

Achieving Optimal Outcomes After Radical Prostatectomy

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ABSTRACT

Purpose

The most favorable outcome that can be achieved after radical prostatectomy is complete tumor resection without recurrence and full recovery of continence and potency. Risks of erectile dysfunction, incontinence, and disease recurrence are well described, but in isolation, do not adequately inform patients of the possibility of becoming cancer-free while at the same time returning to their preoperative functional state. We sought to determine the frequency of optimal outcomes after radical prostatectomy and the time to such outcomes.

Patients and Methods

Patients who underwent radical prostatectomy performed at a tertiary referral center between July 1998 and July 2003 for clinical stage T1 to T3 prostate cancer were identified. Patients were excluded if they were incontinent or impotent preoperatively, or if they had received radiotherapy or neoadjuvant androgen deprivation therapy previously. Six hundred forty-seven patients were analyzed for time to recovery of full continence and potency without cancer recurrence after surgery. Optimal outcome probability was calculated with a Markov state transition model to simulate clinical outcomes in the first 4 years following radical prostatectomy.

Results

Mean patient age was 58 years, and mean pretreatment prostate-specific antigen was 6.9 ng/mL. Cancer-free status with full continence and potency was achieved in 30% of men at 12 months, 42% at 24 months, 47% at 36 months, and 53% at 48 months postoperatively.

Conclusion

Optimal outcomes after radical prostatectomy can be achieved in a small majority of cases. Time to full recovery is primarily dictated by recovery of erectile function. This information is helpful for patients interested in their chances of returning to their preoperative functional state.

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INTRODUCTION

Radical prostatectomy is widely employed as primary treatment for localized prostate cancer and approximately 45% of men diagnosed with prostate cancer will be treated with radical prostatectomy.¹ The most favorable outcome that can be achieved after surgery is complete tumor resection with full recovery of continence and potency. These three goals of radical prostatectomy

are inextricably linked and, at times, may appear to hinder one another in that improvements in the outcome of one may occur at the expense of the others. The technical challenge of radical prostatectomy is to remove sufficient periprostatic tissue to achieve cure while at the same time preserving the cavernosal nerves required for erectile function and the neuro musculature required for continence.

Risks of individual complications and adverse effects of this procedure, such as

erectile dysfunction and incontinence, are reasonably well documented in the literature,²⁻⁹ as are the risks of disease recurrence.¹⁰⁻¹⁴ However, taken by themselves, these risks do not adequately inform patients of the likelihood of becoming cancer free while at the same time returning to their preoperative functional state. Patients considering any surgery with well-known potential for adverse effects may legitimately ask what their chances are of being “normal” after surgery, and how often the surgical goal is realized. They may also want to know how soon they can expect to return to their preoperative level of function.

We therefore sought to determine the frequency of optimal outcomes (free of disease with recovery of both full continence and potency) after radical prostatectomy, as well as the time to these outcomes. Although standard methods of time-to-event analyses can be used to estimate the probability of each event separately (recovery of continence, recovery of potency, and disease recurrence), decision-analytic methods permit the evaluation of all these end points simultaneously. Thus, a decision-analytic model was employed to estimate the probability of achieving an optimal outcome and the time elapsed until this outcome was attained.

PATIENTS AND METHODS

A Markov state-transition model was developed in order to simulate the experience of prostate cancer patients after radical prostatectomy. This model simulates the transition of subjects at discrete time intervals among health states relevant to the clinical situation.¹⁵ Outcomes occurring during each time interval, or Markov cycle, are aggregated across the cohort when a specified number of cycles have elapsed. In this analysis, we simulated outcomes for the first 4 years following surgery using 1-month Markov cycles.

Health states after radical prostatectomy were defined as (1) suboptimal outcome: either impotent, incontinent, or both; (2) optimal outcome: potent, continent, and recurrence free; and (3) biochemical recurrence: a single serum prostate-specific antigen (PSA) value of 0.2 ng/mL or greater after prostatectomy. In the base case, deaths as a result of causes other than cancer were excluded from the model, though we did simulate this event in sensitivity analysis. All patients started in the suboptimal outcome state, and each month they could move to the optimal outcome state, the biochemical recurrence state, or remain in the suboptimal outcome state (Fig 1). Once a patient experienced biochemical recurrence, he could not return to either the suboptimal or optimal state.

