A Critical Analysis of the Long-Term Impact of Radical Prostatectomy on Cancer Control and Function Outcomes

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\textbf{Abstract}

\textbf{Context:} The optimal management strategy for men with newly diagnosed clinically localized prostate cancer remains a matter of debate. Numerous series have reported cancer control and quality-of-life (QoL) outcomes following treatment with radical prostatectomy (RP).

\textbf{Objective:} Critically review published oncologic and functional outcomes after RP, and evaluate factors associated with these outcome measures.

\textbf{Evidence acquisition:} A review of the literature was performed using the Medline and Web of Sciences databases. Relevant reports published between 1980 and 2011 identified using the keywords prostate cancer, radical prostatectomy, prostate-specific antigen, biochemical recurrence, incontinence, and erectile dysfunction were reviewed and summarized.

\textbf{Evidence synthesis:} Cancer control rates following RP largely depend on the definition of treatment efficacy. While up to 40\% of men have been reported to experience postoperative biochemical recurrence on long-term follow-up, death from prostate cancer has been noted in <10\% of men at 15 yr after surgery in contemporary series. For men with high-risk disease, surgery affords pathologic staging, thereby facilitating the selective application of secondary therapies, and has been associated with decreased mortality risk versus radiation in retrospective series. Reported functional outcomes after surgery, particularly urinary incontinence and erectile dysfunction, have varied greatly to date. These assessments have been limited by nonstandardized reporting methodology. The use of robot-assisted radical prostatectomy has increased in recent years, and while follow-up is thus far short, available data do not suggest the superiority of either approach in terms of functional or oncologic outcomes.

\textbf{Conclusions:} RP is associated with excellent long-term cancer control. Continued efforts to conduct prospective assessments of postoperative functional outcomes are necessary using validated QoL instruments. The importance of surgical approach will also require further study, incorporating comparative oncologic, functional, and economic data.

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1. Introduction

Prostate cancer is second only to lung cancer in mortality burden among men in the United States [1]. However, the heterogeneous natural history of the disease, which may be indolent even without treatment [2], together with the not insignificant risk of treatment-related side effects [3], complicate decision making for patients and clinicians. As such, the optimal management strategy for men with newly diagnosed clinically localized prostate cancer remains a matter of debate.

Recent data from the Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) database, a primarily community-based national disease registry, noted that radical prostatectomy (RP) represents the most common treatment for patients with newly diagnosed clinically localized disease, with approximately 50% of such men undergoing surgery [4]. Other population-based data sets have nevertheless documented a decrease in the proportion of patients with localized disease treated with RP over time [5]. Interestingly, substantial variation has been found to exist in management across clinical sites that does not correlate with measurable disease variables or patient characteristics [4] and therefore likely reflects individual practitioner bias or experiences. These data emphasize the need for high-quality comparative effectiveness research to help determine the most appropriate treatment for these men.

A survival benefit to RP compared with watchful waiting was demonstrated in a randomized trial from Scandinavia [6]. In this study, with a median of 12.8 yr of follow-up, the relative risk of death from prostate cancer among men assigned to surgery was 0.62, and a survival benefit was observed even among men with low-risk cancers, although the benefit was confined to men <65 yr of age [6]. A smaller early randomized trial, involving 142 patients from the Veterans Administration Cooperative Urological Research Group, likewise demonstrated improved survival in favor of RP versus expectant management, although after adjustment for imbalances in age distribution, no statistically significant difference in survival could be demonstrated [7]. Recent data presented from the US Prostate Cancer Intervention Versus Observation Trial, which enrolled men considered to have less advanced disease at the time of diagnosis than the Scandinavian cohort, demonstrated no significant reduction in prostate cancer mortality after surgery with follow-up out to 12 yr, and reported that only in men with high-risk tumors might RP be associated with a survival benefit [8]. In addition to this absence of consensus regarding the benefit of surgery versus watchful waiting, contemporary clinical trials remain lacking to compare outcomes following the various active forms of prostate cancer management, including RP, radiation therapy (RT), and androgen-deprivation therapy (ADT). Nevertheless, numerous retrospective studies, reporting on different patient populations and with various designs, have reported cancer control and quality-of-life (QoL) outcomes following treatment.

Our purpose in this paper is to present data from recent series that have evaluated outcomes of RP, both at tertiary referral centers and in larger population-based data sets, to provide an updated assessment of the oncologic efficacy and functional results associated with the surgical management of prostate cancer.

