

# Surgical Management for Prostate Cancer

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**As the results of large randomized trials have become available and technology continues to improve, the role of surgery in the management of PCa continues to evolve.**



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## Abstract

**For prostate cancer, radical prostatectomy remains the gold standard for surgical management. Given the side effects associated with surgery, patients at low risk of prostate cancer-specific mortality should consider active surveillance under the guidance of a urologist to safely delay intervention. For patients with an intermediate risk of cancer-specific mortality and otherwise healthy life expectancy, radical prostatectomy has been demonstrated to improve survival. Finally, even for select patients with advanced prostate cancer—metastatic disease to the lymph nodes or distant sites—radical prostatectomy may provide a survival benefit.**

## Introduction

Although radical prostatectomy (RP) remains the gold standard for surgical management of prostate cancer (PCa), the role for RP and other surgical options have grown increasingly complex due to patient and tumor specific considerations that must be taken into account to balance morbidity with cure. For instance, the most appropriate management for a patient with low risk PCa may range from active

surveillance (AS) to focal ablative therapy to RP, based on the overall health as well as preferences of the patient. On the other hand, for patients with high risk disease, multimodality treatment that includes RP should be considered. Importantly, the role of surgery in the management of PCa requires an informed discussion with the patient weighing the oncologic benefits against the potential risks to urinary and sexual function.

## Active Surveillance

For patients with very low and low risk PCa, AS is the treatment of choice in order to reduce or delay the morbidity of RP. Patients on AS are not initially treated at the time of their PCa diagnosis and are instead followed closely with plans to intervene with evidence of disease progression. AS was conceived based on the natural history of PCa; in studies of men aged 55 to 74 years with localized PCa who did not receive RP, the 20-year PCa-specific mortality was greatly outweighed by non-PCa competing risks of mortality for patients with low risk disease (Gleason  $\leq$  6) across all age groups.<sup>1</sup> The specific criteria for AS candidacy vary from institution to institution. The most stringent criteria require prostate-specific antigen (PSA) less than 10 ng/mL,

Gleason  $\leq 6$  disease, 2 or less biopsy cores positive, and  $\leq 20\%$  involvement of the cores. The least strict criteria require PSA less than 15 ng/mL, Gleason  $\leq 3+4=7$  disease, and less than 50% of the biopsy cores to be positive. Importantly, the PCa-specific mortality for patients on various AS protocols across seven institutions remains very low (0-1%), while approximately one third of patients receive intervention at a median of 2.5 years of AS.<sup>2</sup> The institution with the most relaxed AS criteria also has the longest follow-up duration, and they report PCa specific survival rates of 99% and 97% at 5 and 10 years, respectively.<sup>3</sup> These longitudinal findings have been confirmed by a recent randomized study, ProtecT, in the United Kingdom, where patients were randomized to AS, RP, or radiation therapy. In this study of men aged 50 to 69 years with localized PCa, the 10-year PCa specific survival was nearly identical between AS and RP (98.8% versus 99.0%). Of note, more than half (approximately 53%) of the patients on AS received either RP or radiation therapy during the study period.<sup>4</sup> Finally, the advent of improved imaging (namely 3T multiparametric magnetic resonance imaging) as well as histopathologic genetic markers have allowed for even more careful selection of patients for AS, providing reductions in morbidity by safely delaying RP.<sup>5</sup>

### Radical Prostatectomy for Localized Prostate Cancer

For patients with localized PCa, RP is a surgical treatment performed with curative intent, and has been demonstrated in a number of trials to provide a survival benefit. Conversely, alternative treatment options for localized PCa have not been studied in a controlled fashion. For patients with organ-confined disease who wish to preserve erectile function, a nerve-sparing retropubic approach to RP is the standard of care. With technologic advances, the traditional open retropubic RP has been mostly replaced by laparoscopic and robot-assisted laparoscopic approaches. Importantly, numerous studies have demonstrated that laparoscopic and robotic RP have similar functional and oncologic outcomes when compared to traditional open RP, while also decreasing perioperative morbidity.<sup>6-8</sup> Due to patient demand and perceived technical advantages, the robotic RP has become the standard surgical approach to RP in the United States, despite higher per case costs when

compared to laparoscopic RP.<sup>9</sup> Regardless of the surgical approach (open, laparoscopic, or robotic), the anatomic principles of the retropubic RP remain the same, and thus the results of the following studies can be applied to all techniques.

In the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), RP was compared to watchful waiting (delayed hormonal therapy for metastatic disease) in a randomized fashion for men aged 75 years or less with at least a 10-year life expectancy who were diagnosed with clinically localized PCa. At 13.4 year median follow-up, a significant survival benefit was found for the men who were treated with RP, with PCa-specific mortality of 18% in the RP arm versus 29% in the watchful waiting arm. When the patients were sub-stratified by age, those who were less than 65 years derived the greatest benefit from RP, with a 26% reduction in overall mortality, 16% reduction in PCa-specific mortality, and 16% reduction in the development of metastatic disease. Additionally, patients with intermediate risk disease (PSA between 10 and 20 ng/mL or Gleason  $\geq 7$ ) derived the greatest benefit from RP, with a 15% reduction in overall mortality, 24% reduction in PCa-specific mortality, and a 20% reduction in the development of metastatic disease.<sup>10</sup>