Transition probabilities (Table 1) were obtained from a clinical prostate cancer database of men seen by our tertiary referral institution’s outpatient urology service between July 1998 and July 2003. From this database, 1,133 patients who had a radical prostatectomy performed by either of two surgeons (P.T.S. and J.A.E.) for clinical stage T1 to T3 prostate cancer were identified. During preoperative evaluation and postoperative follow-up, serum PSA levels were measured, and continence and erectile function were routinely evaluated and assigned a grade of 1 to 5 corresponding with the scheme listed in Table 2. In this analysis, patients were

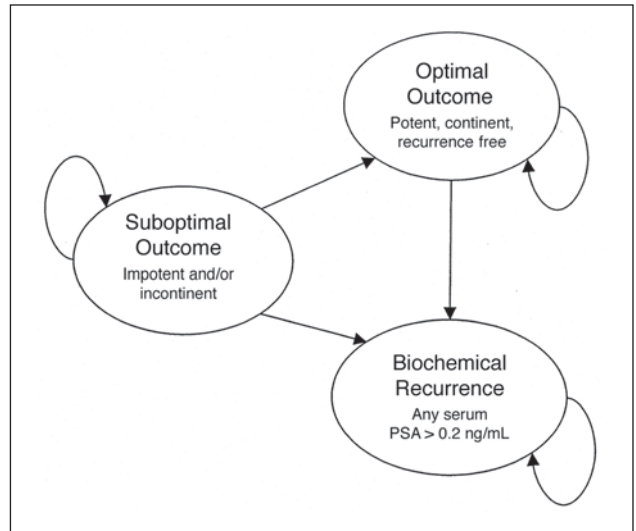


Fig 1. Possible health states and transitions after radical prostatectomy. All patients begin in the suboptimal outcome state. Each month they can transition to the optimal outcome state, the biochemical recurrence state, or remain in the suboptimal outcome state. A patient who recurs may not return to the suboptimal or optimal states. PSA, prostate-specific antigen.

considered potent if they were capable of full erections (grade 1 or 2) with or without the use of oral 5-phosphodiesterase inhibitors, and deemed continent if they required no incontinence pads (grade 1). Patients were excluded if they had preoperative incontinence (13 patients) or impotence (193 patients), had received preoperative radiation (36 patients) or neoadjuvant hormonal therapy (92 patients), or if the patient’s postoperative follow up data were incomplete (215 patients). Several patients met more than one exclusion criterion. Altogether, 486 patients were excluded from the study. A total of 647 patients were analyzed for time to recovery of both full continence and potency, and cancer recurrence.

Probabilities of achieving optimal postoperative outcomes and of experiencing biochemical recurrence were estimated using the cumulative incidence method. Cumulative transition probabilities of this sample at 6, 12, 24, and 48 months after surgery were utilized to estimate monthly transition probabilities, assuming constant hazards within each of the specified time intervals. Although a proportion of men who experience biochemical

Time Interval	Suboptimal to Optimal Outcome (%)	Suboptimal Outcome to BCR (%)	Optimal Outcome to BCR (%)
Months 1-6	3.40	0.57	0.53
Months 7-12	2.73	0.38	0.24
Months 13-24	1.87	0.13	0.12
Months 25-48	1.09	0.13	0.12

NOTE. This table states the percent chance each month of moving from one health state to another during a specific time interval. (Example: in this cohort, a patient in the first 6 months after surgery had a 3.4% chance per month of moving from the suboptimal health state to the optimal health state.)
Abbreviation: BCR, biochemical recurrence.

Table 2. Assessment of Continence and Erectile Function

Grade	Description
Continence	
1	Continent (no pads)
2	Mild SUI (leaks only during heavy activity/1-2 pads per day)
3	Moderate SUI (leaks with moderate activity/3-4 pads per day)
4	Severe SUI (leaks with normal activity, dry at night or at rest)
5	Total incontinence (continuous leakage at rest)
Potency	
1	Normal, full erection
2	Full, but diminished from normal
3	Partial erection, occasionally satisfactory for intercourse
4	Partial erection, unsatisfactory for intercourse
5	Impotent

Abbreviation: SUI, stress urinary incontinence.

recurrence would be expected to eventually die of disease, we did not model death as a result of prostate cancer because only two patients in the analysis died, both from causes other than prostate cancer, and had undetectable serum PSA at last assessment. To illustrate the postoperative characteristics of the patient cohort, the probabilities of impotence, incontinence, and freedom from recurrence were estimated with the Kaplan-Meier method. This study received institutional review board approval.

