WHITE PAPER – Prostate Cancer and Stereotactic Radiosurgery

I. Introduction

This white paper will focus on carcinoma of the prostate with sections one through six (I-VI) comprising a general review of prostatic carcinoma from the National Cancer Institute, more information can be found at cancer.gov. Section seven (VII) will provide a literature review on stereotactic radiosurgery (SRS) for the prostate and section eight (VIII) (for society members only) will provide clinical indications and treatment guidelines on stereotactic radiosurgery for the prostate.

II. Definition and Incidence

SRS is an emerging treatment approach for early-stage prostate cancer, made possible by technological advancements in radiation treatment delivery systems. It is estimated that there were 192,280 new cases of prostate cancer in 2009 and 27,360 deaths from prostate cancer in the United States in 2009.\(^1\) Carcinoma of the prostate is predominantly a tumor of older men, which frequently responds to treatment when widespread and may be cured when localized. The rate of tumor growth varies from very slow to moderately rapid, and some patients may have prolonged survival even after the cancer has metastasized to distant sites such as bone. Because the median age at diagnosis is 72 years, many patients—especially those with localized tumors—may die of other illnesses without ever having suffered significant disability from the cancer. The approach to treatment is influenced by age and coexisting medical problems. Side effects of various forms of treatment should be considered in selecting appropriate management. Controversy exists in regard to the value of screening, the most appropriate staging evaluation, and the optimal treatment of each stage of the disease.\(^2\)

A complicating feature of any analysis of survival after treatment of prostate cancer and comparison of the various treatment strategies is the evidence of increasing diagnosis of nonlethal tumors as diagnostic methods have changed over time. Nonrandomized comparisons of treatments may therefore be confounded not only by patient-selection factors but also by time trends. For example, a population-based study in Sweden showed that from 1960 to the late 1980’s, before the use of prostate-specific antigen (PSA) for screening purposes, long-term relative survival rates after the diagnosis of prostate cancer improved substantially as more sensitive methods of diagnosis were introduced. This occurred despite the use of watchful waiting or palliative hormonal treatment as the most common treatment strategies for localized prostate cancer during the entire era (<150 radical prostatectomies per year were performed in Sweden during the late 1980s). The investigators estimated that if all cancers diagnosed between 1960 and 1964 were of the lethal variety, then at least 33% of cancers diagnosed between 1980 and 1984 were of the nonlethal variety.\(^3\) With the advent of PSA screening, the ability to diagnose nonlethal prostate cancers may increase further. Another issue complicating comparisons of outcomes among nonconcurrent series of patients is the possibility of changes in criteria for histologic diagnosis of prostate cancer.\(^4\) This phenomenon creates a statistical artifact...
that can produce a false sense of therapeutic accomplishment and may also lead to more aggressive therapy. For example, prostate biopsies from a population-based cohort of 1,858 men diagnosed with prostate cancer from 1990 through 1992 were re-read in 2002 to 2004. The contemporary Gleason score readings were an average of 0.85 points higher (95% confidence interval [CI], 0.79–0.91; P < .001) than the same slides read in 1990 to 1992. As a result, Gleason score-standardized prostate cancer mortality for these men was artifactually improved from 2.08 to 1.50 deaths per 100 person years—a 28% decrease even though overall outcomes were unchanged.

The issue of screening asymptomatic men for prostate cancer with digital rectal examination (DRE), PSA, and/or ultrasound is controversial. Serum PSA and transrectal ultrasound are more sensitive and will increase the diagnostic yield of prostate cancer when used in combination with rectal examination; however, these screening methods are also associated with high false-positive rates and may identify some tumors that will not threaten the patient’s health. The issue is further complicated by the morbidity associated with work-up and treatment of such tumors and the considerable cost beyond a routine DRE. Furthermore, because a high percentage of tumors identified by PSA screening alone have spread outside the prostate, PSA screening may not improve life expectancy. In any case, the clinician who uses PSA for the detection of prostate cancer should be aware that no uniform standard exists; if a laboratory changes to a different assay kit, serial assays may yield nonequivalent PSA values. In addition, the upper limit of the normal range of PSA, and therefore the threshold at which to biopsy, is not well-defined. A multicenter trial (PLCO-1) sponsored by the National Cancer Institute was conducted to test the value of early detection in reducing mortality.

III. Prognostic Factors

Survival of the patient with prostatic carcinoma is related to the extent of the tumor. When the cancer is confined to the prostate gland, median survival in excess of 5 years can be anticipated. Patients with locally advanced cancer are not usually curable, and a substantial fraction will eventually die of the tumor, though median survival may be as long as 5 years. If prostate cancer has spread to distant organs, current therapy will not cure it. Median survival is usually 1 to 3 years, and most such patients will die of prostate cancer. Even in this group of patients, however, indolent clinical courses lasting for many years may be observed.

