or survival may not be apparent for years. After radical surgery to remove all prostate tissue, PSA should become undetectable in the blood within 6 weeks. If PSA remains or becomes detectable after radical prostatectomy, the patient is considered to have persistent disease. After radiation therapy, in contrast, PSA does not become undetectable because the remaining nonmalignant elements of the gland continue to produce PSA even if all cancer cells have been eliminated. Similarly, cancer control is not well defined for a patient managed by active surveillance because PSA levels will continue to rise in the absence of therapy. Other outcomes are time to objective progression (local or systemic), cancer-specific survival, and overall survival; however, these outcomes may take years to assess.

The more advanced the disease, the lower the probability of local control and the higher the probability of systemic relapse. More important is that within the categories of T1, T2, and T3 disease are cancers with a range of prognoses. Some T3 tumors are curable with therapy directed solely at the prostate, and some T1 lesions have a high probability of systemic relapse that requires the integration of local and systemic therapy to achieve cure. For T1c cancers in particular, stage alone is inadequate to predict outcome and select treatment; other factors must be considered.

Nomograms To better assess risk and guide treatment selection, many groups have developed prognostic models or nomograms that use a combination of the initial clinical T stage, biopsy Gleason score, and baseline PSA. Some use discrete cut points (PSA <10 or ≥10 ng/mL; Gleason score of ≤6, 7, or ≥8); others employ nomograms that use PSA and Gleason score as continuous variables. More than 100 nomograms have been reported to predict the probability that a clinically significant prostate cancer is present, disease extent (organ-confined vs non–organ-confined, node-negative or -positive), or the probability of success of treatment for specific local therapies using pretreatment variables. Considerable controversy exists over what constitutes "high risk" based on a predicted probability of success or failure. In these situations, nomograms and predictive models can only go so far. Exactly what probability of success or failure would lead a physician to recommend and a patient to seek alternative approaches is controversial. As an example, it may be appropriate to recommend radical surgery for a younger patient with a low probability of cure. Nomograms are being refined continually to incorporate additional clinical parameters, biologic determinants, and year of treatment, which can also affect outcomes, making treatment decisions a dynamic process.

Treatment-Related Adverse Events The frequency of adverse events varies by treatment modality and the experience of the treating team. For example, following radical prostatectomy, incontinence rates range from 2–47% and impotence rates range from 25–89%. Part of the variability relates to how the complication is defined and whether the patient or physician is reporting the event. The time of the assessment is also important. After surgery, impotence is immediate but may reverse over time, while with radiation therapy impotence is not immediate but may develop over time. Of greatest concern to patients are the effects on continence, sexual potency, and bowel function.

Radical Prostatectomy The goal of radical prostatectomy is to excise the cancer completely with a clear margin, to maintain continence by preserving the external sphincter, and to preserve potency by sparing the autonomic nerves in the neurovascular bundle. The procedure is advised for patients with a life expectancy of 10 years or more and is performed via a retropubic or perineal approach or via a minimally invasive robotic-assisted or hand-held laparoscopic approach. Outcomes can be predicted using postoperative nomograms that consider pretreatment factors and the pathologic findings at surgery. PSA failure is usually defined as a value greater than 0.1 or 0.2 ng/mL. Specific criteria to guide the choice of one approach over another are lacking. Minimally invasive approaches offer the advantage of a shorter hospital stay and reduced blood loss. Rates of cancer control, recovery of continence, and recovery of erectile function are comparable between open and minimally invasive approaches. The individual surgeon rather than the surgical approach used is most important in determining outcomes after surgery.

Neoadjuvant hormonal therapy has also been explored in an attempt to improve the outcomes of surgery for high-risk patients, using a variety of definitions. The results of several large trials testing 3 or 8 months of androgen depletion before surgery showed that serum PSA levels decreased by 96%, prostate volumes decreased by 34%, and margin positivity rates decreased from 41% to 17%. Unfortunately, hormones did not produce an improvement in PSA relapse–free survival. Thus, neoadjuvant hormonal therapy is not recommended.

Factors associated with incontinence following radical prostatectomy include older age and urethral length, which impacts the ability to preserve the urethra beyond the apex and the distal sphincter. The skill and experience of the surgeon are also factors. Recovery of erectile function is associated with younger age, quality of erections before surgery, and the absence of damage to the neurovascular bundles. In general, erectile function begins to return about 6 months after surgery if both neurovascular bundles are preserved. Potency is reduced by half if at least one neurovascular bundle is sacrificed. Overall, with the availability of drugs such as phosphodiesterase-5 (PDE5) inhibitors, intraurethral inserts of alprostadil, and intracavernosal injections of vasodilators, many patients recover satisfactory sexual function.

Radiation Therapy Radiation therapy is given by external beam, by radioactive sources implanted into the gland, or by a combination of the two techniques.

EXTERNAL-BEAM RADIATION THERAPY Contemporary external-beam radiation therapy requires three-dimensional conformal treatment plans to maximize the dose to the prostate and to minimize the exposure of the surrounding normal tissue. Intensity-modulated radiation therapy (IMRT) permits shaping of the dose and allows the delivery of higher doses to the prostate and a further reduction in normal tissue exposure than three-dimensional conformal treatment alone. These advances have enabled the safe administration of doses >80 Gy and resulted in higher local control rates and fewer side effects.

Cancer control after radiation therapy has been defined by various criteria, including a decline in PSA to <0.5 or 1 ng/mL, "nonrising" PSA values, and a negative biopsy of the prostate 2 years after completion of treatment. The current standard definition of biochemical failure (the Phoenix definition) is a rise in PSA by ≥2 ng/mL higher than the lowest PSA achieved. The date of failure is "at call" and not backdated.

Radiation dose is critical to the eradication of prostate cancer. In a representative study, a PSA nadir of <1.0 ng/mL was achieved in 90% of patients receiving 75.6 or 81.0 Gy versus 76% and 56% of those receiving 70.2 and 64.8 Gy, respectively. Positive biopsy rates at 2.5 years were 4% for those treated with 81 Gy versus 27% and 36% for those receiving 75.6 and 70.2 Gy, respectively.

Overall, radiation therapy is associated with a higher frequency of bowel complications (mainly diarrhea and proctitis) than surgery. The frequency relates directly to the volume of the anterior rectal wall receiving full-dose treatment. In one series, grade 3 rectal or urinary toxicities were seen in 2.1% of patients who received a median dose of 75.6 Gy, whereas grade 3 urethral strictures requiring dilatation developed in 1% of cases, all of whom had undergone a transurethral resection of the prostate (TURP). Pooled data show that the frequency of grade 3 and 4 toxicities is 6.9% and 3.5%, respectively, for patients who received >70 Gy. The frequency of erectile dysfunction is related to the age of the patient, the quality of erections pretreatment, the dose administered, and the time of assessment. Postradiation erectile dysfunction is related to a disruption of the vascular supply and not the nerve fibers.

Neoadjuvant hormone therapy before radiation therapy has the aim of decreasing the size of the prostate and, consequently, reducing the exposure of normal tissues to full-dose radiation, increasing local control rates, and decreasing the rate of systemic failure.