2. Evidence acquisition

A review of the literature from 1980 to 2011 was conducted in June 2011 using the Medline and Web of Science databases to identify original articles, review articles, and editorials regarding oncologic and functional outcomes following RP. The Medline search, consistent with a recent similar analysis [9], was performed using a free-text protocol with the terms radical prostatectomy and robotic prostatectomy across the Title and Abstract fields of the records, individually and in combination with the terms prostate cancer, prostate-specific antigen, biochemical recurrence, cancer-specific survival, mortality, surgeon volume, urinary incontinence, sexual potency, erectile dysfunction, and trifecta. The Web of Science database search used the same free-text protocol and the same keywords. The search results were then pooled, and the following limits were used: human subjects and English language.

The articles with the highest level of evidence were reviewed, analyzed, and summarized, with the consensus of all of the authors of this paper. In particular, the published randomized clinical trials that have assessed outcomes following RP versus expectant management or RP versus RT were identified for inclusion. For the analysis of cancer control after RP, retrospective nonrandomized observational series that contain 10-yr follow-up and report the outcome of cancer-specific or all-cause mortality were preferentially selected. Other significant studies cited in the reference lists of the selected papers were evaluated as well. When multiple updated series were reported on the same subject from the same institution/data set, the most recent publication was included. With regard to functional results, prospective comparative assessments of outcomes following different prostate cancer treatment modalities, as well as studies that reported outcomes using validated QoL instruments, were identified for inclusion.

Importantly, given the large number of publications in this field, we acknowledge the potential for selection bias in the articles we have chosen for review.

3. Evidence synthesis

3.1. Oncologic outcomes following radical prostatectomy

3.1.1. Reported surgical outcomes

One critical component in assessing the oncologic efficacy of RP from published series and being able to perform comparative analyses of results is the outcome measure being reported. On a most basic level, establishing the outcome measure of interest is critical to answering this common patient question: “What is the expected success rate of surgery?” To date, the most common reported measure of cancer control following surgery for prostate cancer has been biochemical recurrence (BCR).
Porter et al. [10], in a series of 787 men who underwent RP at Virginia Mason Medical Center between 1954 and 1994, found that the BCR-free survival rate ranged from 85% at 5 yr to 61% at 15 yr and 55% at 25 yr. Han and colleagues [11] reported a 5-, 10-, and 15-yr BCR-free survival of 84%, 74%, and 66%, respectively, in men who underwent surgery between 1982 and 1999; Roehl et al. [12], in 3478 men treated with RP from 1983 to 2003, noted a 10-yr BCR-free survival of 68%. A series of 4277 patients undergoing RP at a single European center between 1992 and 2005 reported an 8-yr BCR-free survival of 61% [13]. Higher preoperative prostate-specific antigen (PSA) level, increased Gleason score, and advanced pathologic tumor stage, particularly with regard to seminal vesicle and/or lymph node invasion, have consistently been associated with an increased risk of recurrence [10–15]. Increasing surgeon volume [16] and a more recent year of surgery, likely reflecting changes in clinicopathologic parameters [17] over the course of the PSA era [18], have been associated with improved outcomes as well [12,19].

One aspect of BCR that posed a particular hurdle to efforts at assessing the relative cancer control for various treatment modalities is the difficulty in comparing BCR between RP and RT, due to the disparate definitions of BCR used with each treatment. That is, although the PSA should become undetectable following RP, this is not the case after RT. In fact, the “optimal” PSA level after RT, which may not ablate all of the functional prostate epithelium, has not been well established. Instead, the definition of BCR which is currently used following external-beam RT (EBRT) is a PSA value ≥2 ng/ml greater than the absolute nadir [20]. As one might imagine, when this definition was applied to RP patients, BCR-free survival was significantly overestimated [21]. Specifically, the actuarial 5-, 10-, and 15-yr BCR-free survival was noted to be 88.6%, 81.2%, and 78.1%, respectively, with failure defined as a PSA ≥0.2 ng/ml versus 94.6%, 89.4%, and 84.3%, respectively, when failure was defined as a PSA level ≥2 ng/ml (p < 0.0001) [21].

In addition to the difficulty in comparing BCR following surgery and radiation, it is also important to note the heterogeneous natural history of PSA failure. BCR precedes systemic relapse in nearly all cases, and patients with BCR have been demonstrated to be at increased risk for needing additional cancer treatments [22], as well as the development of subsequent metastases and mortality [23]. However, BCR does not always translate into clinical progression [24–29]. In fact, because men with prostate cancer are generally ≥60 yr of age, it has been suggested that competing causes of mortality may obscure the ability of BCR to predict death from prostate cancer [30]. Indeed, men have been found to be as likely to die within 15 yr of BCR from competing causes as from prostate cancer [31].