Other factors affecting the prognosis of patients with prostate cancer that may be useful in making therapeutic decisions include histologic grade of the tumor, patient’s age, other medical illnesses, and level of PSA. Poorly differentiated tumors are more likely to have already metastasized by the time of diagnosis and are associated with a poorer prognosis. For patients treated with radiation therapy, the combination of clinical tumor stage, Gleason score, and pretreatment PSA level can be used to more accurately estimate the risk of relapse. In most studies, flow cytometry has shown that nuclear DNA ploidy is an independent prognostic indicator for progression and for cause-specific survival in patients with pathologic stages III and IV prostate cancer without metastases (Jewett stages C and D1). Diploid tumors have a more favorable outcome than either tetraploid or aneuploid tumors. The use of flow cytometry techniques and histogram analysis to determine prognosis will require standardization. Often, baseline rates of PSA changes are thought to be markers of tumor progression. Even
though a tumor marker or characteristic may be consistently associated with a high risk of prostate cancer progression or death, it may be a very poor predictor and therefore of very limited utility in making therapeutic decisions. For example, baseline PSA and rate of PSA change were associated with subsequent metastasis or prostate cancer death in a cohort of 267 men with clinically localized prostate cancer who were managed by watchful waiting in the control arm of a randomized trial comparing radical prostatectomy to watchful waiting. Nevertheless, the accuracy of classifying men into groups whose cancer remained indolent versus those whose cancer progressed was poor at all examined cut points of PSA or PSA rate of change.

Several nomograms have been developed to predict outcomes either prior to or after radical prostatectomy with intent to cure. Preoperative nomograms are based on clinical stage, PSA, Gleason score, and the number of positive and negative prostate biopsy cores. One independently validated nomogram demonstrated increased accuracy in predicting biochemical recurrence-free survival by including preoperative plasma levels of transforming growth factor B1 and interleukin-6 soluble receptor. Postoperative nomograms add pathologic findings, such as capsular invasion, surgical margins, seminal vesicle invasion, and lymph node involvement. The nomograms, however, were developed at academic centers and may not be as accurate when generalized to nonacademic hospitals, where the majority of patients are treated.

In addition, the nomograms use nonhealth (intermediate) outcomes such as PSA rise or pathologic surgical findings and subjective endpoints such as the physician's perceived need for additional therapy. In addition, the nomograms may be affected by changing methods of diagnosis or neoadjuvant therapy. Definitive treatment is usually considered for younger men with prostate cancer and no major comorbid medical illnesses because younger men are more likely to die of prostate cancer than older men or men with major comorbid medical illness. Elevations of serum acid phosphatase are associated with poor prognosis in both localized and disseminated disease. PSA, an organ-specific marker with greater sensitivity and high specificity for prostate tissue, is often used as a tumor marker. After radical prostatectomy, detectable PSA levels identify patients at elevated risk of local treatment failure or metastatic disease; however, a substantial proportion of patients with elevated or rising PSA levels after surgery may remain clinically free of symptoms for extended periods of time. Biochemical evidence of failure on the basis of elevated or slowly rising PSA alone therefore may not be sufficient to alter treatment. For example, in a retrospective analysis of nearly 2,000 men who had undergone radical prostatectomy with curative intent and who were followed for a mean of 5.3 years, 315 men (15%) demonstrated an abnormal PSA of 0.2 ng/mL or higher, which is evidence of biochemical recurrence. Of these 315 men, 103 men (34%) developed clinical evidence of recurrence. The median time to development of clinical metastasis after biochemical recurrence was 8 years. After the men developed metastatic disease, the median time to death was an additional 5 years.

After radiation therapy with curative intent, persistently elevated or rising PSA may be a prognostic factor for clinical disease recurrence; however, reported case series have used a variety of definitions of PSA failure. Criteria have been developed by the American Society for Therapeutic Radiology and Oncology Consensus Panel.