RESULTS

There were 647 patients in the analysis; they had a mean age of 58 years (median, 58 years; range, 39 to 75 years). Mean preoperative serum PSA was 6.9 ng/mL (median, 5.6 ng/mL; range, 0.3 to 113.4 ng/mL). Clinical data for all patients were summarized in Table 3. The positive surgical margins rate was 13%. All patients underwent bilateral nerve-sparing radical prostatectomy, except for 43 patients (6.6%) who had a unilateral nerve resection and 6 patients (0.9%) with bilateral nerve resections (five of whom received bilateral nerve grafts). Median length of follow-up was 15 months (range, 1 to 60 months), with 205 patients being followed for at least 2 years.

Following radical prostatectomy, the actuarial probability of recovery of full potency was 37% at 1 year (95% CI, 32 to 42), and 62% at 2 years (95% CI, 55 to 69; Fig 2). Sixty-one percent of patients recovering full potency used oral 5-phosphodiesterase inhibitors. The probability of achieving full continence was 87% at 1 year (95% CI, 84 to 90) and 93% at 2 years (95% CI, 90 to 96; Fig 3). The actuarial probability of remaining free of PSA recurrence at 4 and 5 years was 88% (95% CI, 84 to 93; Fig 4).

Using the decision analytic Markov model, we found that the proportion of patients achieving an optimal out-

Table 3. Patient Clinical Data

	No. of Patients	%
Biopsy Gleason Score		
2-6	443	68.5
7	163	25.2
8-10	40	6.2
Clinical stage		
T1c	363	56.2
T2a	146	22.6
T2b	82	12.7
T2c	40	6.2
T3a	14	2.2
T3c	2	0.3
Pretreatment PSA, ng/mL		
0-4	119	18.4
> 4-10	447	69.1
> 10-20	67	10.4
> 20	14	2.2
Pathologic stage		
T0	3	0.5
T2a	125	19.4
T2b	352	54.4
T2c	15	2.5
T3a	110	17
T3b	26	4
T3c	3	0.5
T4	12	1.9

Abbreviation: PSA, prostate-specific antigen.

come by 12, 24, and 36 months postoperatively was 30%, 42%, and 47%, respectively, as shown in Figure 5. By approximately 32 months after surgery, the percentage of patients who had reached a state of optimal outcome was equivalent to the proportion that had not (46%). By approximately 40 months, half the patients had attained an optimal outcome, and by 48 months a small majority of patients (53%) had done so. During the 48-month postoperative period,

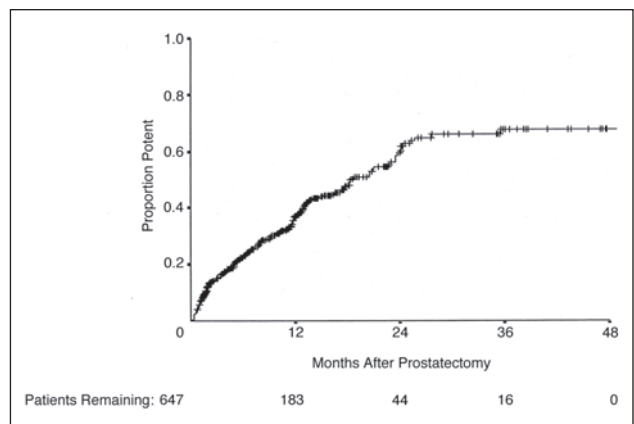


Fig 2. Probability of recovery of potency (full erections) was 37% at 1 year and 62% at 2 years.

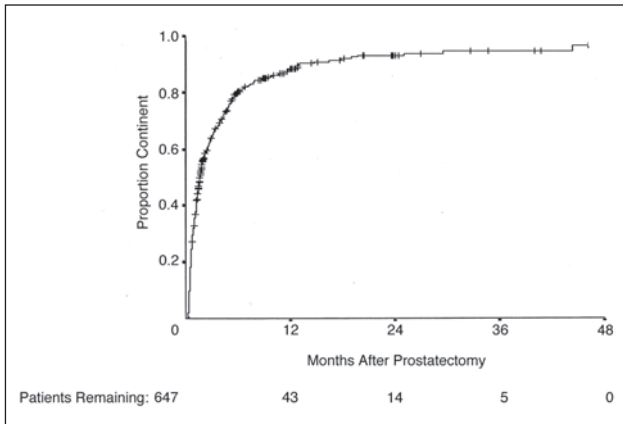


Fig 3. Probability of attaining full continence was 87% at 1 year and 93% at 2 years.

patients spent an average of 17.6 months in the optimal outcome state. Fewer than 10% of patients experienced biochemical recurrence at the end of 4 years.