As such, increasing emphasis has been placed on defining cancer control after RP by mortality rates rather than BCR. Indeed, although multiple models have been developed to predict the presence of adverse tumor pathology and of BCR after RP, few prognostic tools to date have been constructed to assess the risk of prostate cancer–specific mortality [32]. Stephenson and colleagues [19] analyzed a cohort of 12 677 men who underwent RP and determined that the 15-yr prostate cancer–specific mortality was 12%. Eggener et al. [33], in a competing-risk regression model evaluating 11 521 surgically treated patients from the PSA era, reported a 15-yr prostate cancer–specific mortality rate of 7%. Investigators from the Mayo Clinic reported a 10-yr cancer-specific survival (CSS) following RP of 99.7%, 97%, and 95% for patients with the D’Amico classification [34] of low-, intermediate-, and high-risk disease, respectively, among men treated during the PSA era [35], whereas Hull and colleagues [36] noted a mean 10-yr CSS of 97.6% after RP. A separate series from Mayo, using a competing-risks analysis, noted that, in men undergoing RP, the only significant predictor of death from prostate cancer was clinical Gleason score [37].

It must be noted, however, that because these represent retrospective nonrandomized analyses, the independent impact of RP on patients’ risk of death from prostate cancer cannot be discerned with certainty from such data sets, particularly as a more recent year of surgery has been associated with improved outcomes [19,33]. That is, in light of the historically reported 15–25% rate of prostate cancer mortality at 10 yr among men treated without curative intent in the era before PSA screening [38–40], and the 15% death rate from prostate cancer at 15 yr after RP in an unscreened cohort of patients [6], Stephenson et al. [19] appropriately point out that the relatively favorable prognosis from modern surgical series “may be related to the effectiveness of radical prostatectomy (with or without secondary therapy) or the low lethality of screen-detected cancers.” This remains an admitted important limitation of the retrospective data sets that have been used to report outcomes to date. Interestingly, however, PSA-era data from the population-based Surveillance Epidemiology and End Results (SEER) database have demonstrated, after propensity-score matching to adjust for potential selection bias associated with treatment type, that RP decreased the risk of prostate cancer–specific mortality by half in patients ≥65 yr of age relative to observation [41].

3.1.2. Surgery for high-risk prostate cancer

The oncologic outcomes after surgery for patients classified as having high-risk disease merits specific mention, for although over the course of the PSA era the proportion of newly diagnosed prostate cancer patients who would be characterized as having high-risk disease has declined, nevertheless up to 15–30% of patients continue to present with high-risk tumor features [42,43]. The management of patients with high-risk cancers represents one of the biggest challenges in prostate cancer today, with little consensus on the optimal treatment. Retrospective series that compared the outcomes after surgery and radiation for high-risk tumors have demonstrated widely disparate results, with several reporting improved outcomes following RP [44–47], others finding better results following radiation [48,49], and a few [34,50,51], including a small prospective trial [52], noting equivalent efficacy. Unfortunately, no significant improvement in the outcomes of patients with high-risk tumors has been noted over recent
years [53–55]. Nevertheless, the role of surgery for patients with high-risk disease has continued to be evaluated at select centers, and in fact durable survival outcomes following RP have been reported.

Depending on the definition of high-risk disease applied, Yossepowitch et al. [56] found that the 10-yr cumulative incidence of death from prostate cancer among high-risk patients ranged between 3% and 12%, indicating that, even for patients with the highest risk of recurrent disease, surgery was associated with durable oncologic outcomes. A substantial proportion of these patients (ranging based on definition from 35% to 76%) remained free from additional therapy at 10 yr as well [56,57]. Similarly, Boorjian et al. [35] reported on 1513 patients with high-risk disease classified according to the D'Amico risk group stratification [34] and determined a 10-yr CSS of 95%, with 24% of these men having received adjuvant hormonal therapy and 8% having received adjuvant RT. Likewise, Stephenson and colleagues [19] noted a 15-yr prostate cancer–specific mortality of 19% among patients with high-risk disease treated with RP.

One particular benefit to surgery (ie, vs RT) for patients with high-risk prostate cancer is the ability to obtain pathologic staging, which, as suggested previously [43], may guide the selective application of secondary therapies and may, for example, delay or avoid the need for ADT. Indeed, Meng et al. [58] found that patients with high-risk prostate cancer treated with radiation therapy were 3.5 times more likely to receive ADT than patients treated with RP. As increasing data have emerged on the adverse consequences of ADT on QoL [3] and noncancer morbidity of men with prostate cancer, the ability to delay if not avoid ADT may represent a potential advantage to surgery for these patients. As several independent series [35,56] have demonstrated, up to 55–60% of patients classified as having high-risk disease are in fact found to have organ-confined tumors at surgery. Thus these men may not require additional therapy and may be spared the cost and potential side effects of secondary treatment.