It is difficult to base decisions about
instituting additional therapy on biochemical failure. The implication of the various definitions of PSA failure for overall survival (OS) is not known, and as in the surgical series, many biochemical relapses (rising PSA alone) may not be clinically manifested in patients treated with radiation therapy.\textsuperscript{46, 47}

Using surrogate endpoints for clinical decision making is controversial. Preliminary data from a retrospective cohort of 8,669 patients with clinically localized prostate cancer treated with either radical prostatectomy or radiation therapy suggested that short posttreatment PSA doubling time (<3 months in this study) fulfills some criteria as a surrogate endpoint for all-cause mortality and prostate cancer mortality after surgery or radiation therapy.\textsuperscript{48} Likewise, a retrospective analysis has shown that PSA declines of 20% to 40% (but not 50%) at 3 months and 30% or more at 2 months after initiation of chemotherapy for hormone independent prostate cancer, fulfilled several criteria of surrogacy for OS.\textsuperscript{49} These observations should be independently confirmed in prospective study designs and may not apply to patients treated with hormonal therapy. In addition, there are no standardized criteria of surrogacy or standardized cutpoints for adequacy of surrogate endpoints, even in prospective trials.\textsuperscript{50}

After hormonal therapy, reduction of PSA to undetectable levels provides information regarding the duration of progression-free status; however, decreases in PSA of less than 80% may not be very predictive.\textsuperscript{16} Yet, because PSA expression itself is under hormonal control, androgen deprivation therapy can decrease the serum level of PSA independent of tumor response. Clinicians, therefore, cannot rely solely on the serum PSA level to monitor a patient’s response to hormone therapy; they must also follow clinical criteria.\textsuperscript{51}

IV. Cellular Classification

More than 95% of primary prostate cancers are adenocarcinomas, and this discussion is confined to patients with this diagnosis. In general, the degree of tumor differentiation and abnormality of histologic growth pattern directly correlate with the likelihood of metastases and with death. Because of marked variability in tumor differentiation from one microscopic field to another, many pathologists will report the range of differentiation among the malignant cells that are present in a biopsy (Gleason grade).\textsuperscript{52, 53}

When the cytopathologist is experienced in the technique, and the specimen is adequate for analysis, fine-needle aspiration of the prostate (usually performed transrectally) has been shown to have an accuracy of diagnosis equal to that of traditional core-needle biopsy.\textsuperscript{54} Fine-needle aspiration is less painful than core biopsy and, therefore, can be performed as an outpatient procedure and at periodic intervals for serial follow-up. Controversy exists as to whether it is as reliable for grading purposes, particularly with grade range apparent in different fields.\textsuperscript{55} Many urologists now use a bioptic gun with ultrasound guidance, which is relatively painless. The risk of complications with this technique is low. A transperineal, ultrasound-guided approach can be used in those patients who may be at increased risk of complications through a transrectal approach. In a series of 670 men undergoing biopsy with an 18-gauge needle, the complication rate was 2% with only 4 patients requiring hospitalization.\textsuperscript{56}
V. Staging

Detection of asymptomatic metastatic disease in prostate cancer is greatly affected by the staging tests performed. Radionuclide bone scans are currently the most widely used tests for metastases to the bone, which is the most common site of distant tumor spread. Magnetic resonance imaging (MRI) is more sensitive than radionuclide bone scans but is impractical for evaluating the entire skeletal system. Some evidence suggests that serum prostate-specific antigen (PSA) levels can predict the results of radionuclide bone scan in newly diagnosed patients. In one series, only 2 of 852 patients (0.23%) with a PSA of less than 20 µg/L had a positive bone scan in the absence of bone pain. In another series of 265 prostate cancer patients, 0 of 23 patients with a PSA of less than 4 µg/L had a positive bone scan, and 2 of 114 patients with a PSA of less than 10 µg/L had a positive bone scan. Prognosis is worse in patients with pelvic lymph node involvement.

Whether to subject all patients to a pelvic lymph node dissection (PLND) is debatable, but in patients undergoing a radical retropubic prostatectomy, the nodal status is ascertained as a matter of course. In patients who are undergoing a radical perineal prostatectomy in whom the PSA value is less than 20 and the Gleason sum is low, however, evidence is mounting that a PLND is probably unnecessary, especially in patients whose malignancy was not palpable but detected on ultrasound. A PLND remains the most accurate method to assess metastases to pelvic nodes, and laparoscopic PLND has been shown to accurately assess pelvic nodes as effectively as an open procedure. The exact role of PLND in diagnosis and subsequent treatment is being evaluated, though it has already been determined that the length of hospital stay following laparoscopic PLND is shorter than that following an open procedure. The determining factor when deciding if any type of PLND is indicated is whether definitive therapy may be altered. Likewise, preoperative seminal vesicle biopsy may be useful in patients with palpable nodules who are being considered for radical prostatectomy (unless they have a low Gleason score) because seminal vesicle involvement could affect choice of primary therapy and predicts for pelvic lymph node metastasis.

In patients with clinically localized (stage I or stage II) prostate cancer, Gleason pathologic grade and enzymatic serum prostatic acid phosphatase values (even within normal range) predict the likelihood of capsular penetration, seminal vesicle invasion, or regional lymph node involvement. Analysis of a series of 166 patients with clinical stage I and stage II prostate cancer undergoing radical prostatectomy revealed an association between Gleason biopsy score and the risk of lymph node metastasis found at surgery. The risks of node metastasis for patients grouped according to their Gleason biopsy score was 2%, 13%, and 23% for Gleason scores of 5, 6, and 8, respectively.