Including the possibility of death as a result of non-prostate cancer causes, using age-specific monthly mortality rates from US life tables, had little impact on the results. When background mortality was incorporated into the model, 50% of patients achieved an optimal outcome by the end of 48 months, and patients spent an average of 17.5 months in the optimal outcome state. Fewer than 5% of patients died as a result of non-prostate cancer causes.

DISCUSSION

The ultimate goal or optimal outcome of radical prostatectomy is complete cancer resection without recurrence, with full recovery of continence and potency. This study analyzed the experience of patients with prostate cancer after radical prostatectomy to determine the frequency of an

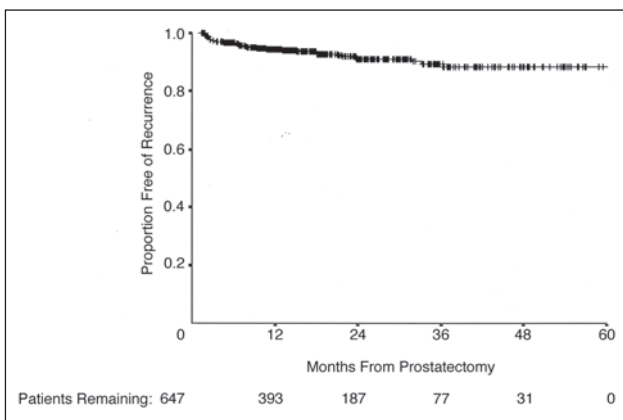


Fig 4. Actuarial probability of remaining recurrence free was 88% at 4 and 5 years.

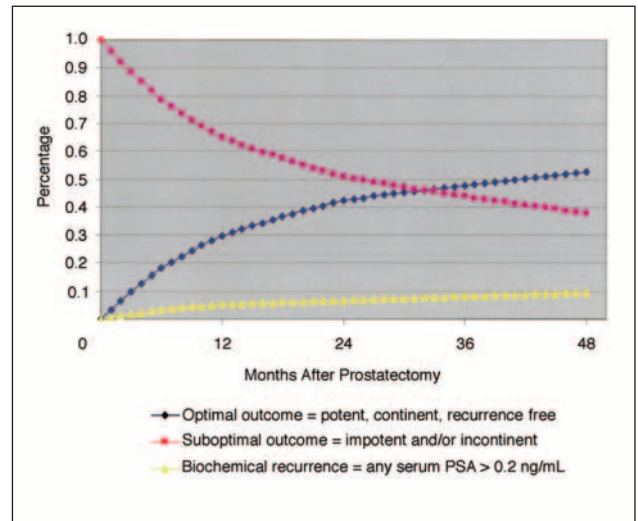


Fig 5. Results of Markov model. At 48 months, 53% of patients have achieved an optimal outcome. PSA, prostate-specific antigen.

optimal outcome, which was defined as a health state free of disease with both full continence and potency, and to determine the time required to achieve this state. As such, strict definitions of continence, potency, and biochemical recurrence were used. Postoperatively, patients could not require incontinence pads, they must have recovered full erections with or without the aid of oral 5-phosphodiesterase inhibitors, and they must not have had a serum PSA above 0.2 ng/mL at any time in order to qualify as an optimal outcome. This was necessary in order to determine patients' probability of returning to their preoperative functional state ("becoming normal again") after radical prostatectomy and to determine how often this surgical goal is attained. This is a valid concern for patients and clinicians alike.

This question is not adequately answered by merely informing patients of the individual risks of incontinence, impotence, or recurrence as cited in the most current radical prostatectomy series in the literature. Nor is it simply a matter of multiplying the probabilities of each event in isolation to obtain the probability of an optimal outcome because of the dependency of these three outcomes on one another and on surgical technique,¹⁶ among other factors. Therefore the Markov model was employed which incorporated the three different competing health states and generated probabilities from a cohort of patients who have several potential outcomes throughout the postoperative period. In this analysis, full recovery of potency and continence and cancer control was achieved in 30% of men at 12 months, 42% at 24 months, 47% at 36 months, and 53% at 48 months after surgery. This indicates that an optimal outcome can eventually be achieved in most men. Attainment of the optimal health state appears to be predominantly dictated by recovery of erectile function.