Interestingly, for patients who have required a multimodal treatment approach for prostate cancer, the differential impact of various sequences in therapy on subsequent QoL has been explored as well. For example, one study noted that patients treated initially with RP and then with salvage RT were less likely to wear pads and less likely to experience erectile dysfunction than patients treated with RT and then salvage RP [59]. Such data further support surgery as the initial management approach for men with high-risk disease.

Among the subset of high-risk prostate cancer patients found to have positive lymph nodes, again multiple previous series have demonstrated long-term cancer control after surgery [60–63], with a 10-yr postoperative CSS of up to 85% [63]. In addition, several studies have shown, albeit in retrospective nonrandomized series, improved survival for such patients who are treated with RP plus hormone therapy compared with patients treated with androgen ablation alone [64–68]. One recent study found that, on multivariate analysis controlling for clinico-pathologic features including the number of positive lymph nodes, patients who did not undergo surgery had a two-fold increased risk of death [67], whereas in a separate study, 10-yr disease-specific survival was 93% versus 56% ($p = 0.002$) among matched patients with lymph node–positive disease who did and did not undergo RP, respectively [68]. The management of patients with clinical evidence for nodal metastases likewise has not been definitively established, and in fact the National Comprehensive Cancer Network (NCCN) guidelines [69] do not at this time recommend surgery for such patients.

3.1.3. Comparative series of surgical outcomes versus radiation therapy

The optimal management strategy for men with newly diagnosed clinically localized prostate cancer remains in debate because contemporary prospective randomized studies comparing the efficacy and side effects following treatments are lacking. Two early trials comparing RP with RT did find a significant reduction in disease progression after RP [70,71]. Nevertheless, these studies have been criticized for relatively small patient numbers ($n = 97$ and 95, respectively) as well as details regarding methodology and reporting [72]. A more recent effort to evaluate treatment outcomes in the clinical trial setting was the Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial, which randomized men to RP or brachytherapy (BT). However, the trial accrued only 56 patients at 31 centers over 2 yr and was closed early [73]. The Prostate Testing for Cancer and Treatment study, which includes arms for RP, EBRT, and watchful waiting, is ongoing, and so it will be years before mature data are available for reporting [74]. Thus it is not surprising that guidelines from the American Urological Association [75], NCCN [69], and European Association of Urology [76] for the management of clinically localized prostate cancer include both surgery and radiation therapy as alternatives, without providing definitive conclusions regarding relative efficacy.

Table 1 presents review data from contemporary retrospective comparative series that evaluated outcomes following surgery and radiation at tertiary referral centers and in larger, population-based data sets.

3.1.3.1. Surgery versus radiation outcomes from institutional series

Patients with cT1–T3b prostate cancer treated at Memorial Sloan–Kettering Cancer Center with intensity-modulated EBRT ($n = 1062$) or RP ($n = 1318$) were recently compared [77]. After controlling for clinico-pathologic variables, treatment with RP was found to be associated with a significantly reduced risk of metastases (hazard ratio [HR]: 0.35; $p < 0.001$) and cancer-specific mortality (HR: 0.32; $p = 0.015$). The improvement in metastatic progression was more substantial for patients with unfavorable-risk disease (7.8% at 8 yr) than for patients with favorable-risk disease (1.9% at 8 yr) [77]. In an effort to assess the comparative outcomes of surgery and radiation specifically for men with high-risk prostate cancer, 1847 patients with high-risk prostate cancer treated with definitive local therapy in the form of RP ($n = 1238$), EBRT alone ($n = 265$), or EBRT with long-term (median: 22.8 mo) adjuvant ADT ($n = 344$) were
evaluated [78]. These investigators found that, when controlling for case mix and patient variables, patients treated with RT plus ADT had a significantly increased risk of all-cause mortality compared with patients who underwent RP (HR: 1.60; p = 0.0002). The 10-yr overall survival after RP was 77%, versus 67% following RT plus ADT and 52% after RT alone. The authors cited as a potential explanation for these results the fact that ADT was given more frequently to patients receiving RT than patients treated with RP [78], and they extrapolate from a previous study that found an association between ADT and an increased risk of cardiac death, particularly in men with coronary artery disease [79], to suggest a similar potential mechanism of noncancer death in their series.