Transrectal ultrasound (TRUS) may facilitate diagnosis by directing needle biopsy; however, ultrasound is operator dependent and does not assess lymph node size. Moreover, a prospective multi-institutional study of preoperative TRUS in men with clinically localized prostate cancer felt to be eligible for radical prostatectomy showed that TRUS was no better than digital rectal examination in predicting extracapsular tumor extension or seminal vesicle involvement. Computed tomography (CT) can detect grossly enlarged nodes but poorly defines intraprostatic features; therefore, it is not reliable for the staging of pelvic node disease when compared to surgical staging. Although MRI has been used to detect extracapsular extension of prostate
cancer, a positive-predictive value of about 70% and considerable interobserver variation are problems that make its routine use in staging uncertain. Ultrasound and MRI, however, can reduce clinical understaging and thereby improve patient selection for local therapy. Preliminary data with the endorectal MRI coil for prostate imaging report the highest sensitivity and specificity for identification of organ-confined and extracapsular disease. MRI is a poor tool for evaluating nodal disease.

Two systems are in common use for the staging of prostate cancer. The Jewett system (stages A through D) was described in 1975 and has since been modified. In 1997, the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer adopted a revised tumor, nodes, metastasis (TNM) system that employs the same broad T stage categories as the Jewett system but includes subcategories of T stage, such as a stage to describe patients diagnosed through PSA screening. This revised TNM system is clinically useful and more precisely stratifies newly diagnosed patients. In 2002, the AJCC further revised the TNM classification system. Both staging systems are shown below, and both are used in this summary to discuss treatment options. A thorough review of the controversies of staging in prostate cancer has been published.

**TNM Definitions**

**Primary tumor (T)**

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1: Clinically inapparent tumor not palpable nor visible by imaging
  - T1a: Tumor incidental histologic finding in 5% or less of tissue resected
  - T1b: Tumor incidental histologic finding in more than 5% of tissue resected
  - T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)
- T2: Tumor confined within prostate*
  - T2a: Tumor involves 50% or less of one lobe
  - T2b: Tumor involves more than 50% of one lobe but not both lobes
  - T2c: Tumor involves both lobes
- T3: Tumor extends through the prostate capsule**
  - T3a: Extracapsular extension (unilateral or bilateral)
  - T3b: Tumor invades seminal vesicle(s)
- T4: Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

* [Note: Tumor that is found in one or both lobes by needle biopsy but is not palpable or reliably visible by imaging is classified as T1c.]

** [Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified as T2 not T3.]
Regional lymph nodes (N)

Regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries. They include the following groups (laterality does not affect the N classification): pelvic (not otherwise specified [NOS]), hypogastric, obturator, iliac (i.e., internal, external, or NOS), and sacral (lateral, presacral, promontory [e.g., Gerota], or NOS). Distant lymph nodes are outside the confines of the true pelvis. They can be imaged using ultrasound, CT, MRI, or lymphangiography and include: aortic (para-aortic, periaortic, or lumbar), common iliac, inguinal (deep), superficial inguinal (femoral), supraclavicular, cervical, scalene, and retroperitoneal (NOS) nodes. Although enlarged lymph nodes can occasionally be visualized, because of a stage migration associated with PSA screening, very few patients will be found to have nodal disease, so false-positive and false-negative results are common when imaging tests are employed. In lieu of imaging, risk tables are generally used to determine individual patient risk of nodal involvement. Involvement of distant lymph nodes is classified as M1a.

- NX: Regional lymph nodes were not assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in regional lymph node(s)

Distant metastasis (M)*

- MX: Distant metastasis cannot be assessed (not evaluated by any modality)
- M0: No distant metastasis
- M1: Distant metastasis
  - M1a: Nonregional lymph node(s)
  - M1b: Bone(s)
  - M1c: Other site(s) with or without bone disease

* [Note: When more than one site of metastasis is present, the most advanced category (pM1c) is used.]