There are several limitations to this study. It utilizes data from only a single institution, though the number of patients evaluated is sizable, and maximum follow-up time is 5 years given the contemporary nature of this cohort of men. Results from highly trained surgeons at a tertiary cancer center in terms of efficacy and/or toxicity may not be generalizable to other surgeons or institutions. As such, our results may represent an upper bound of what is achievable. However, we believe these results are still of value because they convey what the maximum probability of an optimal outcome is. We did not control for known risk factors for progression after radical prostatectomy, such as clinical stage, Gleason grade, and serum PSA, nor for volume of disease. In this study, the clinical stage of more than three-quarters of the tumors was T2a or less, and the vast majority of patients underwent bilateral nerve-sparing procedures, making this a fairly representative series of modern prostatectomies and its results relevant to the average patient considering radical prostatectomy. In addition, the degree of neurovascular preservation was not considered in the analysis though it impacts on the recovery of postprostatectomy erectile function because this cannot be predicted with certainty preoperatively, which again, is the situation for most men undergoing the procedure. Also, the designation of full potency and continence are as a result of physician rather than patient assessment, rather than questionnaire data, though a study from our institution has shown good correlation between the potency grading system utilized in this analysis (Table 1) and the patient-derived International Index of Erectile Function (IIEF), with a potency grade of 1 and 2 corresponding to median IIEF scores of 28.5 and 24 (out of a maximum score of 30), respectively.¹⁷ There is also the inherent selection bias of using an observational data set of patients treated with surgery. Finally, we have not considered patient preferences (utilities) in our analysis. Patients may not view the three outcomes—cure, continence, and potency—as equivalent. Patients may have an occasional episode of incontinence or the requirement for some other manipulation than oral medication for potency and still consider themselves to have had “successful” treatment. Although our three end points may not be of similar importance to a patient, cancer recurrence, incontinence, and impotence are all undesirable. Our model predicts an ideal outcome and is a complement to the more formal decision analysis approach. These end points may not have equal significance, but each is undesirable, and men would prefer not to experience any of them.

Many of these limitations can be addressed with the development of a nomogram, or predictive model, controlling for the clinical features of the disease, the patient’s age and preoperative functional status, and the surgical factors involved. This would likely be a superior way to predict a patient’s probability of realizing an optimal outcome and would be the next step when more patient events and longer follow-up data become available. However, to our knowledge, this is one of the few studies that examined the three parameters of potency, continence, and freedom from malignancy as components of a single health state, and it introduces the concept of an optimal outcome.

Recently, Salomon et al^{18,19} proposed a scoring system to assess functional and oncologic outcomes in 146 men following radical prostatectomy in order to improve evaluation and comparison of results of surgery. With a more liberal definition of potency (able to achieve and maintain an erection suitable for intercourse with or without oral medications), they reported that 22.6% of patients after a maximum follow-up of 1 year were potent, completely continent (not wearing any incontinence pads), and free of disease (biochemical recurrence was a single PSA rise of > 0.2 ng/mL). We agree with their assertion that data on cancer control, continence, or potency in isolation are not sufficient for decision-making, and that the patients agreeing to radical prostatectomy should be informed of functional results in the context of cancer control. The outcome assessment of this patient cohort with increased follow-up will be informative when it becomes available.

It could be argued that by 40 months after radical prostatectomy, obtaining an optimal outcome in just over half of patients is not as favorable a result as would be hoped from a widely practiced localized prostate cancer therapy. It is important to note that this analysis used strict criteria, and that many patients are reportedly quite satisfied choosing surgery, despite having suffered a fairly wide degree of incontinence or impotence, and most would choose radical prostatectomy again.^{20,21} However, these results do suggest that there is room for improvement in the results of radical prostatectomy for many men undergoing the procedure. Similar studies examining the outcomes after other forms of therapy, such as external-beam radiotherapy or brachytherapy are needed to better inform clinicians and patients about reasonable expectations after localized prostate cancer treatment.

Authors’ Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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