3.1.3.2. Surgery versus radiation outcomes from population-based data sets. Because concerns exist regarding the ability to extrapolate results from tertiary referral centers to patients treated in other settings, it is important as well to review the outcomes from population-based data sets that have evaluated comparative survival following surgery and radiation. Cooperberg et al. [80] analyzed treatment outcomes from the CaPSURE data set and found that, after adjusting for patient age and disease risk, the HR for death from prostate cancer after RT relative to RP was 2.21. Other studies have evaluated outcomes following RP and RT using the SEER database [5,72,81]. Liu and colleagues [72], using SEER-Medicare linked data, identified 5845 men diagnosed with local/regional prostate cancer at age 65–74 yr who they defined as potential candidates for RP. Of these patients, 2567 underwent RP, 2006 received RT, 302 underwent RT plus RT, and 970 were managed with watchful waiting. The authors found that the 10-yr prostate cancer–specific survival was significantly better following RP (98.1%) than RT (93.8%; p < 0.0001) [72].

A separate study by Abdollah et al. [5] evaluated prostate cancer mortality and other-cancer mortality following RP, RT, and observation using the SEER data set. Using a competing-risks survival analysis in 404 604 patients with clinically localized disease, these investigators found that, for men with low- to intermediate-risk prostate cancer, the lowest cancer-specific and overall mortality rates for men <80 yr of age were recorded in RP patients. For men with high-risk disease who were <70 yr of age, RP was again associated with the lowest cancer-specific and overall mortality rates [5]. In a third investigation through SEER, Johnstone and colleagues [81] found that men with clinical stage T4 prostate cancer and regional lymph node involvement treated with RT alone had a >18-fold increased risk of mortality versus patients who underwent RP, and even men who received RT plus ADT had an approximately 7-fold increased mortality risk compared with surgically managed patients. These results reflect the trends noted earlier in tertiary referral center series. Nevertheless, in the absence of prospective trial data, the potential exists for selection bias to have had an impact on these findings. For example, in a previous large study that detailed outcomes following RP and RT for 7316 patients treated at various US institutions, the time to death from causes other than prostate cancer after PSA failure was significantly shorter for men treated with RT versus RP among men <70 yr of age [82]. These data likely reflect the practice pattern whereby patients selected for RT in this age category are less healthy than patients undergoing RP [82].

### Table 1 – Recent comparative series evaluating oncologic outcomes following radical prostatectomy versus radiation therapy for prostate cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Median follow-up, yr</th>
<th>Outcome: RP versus RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu et al. [72]</td>
<td>2567</td>
<td>11 (not separately listed for RP and RT)</td>
<td>10-yr cancer-specific survival: 98.1% versus 93.8% (p &lt; 0.0001)</td>
</tr>
<tr>
<td>SEER database</td>
<td>2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zelefsky et al. [77]</td>
<td>1318</td>
<td>5.1</td>
<td>8-yr metastases-free survival: 97% versus 93%*</td>
</tr>
<tr>
<td>MSKCC database</td>
<td>1062</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Cooperberg et al. [80]</td>
<td>5066</td>
<td>3.9</td>
<td>HR for prostate-cancer death 2.2 after RT versus RP*</td>
</tr>
<tr>
<td>CaPSURE database</td>
<td>1143</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Boorjian et al. [78]</td>
<td>1238</td>
<td>10.2</td>
<td>10-yr overall survival: 77% versus 67% (RT plus ADT) versus 52% (RT)*</td>
</tr>
<tr>
<td>Mayo Clinic/FCCC</td>
<td>265 (RT)</td>
<td>6.0 (RT)</td>
<td></td>
</tr>
<tr>
<td>Abdollah et al. [5]</td>
<td>344 (RT plus ADT)</td>
<td>7.3 (RT plus ADT)</td>
<td>10-yr cancer-specific mortality: 3.6% versus 6.5%†</td>
</tr>
<tr>
<td>SEER database</td>
<td>149 967</td>
<td>61 mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td>160 787</td>
<td>52 mo</td>
<td></td>
</tr>
</tbody>
</table>

RP = radical prostatectomy; RT = radiation therapy; SEER = Surveillance, Epidemiology, and End Results registries; MSKCC = Memorial Sloan-Kettering Cancer Center; HR = hazard ratio; CaPSURE = Cancer of the Prostate Strategic Urologic Research Endeavor; HR = hazard ratio; FCCC = Fox Chase Cancer Center; ADT = androgen-deprivation therapy.