In the Prostate Cancer Intervention Versus Observation Trial (PIVOT), RP was compared to watchful waiting in a randomized fashion for men aged 75 years of less, with PSA less than 50 ng/mL, with at least a 10-year life expectancy who were diagnosed with clinically localized PCa. An important consideration compared to SPCG-4 is that 50% of patients in PIVOT (versus 12% in SPCG-4) had non-palpable PCa. At 10 year median follow-up, no significant differences were found between the treatment groups for overall and cancer-specific survival. However, the patients who received RP had significantly less bone metastasis (5 versus 11%).<sup>11</sup> The recently published update of PIVOT confirms a statistically insignificant benefit in PCa-specific mortality for RP over observation (11.4 versus 7.4%,  $p=0.06$ ).<sup>12</sup> The ProtecT study demonstrated a similar finding when comparing RP to AS—no significant differences in overall or cancer-specific mortality at median 10 year follow-up, but a significant reduction in the development of metastatic disease with RP.<sup>4</sup> In PIVOT, similar to SPCG-4, patients with intermediate

risk disease did experience a significant reduction in overall mortality with RP, 31% relative reduction and 13% absolute risk reduction.<sup>11,12</sup> Combining the findings from PIVOT and SPCG-4 suggests that RP provides a survival advantage in patients with intermediate risk disease, particularly those who are less than 65 years of age.

### Radical Prostatectomy for Locally Advanced Prostate Cancer

Traditionally, surgical removal of the prostate was believed to provide no benefit to patients who had lymph node metastatic PCa. As the above trials determining the survival benefit of RP for patients with localized PCa were being performed, the role of surgery for patients with locally advanced PCa (with metastasis to the pelvic lymph nodes) was also being explored. In two retrospective studies of patients who received RP despite lymph node involvement, a minority of patients were found to have no evidence of disease at intermediate to long term follow-up. Examining patients from 1989 to 1999 in Switzerland, Bader et al. report approximately 25% (92/367) of patients receiving RP were found to have lymph node involvement. Of these patients, 24% (21/88) with available follow-up were found to have no evidence of disease recurrence at a median follow-up of 45 months.<sup>13</sup> Similarly in a study between 1972 to 1999 in the United States, Daneshmand et al. report approximately 12% (235/1936) of patients receiving RP were found to have disease that had spread to the lymph nodes. At 137 month median follow-up, the estimated recurrence-free survival was 80%, 65%, and 58% at 5, 10, and 15 years, respectively.<sup>14</sup> More important than the finding that a minority of patients with lymph node metastatic PCa have a durable cure after RP, Engel et al. found that survival for patients who had RP was significantly improved over patients who had RP aborted due to lymph node involvement. Using the Munich Cancer Registry between 1988 and 2007, they found that the 5 and 10 year estimated cancer-specific survival was 95% and 86% for RP but 70% and 40% with aborted RP.<sup>15</sup> As a result of these studies, the role of RP in locally advanced (lymph node metastatic) disease has been established as providing survival benefit to most patients, while providing cure to some.

### Radical Prostatectomy for Metastatic Prostate Cancer

More recently, a role for RP in the treatment of patients with metastatic PCa has been proposed. Retrospective studies using the Munich Cancer Registry and the Surveillance Epidemiology and End Results (SEER) database have demonstrated a survival advantage of RP over radiation or no local therapy in patients with metastatic PCa. In the Munich Cancer Registry from 1998 to 2010, 5% (74/1538) of patients with newly diagnosed metastatic PCa received RP. Although these likely represent carefully selected patients, the survival advantage was significant— 5-year survival of 55% versus 21% for RP versus any other therapy (radiation or systemic therapy alone), respectively.<sup>16</sup> The same findings were echoed in the SEER based study from 2004 to 2010, where roughly 3% (245/8185) of patients underwent RP in the setting of metastatic PCa. For those who received RP, 5-year survival was 67%, while 5-year survival was 23% for patients receiving no therapy.<sup>17</sup> Based on these studies and others,<sup>18</sup> three prospective trials examining the role of RP in metastatic disease have been opened: 1) a multicenter United States randomized trial of best systemic therapy versus best systemic therapy plus local therapy (RP or radiation), 2) a United Kingdom randomized trial of RP plus usual therapy versus usual therapy alone in patients with bone only low metastatic disease burden, 3) a German randomized trial of RP plus hormone therapy versus hormone therapy alone in patients with limited bone metastasis. As the results of these trials become available, evaluating the quality of life effects of RP in this patient population must be carefully weighed against the survival benefit that surgery may provide.

### Focal (Partial Gland) Therapy for Localized Prostate Cancer

As PCa is considered to be a multifocal disease in the majority of cases, surgical treatments aimed at part of the prostate rather than the entire gland have been met with skepticism. However, more recent advances in imaging, such as 3-Tesla multiparametric MRI and new radiotracers for PET/CT or PET/MRI, provide an opportunity for more accurate diagnosis and targeting of lesions within the prostate.<sup>19</sup> Multiple energy sources have been investigated for use in focal prostate ablation, including high-intensity focused ultrasound, cryotherapy, and photothermal devices. Regardless of the energy source, risks to urinary and sexual function exist, but

may be substantially lower than for RP, particularly if used on a limited portion of the prostate. More clinically meaningful for the successful uptake of focal therapy in PCa is the identification of the appropriate patient who is neither ideally suited for AS nor RP. The ideal patient would harbor enough risk of PCa-specific mortality to justify intervention but not high enough risk to require RP.<sup>20</sup> Despite significant improvements in imaging and image guided intervention, the state of available technology remains imperfect as a diagnostic tool, and so, focal treatments of the prostate cannot be considered a curative approach to PCa at this time.<sup>21</sup>

## Conclusions

As the results of large randomized trials have become available and technology continues to improve, the role of surgery in the management of PCa continues to evolve. RP remains the mainstay of surgical treatment for PCa, representing a curative option for those with localized disease and a survival benefit for those with advanced disease. As the role for AS and focal therapy continue to change, the appropriate risk stratification and selection of patients for those treatment options will be critically important.

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## Disclosure

None reported.

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