Histopathologic grade (G)

- GX: Grade cannot be assessed
- G1: Well differentiated (slight anaplasia) (Gleason score of 2–4)
- G2: Moderately differentiated (moderate anaplasia) (Gleason score of 5–6)
- G3-4: Poorly differentiated or undifferentiated (marked anaplasia) (Gleason score of 7–10)

AJCC Stage Groupings

**Stage I**

- T1a, N0, M0, G1
Stage II

- T1a, N0, M0, G2–4
- T1b, N0, M0, any G
- T1c, N0, M0, any G
- T1, N0, M0, any G
- T2, N0, M0, any G

Stage III

- T3, N0, M0, any G

Stage IV

- T4, N0, M0, any G
- Any T, N1, M0, any G
- Any T, any N, M1, any G

Jewett Staging System

Stage A

Stage A is clinically undetectable tumor confined to the prostate gland and is an incidental finding at prostatic surgery.
- Substage A1: well differentiated with focal involvement and usually left untreated
- Substage A2: moderately or poorly differentiated or involves multiple foci in the gland

Stage B

Stage B is tumor confined to the prostate gland.
- Substage B0: nonpalpable and PSA detected
- Substage B1: single nodule in one lobe of the prostate
- Substage B2: more extensive involvement of one lobe or involvement of both lobes

Stage C

Stage C is tumor clinically localized to the periprostatic area but extending through the prostatic capsule; seminal vesicles may be involved.
- Substage C1: clinical extracapsular extension
- Substage C2: extracapsular tumor producing bladder outlet or ureteral obstruction

Stage D

Stage D is metastatic disease.
- Substage D0: clinically localized disease (prostate only) but persistently elevated enzymatic serum acid phosphatase titers
• Substage D1: regional lymph nodes only
• Substage D2: distant lymph nodes and metastases to bone or visceral organs
• Substage D3: D2 prostate cancer patients who relapsed after adequate endocrine therapy

VI. Treatment Options

State-of-the-art treatment in prostate cancer provides prolonged disease-free survival for many patients with localized disease but is rarely curative in patients with locally extensive tumor. Even when the cancer appears clinically localized to the prostate gland, a substantial fraction of patients will develop disseminated tumor after local therapy with surgery or radiation therapy. This development is the result of the high incidence of clinical understaging, even with current diagnostic techniques. Metastatic tumor is currently not curable.

Surgery is usually reserved for patients in good health who elect surgical intervention. Surgery is usually reserved for patients in good health who elect surgical intervention. 

Tumors in these patients should be confined to the prostate gland (stage I and stage II). Prostatectomy can be performed by the perineal or retropubic approach. The perineal approach requires a separate incision for lymph node dissection. Laparoscopic lymphadenectomy is technically possible and accomplished with much less patient morbidity. For small, well-differentiated nodules, the incidence of positive pelvic nodes is less than 20%, and pelvic node dissection may be omitted. 

With larger, less differentiated tumors, a pelvic lymph node dissection is more important. The value of pelvic node dissection (i.e., open surgical or laparoscopic) is not therapeutic but spares patients with positive nodes the morbidity of prostatectomy. Radical prostatectomy is not usually performed if frozen section evaluation of pelvic nodes reveals metastases; such patients should be considered for entry into existing clinical trials or receive radiation therapy to control local symptoms. The role of preoperative (neoadjuvant) hormonal therapy is not established.

Following radical prostatectomy, pathological evaluation stratifies tumor extent into organ-confined, specimen-confined, and margin-positive disease. The incidence of disease recurrence increases when the tumor is not specimen-confined (extracapsular) and/or the margins are positive. Results of the outcome of patients with positive surgical margins have not been reported. Patients with extraprostatic disease are suitable candidates for clinical trials such as RTOG-9601, for example. These trials include evaluation of postoperative radiation delivery, cytotoxic agents, and hormonal treatment using luteinizing hormone-releasing hormone (LHRH) agonists and/or antiandrogens.

Cryosurgery is a surgical technique under development that involves destruction of prostate cancer cells by intermittent freezing of the prostate tissue with cryoprobes, followed by thawing. Cryosurgery is a surgical technique under development that involves destruction of prostate cancer cells by intermittent freezing of the prostate tissue with cryoprobes, followed by thawing.