* p < 0.05 noted on multivariate analysis.
† Only included high-risk patients as defined by the National Comprehensive Cancer Network.
‡ Cancer-specific mortality significantly (p < 0.05) lower after RRP versus RT for high-risk patients <69 yr of age.
evaluate QoL measures following RP relative to other forms of therapy. As with oncologic outcomes, there remains the difficulty of extrapolating the reported results from tertiary referral centers to population-based cohorts. In addition, studies have historically been limited by a lack of baseline functional assessment of patients and by a relatively limited use of validated instruments. This last point is particularly relevant because significant differences have been found between physician and patient assessment of QoL domains in men with prostate cancer, with urologists underestimating patient symptoms in all functional domains [84–86].

3.2.1. Urinary function following radical prostatectomy
The assessment of patients’ urinary function after RP has focused primarily on continence because multiple studies have shown that postoperative incontinence has a negative impact on patients’ QoL [87,88]. The etiology of post-RP urinary incontinence is thought to be related to intrinsic sphincter deficiency and de novo detrusor instability [89]. Factors associated on multivariate analysis with the persistence of incontinence after surgery are increasing patient age and the development of an anastomotic stricture [90,91]. Body weight and prostate volume have not been consistently associated with continence [90,92,93]. Of note, conflicting evidence has been reported regarding the importance of preservation of the cavernosal nerves for postoperative urinary continence [89]. Nevertheless, modifications in surgical technique, including minimal manipulation of the urethra, preservation of the periurethral tissue distal to the apex of the prostate, and full-thickness eversion of the bladder neck, have been noted to improve continence rates as well [90,94]. In addition, preservation of the full functional-length urethra and of the anatomic fixation of the urethral sphincter complex have also been found to result in increased early urinary continence rates [95].

A specific definition for post-RP incontinence has not been established [96], and as such, no consensus on how to quantify or report urinary leakage after RP exists. In addition, urinary control has been shown to improve over time following surgery, and therefore an assessment of urinary control also depends on the timing relative to RP. Not surprisingly, reported rates of incontinence following RP have ranged from 5% to 72% [83,90,92,97–101]. The heterogeneous manner in which incontinence may be defined has been in large part responsible for these widely disparate figures. For example, 72.2% and 65.6% of men in separate series reported any degree of incontinence after RP on a patient self-reported questionnaire, whereas 39% and 33%, respectively, reported incontinence requiring protection [99,100]. In one series of Medicare patients, 6.7% required a second procedure for urinary incontinence in the first year after surgery [102]. In a single-surgeon series that defined continence as wearing no pads, 93% of patients were dry [97].

3.2.2. Sexual function following radical prostatectomy
Since the anatomic approach to neurovascular bundle preservation was described by Walsh and Donker [103], it has become the preferred method of surgery for most patients undergoing RP who are potent and who have clinically organ-confined disease [104]. In addition to bilateral nerve sparing, potency following RP has been linked to younger patient age and preoperative potency status [105]. Importantly, however, reported erectile function rates after surgery vary widely. Even among sexually active men with organ-confined disease who undergo bilateral nerve-sparing surgery, potency rates ranging from 31% to 86% have been recorded [104]. These vary in part with both the definition of potency used, as well as the populations studied. For example, in one study, 64 preoperatively potent men from a single high-volume surgeon were administered a validated disease-specific QoL survey preoperatively and at intervals up to 18 mo after RP [97]. A total of 86% of men reported potency, defined as the ability to have intercourse with or without the use of sildenafil, by 18 mo following surgery [97]. Likewise, Kundu et al. [91] reviewed the results from a separate high-volume center and noted potency in 78% of men who underwent a bilateral nerve-sparing procedure.

At the same time, however, data from the Prostate Cancer Outcomes Study, a community-based longitudinal cohort study, revealed that only 44% of men who were potent before surgery and who underwent bilateral nerve-sparing procedures were potent >18 mo after surgery [98]. Other population-based and single-center series have reported overall rates of erectile function sufficient for intercourse ranging from 11% to 17% [88,99,100,106,107], although the nerve-sparing status of surgery has not been consistently assessed. In the setting of such widely disparate published outcomes, appropriate patient counseling regarding expected results for an individual remain challenging. To address this issue, a recent analysis of the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment was undertaken to develop a model predicting erectile function 2 yr after treatment [108]. It was found that 35% of men reported the ability to attain a functional erection suitable for intercourse at 2 yr after RP. On multivariable analysis, younger patient age, lower PSA level, better pretreatment sexual functioning score, and nerve-sparing surgery were associated with increased odds of functional postoperative erections. As the authors noted, the resulting model may “help physicians and patients to set personalized expectations regarding prospects for erectile function in the years following primary treatment” [108].

