Short-term hormone therapy can reduce toxicities and improve local control rates, but long-term treatment (2–3 years) is needed to prolong the time to PSA failure and lower the risk of metastatic disease in men with high-risk cancers. The impact on survival has been less clear.

BRACHYTHERAPY Brachytherapy is the direct implantation of radioactive sources (seeds) into the prostate. It is based on the principle that the deposition of radiation energy in tissues decreases as a function of the square of the distance from the source **(Chap. 103e)**. The goal is to deliver intensive irradiation to the prostate, minimizing the exposure of the surrounding tissues. The current standard technique achieves a more homogeneous dose distribution by placing seeds according to a customized template based on imaging assessment of the cancer and computer-optimized dosimetry. The implantation is performed transperineally as an outpatient procedure with real-time imaging.

Improvements in brachytherapy techniques have resulted in fewer complications and a marked reduction in local failure rates. In a series of 197 patients followed for a median of 3 years, 5-year actuarial PSA relapse–free survival for patients with pretherapy PSA levels of 0–4, 4–10, and >10 ng/mL were 98%, 90%, and 89%, respectively. In a separate report of 201 patients who underwent posttreatment biopsies, 80% were negative, 17% were indeterminate, and 3% were positive. The results did not change with longer follow-up. Nevertheless, many physicians feel that implantation is best reserved for patients with good or intermediate prognostic features.

Brachytherapy is well tolerated, although most patients experience urinary frequency and urgency that can persist for several months. Incontinence has been seen in 2–4% of cases. Higher complication rates are observed in patients who have undergone a prior TURP, whereas those with obstructive symptoms at baseline are at a higher risk for retention and persistent voiding symptoms. Proctitis has been reported in <2% of patients.

Active Surveillance Although prostate cancer is the most common form of cancer affecting men in the United States, patients are being diagnosed earlier and more frequently present with early-stage disease. Active surveillance, described previously as *watchful waiting* or *deferred therapy*, is the policy of monitoring the illness at fixed intervals with DREs, PSA measurements, and repeat prostate biopsies as indicated until histopathologic or serologic changes correlative of progression warrant treatment with curative intent. It evolved from studies that evaluated predominantly elderly men with well-differentiated tumors who demonstrated no clinically significant progression for protracted periods, recognition of the contrast between incidence and disease-specific mortality, the high prevalence of autopsy cancers, and an effort to reduce overtreatment. A recent screening study estimated that between 50–100 men with low-risk disease would need to be treated to prevent one prostate cancer–specific death.

Arguing against active surveillance are the results of a Swedish randomized trial of radical prostatectomy versus active surveillance. With a median follow-up of 6.2 years, men treated by radical surgery had a lower risk of prostate cancer death relative to active surveillance patients (4.6% vs 8.9%) and a lower risk of metastatic progression (hazard ratio 0.63). Case selection is critical, and determining clinical parameters predictive of cancer aggressiveness that can be used to reliably select men most likely to benefit from active surveillance is an area of intense study. In one prostatectomy series, it was estimated that 10–15% of those treated had "insignificant" disease. One set of criteria includes men with clinical T1c tumors that are biopsy Gleason grade 6 or less involving three or fewer cores, each of them having less than 50% involvement by tumor and a PSA density of less than 0.15.

Concerns about active surveillance include the limited ability to predict pathologic findings by needle biopsy even when multiple cores are obtained, the recognized multifocality of the disease, and the possibility of a missed opportunity to cure the disease. Nomograms to help predict which patients can safely be managed by active surveillance continue to be refined, and as their predictive accuracy improves, it can be anticipated that more patients will be candidates.

RISING PSA AFTER DEFINITIVE LOCAL THERAPY

This term is applied to a group of patients in whom the sole manifestation of disease is a rising PSA after surgery and/or radiation therapy. By definition, there is no evidence of disease on an imaging study. For these patients, the central issue is whether the rise in PSA results from persistent disease in the primary site, systemic disease, or both. In theory, disease in the primary site may still be curable by additional local treatment.

The decision to recommend radiation therapy after prostatectomy is guided by the pathologic findings at surgery, because imaging studies such as CT and bone scan are typically uninformative. Some recommend a choline-11 positron emission tomography (PET) scan, but availability in the United States is limited. Others recommend that a biopsy of the urethrovesical anastomosis be obtained before considering radiation, whereas others treat empirically based on risk. Factors that predict for response to salvage radiation therapy are a positive surgical margin, lower Gleason score in the radical prostatectomy specimen, long interval from surgery to PSA failure, slow PSA doubling time, absence of disease in the lymph nodes, and a low (<0.5–1 ng/mL) PSA value at the time of radiation treatment. Radiation therapy is generally not recommended if the PSA was persistently elevated after surgery, which usually indicates that the disease has spread outside of the area of the prostate bed and is unlikely to be controlled with radiation therapy. As is the case for other disease states, nomograms to predict the likelihood of success are available.

For patients with a rising PSA after radiation therapy, salvage local therapy can be considered if the disease was "curable" at the time of diagnosis, if persistent disease has been documented by a biopsy of the prostate, and if no metastatic disease is seen on imaging studies. Unfortunately, case selection is poorly defined in most series, and morbidities are significant. Options include salvage radical prostatectomy, salvage cryotherapy, salvage radiation therapy, and salvage irreversible electroporation.

The rise in PSA after surgery or radiation therapy may indicate subclinical or micrometastatic disease with or without local recurrence. In these cases, the need for treatment depends, in part, on the estimated probability that the patient will develop clinically detectable metastatic disease on a scan and in what time frame. That immediate therapy is not always required was shown in a series where patients who developed a biochemical recurrence after radical prostatectomy received no systemic therapy until metastatic disease was documented. Overall, the median time to metastatic progression by imaging was 8 years, and 63% of the patients with rising PSA values remained free of metastases at 5 years. Factors associated with progression included the Gleason score of the radical prostatectomy specimen, time to recurrence, and PSA doubling time. For those with Gleason grade ≥8, the probability of metastatic progression was 37%, 51%, and 71% at 3, 5, and 7 years, respectively. If the time to recurrence was <2 years and PSA doubling time was long (>10 months), the proportions with metastatic disease at the same time intervals were 23%, 32%, and 53%, versus 47%, 69%, and 79% if the doubling time was short (<10 months). PSA doubling times are also prognostic for survival. In one series, all patients who succumbed to disease had PSA doubling times of 3 months or less.

Most physicians advise treatment if the PSA doubling time is 12 months or less. A difficulty with predicting the risk of metastatic spread, symptoms, or death from disease in the rising PSA state is that most patients receive some form of therapy before the development of metastases. Nevertheless, predictive models continue to be refined.

METASTATIC DISEASE: NONCASTRATE

The state of *noncastrate metastatic prostate cancer* includes men with metastases visible on an imaging study and noncastrate levels of testosterone (>150 ng/dL). The patient may be newly diagnosed