Cryosurgery is less well established than standard prostatectomy, and long-term outcomes are not as well established as with prostatectomy or radiation therapy. Serious toxic effects include bladder outlet injury, urinary incontinence, sexual impotence, and rectal injury. Impotence is common. The frequency of other side effects and the probability of cancer control at 5 years' follow-up have varied among reporting centers, and series are small compared with surgery and radiation therapy.
Candidates for definitive radiation therapy must have a confirmed pathological diagnosis of cancer that is clinically confined to the prostate and/or surrounding tissues (stage I, stage II, and stage III). Patients should have a computed tomographic scan negative for metastases, but staging laparotomy and lymph node dissection are not required. Prophylactic radiation therapy to clinically or pathologically uninvolved pelvic lymph nodes does not appear to improve overall survival (OS) or prostate cancer-specific survival as seen in the RTOG-7706 trial, for example.\textsuperscript{86} In addition, patients considered poor medical candidates for radical prostatectomy can be treated with an acceptably low complication rate if care is given to the delivery technique.\textsuperscript{87} Long-term results with radiation therapy are dependent on stage. A retrospective review of 999 patients treated with megavoltage radiation therapy showed cause-specific survival rates to be significantly different at 10 years by T-stage: T1 (79%), T2 (66%), T3 (55%), and T4 (22%).\textsuperscript{88} An initial serum prostate-specific antigen (PSA) level higher than 15 ng/mL is a predictor of probable failure with conventional radiation therapy.\textsuperscript{89} Several randomized studies have demonstrated an improvement in freedom from biochemical (PSA-based) recurrence with higher doses of radiation therapy (78 Gy–79 Gy) as compared to conventional doses (68 Gy–70 Gy).\textsuperscript{90} The higher doses were delivered using conformal techniques. None of the studies demonstrated a cause-specific survival benefit to higher doses; however, an ongoing study through the Radiation Therapy Oncology Group will be powered for OS.

Interstitial brachytherapy has been employed in several centers, generally for patients with T1 and T2 tumors. Patients are selected for favorable characteristics, including low Gleason score, low PSA level, and stage T1 to T2 tumors. Information and further study are required to better define the effects of modern interstitial brachytherapy on disease control and quality of life and to determine the contribution of favorable patient selection to outcomes.\textsuperscript{93} Information about ongoing clinical trials is available from the NCI Web site.

There is interest in the use of novel radiation techniques (e.g., intensity-modulated radiation therapy - IMRT, proton-beam therapy, stereotactic radiosurgery - SRS) for the treatment of prostate cancer. Although proton therapy could theoretically improve the therapeutic ratio of prostate radiation, allowing for an increase in dose to the tumor without a substantial increase in side effects, no randomized controlled trials have been conducted to compare its efficacy and toxicity with those of other forms of radiation therapy.

Asymptomatic patients of advanced age or with concomitant illness may warrant consideration of careful observation without immediate active treatment.\textsuperscript{94} \textsuperscript{95} One population-based study with 15 years of follow-up (mean observation time = 12.5 years) has shown excellent survival without any treatment in patients with well-differentiated or moderately well-differentiated tumors clinically confined to the prostate, irrespective of age.\textsuperscript{81} None of these men were detected by PSA screening, since PSA was not available at the time. The patient cohort was followed for a mean of 21 years after initial diagnosis.\textsuperscript{96} The risk of prostate cancer progression and prostate cancer death persisted throughout the follow-up period. By the end of follow-up, 91% of the cohort had died; 16% had died of prostate cancer. A second, smaller population-based study of 94 patients with clinically localized prostate cancer managed by a watch and wait strategy gave very similar results at 4 to 9 years of follow-up.\textsuperscript{97} In a selected series of 50 stage C patients, 48 of whom had well-differentiated or moderately well-differentiated tumors, the prostate cancer-specific survival rates at 5 and 9 years were 88% and 70%, respectively.\textsuperscript{82}
Long-term follow-up of a population-based cohort of 767 men with clinically localized prostate cancer diagnosed in the pre-PSA era and managed with either watchful waiting or androgen withdrawal has also been reported in the United States. After a follow-up of 20 years, prostate cancer-specific mortality was 6 per 1,000 person-years in men with Gleason scores of 2 to 4. Men with Gleason scores of 8 to 10, however, had a prostate cancer-specific mortality of 121 per 1,000 person years, and men with Gleason scores of 5 to 7 had intermediate prostate cancer mortality (i.e., 12, 30, and 65 deaths per 1,000 person years for Gleason scores 5, 6, and 7, respectively).

Many men with screen-detected prostate cancer are candidates for active surveillance, with definitive therapy reserved for signs of tumor progression. In a retrospective analysis from four of the centers of the European Randomized Study of Screening for Prostate Cancer (ERSPC), 616 men (mean age 66.3 years) in the screening arm represented between 27% and 38% of the men diagnosed with prostate cancer in the trial. The 616 men met the following criteria for active surveillance:99

- PSA ≤10 ng/ml.
- PSA density <0.2 ng/ml.
- Tumor stage T1c/T2.
- Gleason score ≤3 + 3 = 6.
- ≤2 positive biopsy cores.

With a median follow-up of 3.91 years, the 10-year prostate cancer-specific survival rate was 100%. By 7.75 years, 50% of men had received active treatment (but 55.8% of these men received treatment despite continued favorable PSA and PSA–doubling time). The OS rate at 10 years was 77%.100

Since the early 1980s, a dramatic increase has occurred in the rates of radical prostatectomy in the United States for men aged 65 to 79 years (5.75-fold rise from 1984 to 1990). Wide geographic variation is seen with these rates.100 A structured literature review of 144 papers has been done in an attempt to compare the three primary treatment strategies for clinically localized prostate cancer:101

- Radical prostatectomy.
- Definitive radiation therapy.
- Watchful waiting.