3.2.3. Comparative functional outcomes across prostate cancer treatment modalities
Although little exists in terms of randomized trial data to compare QoL measures following RP and RT, several prospective series have been reported using validated QoL instruments and incorporating pretreatment functional data that merit mention (Table 2). Litwin et al. [109] evaluated 580 men with clinically localized prostate cancer who were undergoing RP (n = 307), EBRT (n = 78), or BT (n = 90). These investigators found that obstructive and irritative urinary symptoms were more common after BT, whereas men who underwent RP had worse urinary control and sexual function than either radiation cohort (p < 0.001) [109]. Interestingly, however, beyond 4 mo post-treatment, the proportion of
men reporting severe urinary bother did not differ significantly among treatment groups; beyond 8 mo after treatment, the proportion of men reporting severe sexual bother did not differ significantly among treatment groups, largely due to an improvement in sexual bother score among RP patients over time [109]. Bowel dysfunction was more common among patients who underwent either form of radiation versus RP (p < 0.001) [109].

Sanda and colleagues [3] conducted a prospective multicenter evaluation assessing outcomes from 1201 patients and 625 spouses or partners before and after RP, BT, or EBRT. They noted that sexual QoL was adversely affected after each treatment compared with baseline (p < 0.001), with nerve sparing mitigating some of the adverse effects of RP. Although urinary incontinence was noted after surgery, mean scores on urinary irritation or obstruction improved after RP. In fact, at 1 yr after treatment, moderate or worse distress from overall urinary symptoms was reported by 18% of BT patients, 11% in the radiotherapy group, and 7% of RP patients. Both forms of RT were associated with a reduced QoL related to bowel function after treatment, whereas no change in bowel symptoms was noted after RP [3].

Similarly, the Spanish Multicentric Study of Clinically Localized Prostate Cancer prospectively enrolled 435 patients treated with RP, EBRT, and BT without neoadjuvant or adjuvant hormonal therapy for evaluation [110]. These investigators found that, compared with patients undergoing RP, patients treated with BT or EBRT demonstrated significantly worse urinary irritative-obstructive and bowel scores, respectively, during the last 2 yr of follow-up. Among patients with urinary irritative-obstructive symptoms at baseline, improvement was noted in 64% who underwent nerve-sparing RP. However, sexual and urinary incontinence deterioration was greater among surgical patients [110]. Collectively, these studies indicate that RT tends to have an adverse impact on bowel function after treatment, whereas no change in bowel symptoms was noted after RP [3].

Differences between these treatments tend to equilibrate over time. Additional large-scale prospective evaluations, ideally in a randomized clinical trial setting, are needed to provide better evidence for counseling patients regarding the comparative toxicities of the various treatment options for newly diagnosed prostate cancer.

### 3.3. The impact of the surgical approach to prostatectomy on outcome

Minimally invasive approaches to prostatectomy started with the description of laparoscopic radical prostatectomy (LRP) in 1991 [111] and have continued with developments in surgical technology that have given rise to robot-assisted radical prostatectomy (RARP). RARP was first described by Abbou et al. [112] in 2001 and subsequently standardized and popularized by Menon et al. [113]. Although LRP has been demonstrated to afford effective long-term cancer control [114], the use of RARP in the United States has increased rapidly and dramatically [115,116], such that it has now been demonstrated that robot acquisition is associated with performing an increased number of prostatectomies at the regional and hospital levels [117]. Because the increased application of this technology has occurred without randomized clinical trial data to demonstrate efficacy, results to date for RARP consist of reports from various institution experiences, as well as population-based data sets. From these, a few comparisons of the outcomes have emerged between RARP and open RP and are discussed.

Given the relatively recent application of RARP, attention has primarily focused on evaluating positive margin rates as a pathologic surrogate for oncologic efficacy. Margin rates, however, are subject to cancer extent, technical error (which may reflect surgeon experience), surgical artifact, and pathologic processing, and therefore they remain a problematic end point for comparative analyses. One study comparing margin rates in 200 patients treated with open RP with 200 patients treated with RARP demonstrated significantly lower positive margin rates with RARP (15%)
than with the open procedure (35%), particularly for patients with pT2 tumors (9.4% vs 24.1%) [118]. However, patients in this study who were treated with the open procedure had higher risk features, including higher PSA, clinical stage, and Gleason score, which may have influenced the results [118]. In a matched comparison of open and robot-assisted prostatectomy that did assess comparative oncologic outcomes controlling for year of surgery, age, preoperative PSA, clinical stage, and biopsy Gleason score, Krambeck et al. [119] demonstrated no difference in biochemical progression-free survival between open and robot-assisted prostatectomy at 3 yr.

