlled trials. Additionally, radical prostatectomy may have some oncologic benefit over radiation therapy. All aggressive therapy for prostate cancer negatively impacts erectile function and urinary continence. The decision for which treatment modality to pursue should incorporate shared decision making and consider cancer risk and severity in addition to patient preferences.

1. Introduction

Prostate cancer is the most common non-skin cancer and the second leading cause of cancer deaths among men in the United States [1]. There will be an estimated 161,360 new cases diagnosed in 2017, representing 19% of new cancer cases, and 26,730 deaths [2]. The introduction of widespread prostate-specific antigen (PSA)-based prostate cancer screening in the late 1980s has resulted in a significant stage migration, with the majority of cancers now detected when they are organ-confined and very few when they have metastasized [2–4].

The aggressiveness of organ-confined prostate cancer varies significantly between indolent diseases to highly aggressive cancer ultimately resulting in death. Several classification tools have been proposed to stratify disease risk and help guide treatment decisions. The most commonly used risk stratification scheme combines clinical stage, PSA, and Gleason score [5] (Table 1). Patients are stratified to low-risk (clinical stage T1-2a, PSA ≤10 ng/mL and Gleason score ≤6), intermediate-risk (stage T2b or 10 < PSA ≤20 ng/mL or Gleason score 7), or high-risk disease (stage ≥T2c or PSA >20 ng/mL or Gleason score ≥8), which correlates with disease-free survival 10 years after radical prostatectomy (RP); low risk 83%, intermediate risk 46%, and high risk 29% [5,6]. The Cancer of the Prostate Risk Assessment (CAPRA) score is a validated risk assessment method that assigns points for PSA, Gleason score, clinical stage, percentage of positive cores on biopsy, and age [7,8] (Table 2). Total scores range from 1 to 10 and the risk of recurrence doubles with each 2-point increase; score 0–1, recurrence-free survival (RFS) at 5 years 81%–92% versus score 7–10, 8%–27%. Pretreatment risk stratification is essential for patient counseling and shared decision-making.

Given the multitude of treatment options, ranging from active surveillance (AS), to radiation therapy (RT), to local ablative therapies (cryotherapy, high-intensity focused ultrasound), to RP and more, patients are faced with the difficult decision on how they should treat their disease. Herein, we review the role of RP in the management of organ-confined prostate cancer.

2. Natural history of prostate cancer

When counselling men on the treatment of prostate cancer, it is essential to understand the natural history of conservatively managed localized prostate cancer because this disease tends to have a protracted course. Several historic observational cohorts that offer insight into this topic are summarized in Table 3.

Some of the studies include patients from the pre-PSA era, many of whom were diagnosed at the time of transurethral resection of prostate (TURP) and few via needle biopsy, which somewhat limits their utility in assessing contemporary patients [9,10], while others report data from the PSA era [11,12] with a range of prostate cancer-specific mortality (PCSM). At the same time, properly selected men with low-risk prostate cancer have a nearly 100% chance of metastasis-free and cancer-specific survival when managed with AS over 15 years [13,14].

3. Indications for surgery

The effectiveness and outcomes of treatments for prostate cancer have been studied for decades. RP is unique in that it has

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Table 1
D'Amico risk assessment scheme [5,6].

Risk assessment	Clinical stage	PSA	Gleason score	10-year DFS
Low	T1–2a	≤10 ng/mL	≤6	83%
Intermediate	T2b	10–≤20 ng/mL	7	46%
High	≥T2c	> 20 ng/mL	≥8	29%

Abbreviations: DFS, disease-free survival; PSA, prostate-specific antigen.

been investigated in several randomized trials. These trials help inform urologists about which patients gain the most benefit from surgery (Table 4).

3.1. Surgery versus observation

The Scandinavian Prostate Cancer Study Group number 4 (SPCG-4) trial randomized 695 men with well- or moderately-well differentiated localized prostate cancer and a 10-year life expectancy to treatment with RP or watchful waiting between 1989 and 1999 [15]. The primary end points were death from all causes, death from prostate cancer, and risk of metastasis. After a median 13.4 years of follow-up, RP was associated with a significant improvement in overall survival (56.1% *v* 68.9%, relative risk [RR] 0.71 [0.59–0.86]; $P < .001$), with eight patients requiring treatment to prevent one death. RP was also associated with lower PCSM (17.7% *v* 28.7%, RR 0.56 [0.41–0.77]; $P = .001$), a lower risk of metastasis (26.1% *v* 38.3%, RR 0.57 [0.44–0.75]; $P < .001$), and less use of palliative androgen-deprivation therapy (ADT) (42.5% *v* 67.4%, RR 0.49 [0.39–0.60]; $P > .001$). Subgroup analysis indicated the greatest benefit to RP was in patients with intermediate-risk disease and those less than 65 years of age, although there was some benefit to prostatectomy in low-risk tumors as well. Importantly, the benefits of surgery increased over time. One important limitation of this trial was that it took place before widespread prostate cancer screening. Only 12% of men had screen-detected cancers, and the mean PSA at diagnosis was 13 ng/mL.