The authors concluded that poor reporting and selection factors within all series precluded a valid comparison of efficacy for the three management strategies. In another literature review of a case series of patients with palpable, clinically localized disease, the authors found that 10-year prostate cancer-specific survival rates were best in radical prostatectomy series (about 93%), worst in radiation therapy series (about 75%), and intermediate with deferred treatment (about 85%).102 Because it is highly unlikely that radiation therapy would worsen disease-specific survival, the most likely explanation is that selection factors affect choice of treatment. Such selection factors make comparisons of therapeutic strategies imprecise.103 A retrospective
analysis of outcomes of men demonstrated a 10-year disease-specific survival rate of 94% for expectant management for Gleason score 2 to 4 tumors and 75% for Gleason score 5 to 7 tumors; this is similar to a previous study using the Surveillance, Epidemiology, and End Results database with survival rates of 93% and 77%, respectively.

Radical prostatectomy has been compared to watchful waiting in men with early-stage disease (i.e., clinical stages T1b, T1c, or T2) in a randomized clinical trial performed in Sweden in the pre-PSA screening era. Only about 5% of the men in the trial had been diagnosed by PSA screening. The estimated overall mortality difference after 12 years between the radical prostatectomy and watchful waiting arms of the study was not statistically significant: 32.7% versus 39.8%, \( P = .09 \). In a post hoc subset analysis, there was a statistically significant difference in overall mortality favoring prostatectomy for men aged 65 years and younger: 21.9% versus 40.2%, \( P = .004 \) (relative risk [RR] of death = 0.59; 95% confidence interval [CI], 0.41–0.85). In contrast, for men aged 65 years or older, the overall mortality at 12 years for the prostatectomy and watchful waiting arms was 42% versus 39.3%; \( P = 0.81 \) (RR of death = 1.04; 95% CI, 0.77–1.40). Overall prostate cancer–specific mortality in the full trial at 12 years favored prostatectomy: 12.5% versus 17.9%, \( P = .03 \); RR = 0.65; 95% CI, 0.45–0.94.

Results from the Prostate Intervention Versus Observation Trial (PIVOT-1), an ongoing randomized trial in the United States that compared radical prostatectomy with watchful waiting, have not been reported. The PIVOT uses overall mortality as its primary endpoint.

Cryotherapy is also under evaluation for the treatment of localized prostate cancer. There is limited evidence on its efficacy and safety compared to the more commonly used local therapies, and the technique is evolving in an attempt to reduce local toxicity and normal tissue damage (see below). The quality of evidence on efficacy is low, currently limited to case series of relatively small size, short follow-up, and surrogate outcomes of efficacy.

Surgical Complications

Complications of radical prostatectomy can include urinary incontinence, urethral stricture, impotence, and the morbidity associated with general anesthesia and a major surgical procedure. An analysis of Medicare records on 101,604 radical prostatectomies performed from 1991 to 1994 showed a 30-day operative mortality rate of 0.5%, a rehospitalization rate of 4.5%, and a major complication rate of 28.6%; over the study period, these rates decreased by 30%, 8%, and 12%, respectively. Prostatectomies done at hospitals where fewer prostatectomies were performed were associated with higher rates of 30-day postoperative mortality, major acute surgical complications, longer hospital stays, and higher rates of rehospitalization than those done at hospitals where more prostatectomies were performed. Morbidity and mortality rates increase with age. Comorbidity, especially underlying cardiovascular disease and a history of stroke, accounts for a portion of the age-related increase in 30-day mortality. In a cohort of all men with prostate cancer who underwent radical prostatectomy from 1990 to 1999 in Ontario, 75-year-old men with no comorbidities had a predicted 30-day mortality of 0.74%. Thirty-day surgical complication rates also depended more on comorbidity than age (i.e., about 5% vs. 40% for 0 vs. 4 or more underlying comorbid conditions).
In one large case series of men undergoing the anatomic (nerve-sparing) technique of radical prostatectomy, approximately 6% of the men required the use of pads for urinary incontinence, but an unknown additional proportion of men had occasional urinary dribbling. About 40% to 65% of the men who were sexually potent before surgery retained potency adequate for vaginal penetration and sexual intercourse. Preservation of potency with this technique is dependent on tumor stage and patient age, but the operation probably induces at least a partial deficit in nearly all patients.