In terms of functional outcomes, limited comparative data exist to evaluate RP versus RARP for QoL outcomes based on validated instruments. Miller and colleagues [120] prospectively compared patient-reported health outcomes using the Short Form-12 Health Survey, a validated QoL instrument that assesses physical and mental health status, in patients undergoing RARP (n = 42) with patients treated with open RP (n = 120). These investigators reported significantly higher Physical Component Scores in the RARP cohort beginning 1 wk after surgery and continuing for 6 wk, indicating that patients treated with RARP had a greater sense of physical well-being and function [120]. In a prospective longitudinal evaluation of health-related QoL outcomes where the Expanded Prostate Cancer Index Composite (EPIC) questionnaire was administered prospectively and at 1, 3, 6, 9, 12, and 18 mo postoperatively, Tseng et al. [121] found that patients undergoing RARP had a better QoL recovery profile compared favorably with the published results for both open RP and radical perineal prostatectomy. These investigators reported that 71% and 81% of RARP patients had recovered their baseline urinary function and bother scores, respectively, by 12 mo after surgery, with a continence rate at 1 yr of 92% [121].

Again, however, the importance of the definition of outcome measure on reported success rates may be seen, as the authors note, these data demonstrate how a strict definition of continence may result in a more conservative postoperative outcome [122].

Because the bulk of data to date for RARP has been reported primarily from a few high-volume centers of excellence, the importance of assessing comparative outcomes at a population-based level to better gauge the broader impact of RARP on the outcome of men with prostate cancer cannot be overstated. As such, using data from Medicare beneficiaries and SEER-Medicare linked data, minimally invasive prostatectomy has been associated with lower rates of blood transfusions, fewer perioperative complications, and shorter lengths of stay [115,116]. However, in these data sets, minimally invasive prostatectomy was also associated with increased genitourinary complications (4.7% vs 2.1%; p = 0.001) as well as diagnoses of incontinence (15.9 vs 12.2 per 100 person-years; p = 0.02) and erectile dysfunction (26.8 vs 19.2 per 100 person-years; p = 0.009) [116]. In addition, given the noted variability of individual surgeon outcomes [123], the impact of surgical approach on such end points, including operative blood loss and transfusions, is ultimately likely to be provider dependent rather than technique dependent. Interestingly, Schroek et al. [124] mailed surveys to patients who had undergone RP or RARP, and they found among 400 respondents that, on multivariate analysis controlling for sociodemographic variables and EPIC domain scores, patients who underwent RARP were significantly more likely to express regret (HR: 3.02) than patients treated with RP. These data suggest the importance of patient expectations and of preoperative physician counseling.

Overall, although current results suggest that RARP may be associated with a shorter length of hospital stay than RP, available data do not suggest the superiority of either approach in terms of functional or oncologic outcomes.

4. Conclusions

The ideal assessment of the efficacy and toxicity of surgery for prostate cancer would be conducted in the setting of a prospective clinical trial. Notably, RP was found in a randomized trial to be associated with a nearly 40% decrease in the risk of death from prostate cancer compared with watchful waiting, although this benefit was confined to men <65 yr of age [6]. Nevertheless, given the existing lack of relevant outcome data from trials comparing RP with other treatment modalities, and the noted difficulties with organizing such studies, observational series currently remain the primary means of comparative evaluation. Admittedly, the independent impact of RP on patients’ risk of death from prostate cancer cannot be discerned with certainty from such retrospective nonrandomized analyses. Assessment of urinary continence and sexual function after RP has been limited as well by nonstandardized data collection and reporting methodology.

Nevertheless, it should be noted that RP has been associated with excellent long-term cancer control, with the risk of death from prostate cancer after surgery between 5% and 10% in modern series. Although widely variable functional outcomes have been reported, reflecting in part the differing existing definitions of treatment success, both continence and potency have been consistently linked to baseline patient status and surgical technique. Continued investigation into the differing impact of treatments on QoL measures and noncancer morbidities will be necessary going forward to help determine the optimal approach to prostate cancer treatment for an individual patient.

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Acquisition of data: Boorjian.
Analysis and interpretation of data: Eastham, Graefen, Guillonneau, Karnes, Moul, Schaef er, Stief, Zorn.

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