The Prostate Cancer Intervention Versus Observation Trial (PIVOT) recruited men from Veteran's Association hospitals and National Cancer Institutions from 1994 to 2002 and randomized 731 men with localized prostate cancer and a life expectancy of at least 10 years to RP versus observation [16,17]. Fifty percent of men had screen-detected cancers and 66% had intermediate- or high-risk disease [16]. With a median follow-up of 12.7 years, RP was not associated with improvements in overall (61.3% *v* 66.8%, hazard ratio [HR] 0.84 [0.70–1.01]; $P = .06$) or prostate-cancer specific survival (7.4% *v* 11.4%, HR 0.63 [0.39–1.02]; $P = .06$).[17] On subgroup analysis, men with a PSA > 10 ng/mL and those with intermediate-risk tumors had lower mortality with RP. Men treated with RP did have a lower risk of local and systemic disease progression (40.9% *v* 68.4%) and experienced less use of ADT (21.7% *v* 44.4%). Important limitations of this trial were that it accrued only 731 patients out of their goal of 2,000, a significant percentage of men died within 10 years of randomization, and the confidence intervals around the point estimates were often wide, suggesting imprecision because of low patient numbers. In comparison with the SPCG-4 trial, the PIVOT study population had a lower median PSA (7.8 ng/mL) and greater proportion had screen-detected cancers (50%).

Finally, the Prostate Testing for Cancer and Treatment (ProtecT) trial randomized 1,643 men with localized prostate cancer from the United Kingdom to AS, RP, or RT between 1999 and 2009 [18]. The majority of the men in this trial had PSA-detected tumors, and 77% had a Gleason score of 6. Within 3 years of randomization, a quarter of the men assigned to AS went on to have radical treatment, which increased to over half by 10 years. With a median 10-year follow-up, there were a total of 17 prostate cancer deaths. Patients randomized to RP and RT had similar prostate cancer-specific survival at 10 years compared with the AS group (99% *v* 99.6% *v* 98.8%, respectively, $P = .48$). However, men assigned to RP and RT had lower risks of clinical progression and metastasis compared with men treated with AS (clinical progression 8.9 *v* 9.0 *v* 22.9 per 1,000 person-years, $P < .001$; and metastatic disease 2.4 *v* 3.0 *v* 6.3 per 1,000 person-years, $P = .004$). There was no survival benefit from treatment according to PSA, age, or Gleason score. The main finding of this study was that men with low-risk disease can be actively monitored without aggressive treatment, and there is limited benefit to RP or RT for these patients.

The findings from the ProtecT trial reinforce what has been shown in several large cohort studies: AS can safely be used for well-selected patients with low-risk prostate cancer [19–21]. Findings from a large national prostate cancer registry called Cancer of Prostate Strategic Urologic Research Endeavor (CaPSURE) demonstrated a sharp increase seen in men with low-risk disease in the United States being managed with AS, such that after 2010 over 70% have been managed conservatively (Text Box 1) [22]. The growing use of AS avoids unnecessary treatment in a large percentage of men with newly diagnosed prostate cancer.

Table 2
Cancer of the Prostate Risk Assessment (CAPRA) score [7,8].

Age at diagnosis	Under 50	0
	50 or older	1
PSA at diagnosis (ng/mL)	≤6	0
	6.1–10	1
	10.1–20	2
	20.1–30	3
	> 30	4
Gleason score of the biopsy	No pattern 4 or 5	0
	Secondary pattern 4 or 5	1
	Primary pattern 4 or 5	3
Clinical stage (T-stage)	T1 or T2	0
	T3a	1
Percent of biopsy cores positive for cancer	< 34%	0
	> 34%	1
Risk category	Total score	5-year RFS after RP
Low	0–2	81–92%
Intermediate	3–5	42–76%
High	6–10	8–27%

Abbreviation: RFS, recurrence-free survival; RP, radical prostatectomy.

3.2. Surgery versus RT

In all clinical guidelines, both RP and RT with or without ADT are primary treatment options for patients with clinically localized prostate cancer who are candidates for aggressive local treatment (Text Box 2) [23,24]. The ultimate choice on which treatment to pursue is dependent on the shared decision between the patient and physician, ideally in the setting of a multi-disciplinary care team.

Over time there has been an increase in men with intermediate- and high-risk disease being treated with RP over RT [22]. However, there is a paucity of randomized controlled trials comparing RP with RT. The ProtecT trial randomized primarily low-risk men to AS, RP, or RT, and there was no difference in PCSM or progression between the two active treatment arms [18]. Two small, randomized trials comparing RP with RT found no difference in survival or metastasis 5 to 10 years post-treatment [25,26]. However, these trials were underpowered and used older radiation dosing and therefore largely do not inform current decision-making.