A national survey of Medicare patients who underwent radical prostatectomy in 1988 to 1990 reported more morbidity than in the case series. In that survey, more than 30% of the men reported the need for pads or clamps for urinary wetness, and 63% of all patients reported a current problem with wetness. About 60% of the men reported having no erections since surgery; about 90% of the men had no erections sufficient for intercourse during the month before the survey. About 28% of the patients reported follow-up treatment of cancer with radiation therapy and/or hormonal therapy within 4 years after their prostatectomy.

In a population-based longitudinal cohort (Prostate Cancer Outcomes Study) of 901 men aged 55 to 74 years who had recently undergone radical prostatectomy for prostate cancer, 15.4% of the men had either frequent urinary incontinence or no urinary control at 5 years after surgery, and 20.4% of those studied wore pads to stay dry. Inability to have an erection sufficient for intercourse was reported by 79.3% of men. Reasons for the difference in outcomes between the population-based surveys and previous case series could include:

- Age difference among the populations.
- Surgical expertise at the major reporting centers.
- Selection factors.
- Publication bias of favorable series.
- Different methods of collecting information from patients.

Case series of 93, 459, and 89 men who had undergone radical prostatectomy by experienced surgeons showed rates of impotence as high as those in the national Medicare survey when men were carefully questioned about sexual potency, though the men in the case series were on average younger than those in the Medicare survey. One of the case series used the same questionnaire as that used in the Medicare survey and the urinary incontinence rate in that series was also similar to that in the Medicare survey. A cross-sectional survey of prostate cancer patients who were treated in a managed care setting by radical prostatectomy, radiation therapy, or watchful waiting showed substantial sexual and urinary dysfunction in the prostatectomy group. Results reported by the patients were consistent with those from the national Medicare survey. In addition, though statistical power was limited, differences in sexual and urinary dysfunction between men who had undergone either nerve-sparing or standard radical prostatectomy were not statistically significant. This issue requires more study.

Radical prostatectomy may also cause fecal incontinence, and the incidence may vary with surgical method. In a national survey sample of 907 men who had undergone radical
prostatectomy at least 1 year before the survey, 32% of the men who had undergone perineal (nerve-sparing) radical prostatectomy and 17% of the men who had undergone retropubic radical prostatectomy reported accidents of fecal leakage. Ten percent and 4% of the respondents reported moderate and large amounts of fecal leakage, respectively. Fewer than 15% of men with fecal incontinence had reported it to a physician or health care provider.

**Radiation Therapy Complications**

Definitive external-beam radiation therapy (EBRT) can result in acute cystitis, proctitis, and sometimes enteritis. These conditions are generally reversible but may be chronic and rarely require surgical intervention. Potency, in the short term, is preserved with radiation therapy in most cases but may diminish over time. A cross-sectional survey of prostate cancer patients who had been treated in a managed care setting by radical prostatectomy, radiation therapy, or watchful waiting showed substantial sexual and urinary dysfunction in the radiation therapy group.

Morbidity may be reduced with the employment of sophisticated radiation therapy techniques—such as the use of linear accelerators—and careful simulation and treatment planning. Radiation side effects of three-dimensional conformal versus conventional radiation therapy using similar doses (total dose of 60 to 64 Gy) have been compared in a randomized nonblinded study. No differences were observed in acute morbidity, and late side effects serious enough to require hospitalization were infrequent with both techniques; however, the cumulative incidence of mild or greater proctitis was lower in the conformal arm than in the standard therapy arm (37% vs. 56%; \( P = .004 \)). Urinary symptoms were similar in the two groups as were local tumor control and OS rates at 5 years follow-up.

Radiation therapy can be delivered after an extraperitoneal lymph node dissection without an increase in complications if careful attention is paid to radiation technique. The treatment field should not include the dissected pelvic nodes. Previous transurethral resection of the prostate (TURP) increases the risk of stricture above that seen with radiation therapy alone, but if radiation therapy is delayed 4 to 6 weeks after the TURP, the risk of stricture can be minimized. Pretreatment TURP to relieve obstructive symptoms has been associated with tumor dissemination; however, multivariate analysis in pathologically staged cases indicates that this is the result of a worse underlying prognosis of the cases that require TURP rather than the result of the procedure itself.

A population-based survey of Medicare recipients who had received radiation therapy as primary treatment of prostate cancer (similar in design to the survey of Medicare patients who underwent radical prostatectomy described above) has been reported, showing substantial differences in post-treatment morbidity profiles between surgery and radiation therapy. Although the men who had undergone radiation therapy were older at the time of initial therapy, they were less likely to report the need for pads or clamps to control urinary wetness (7% vs. more than 30%). A larger proportion of patients treated with radiation therapy before surgery reported the ability to have an erection sufficient for intercourse in the month before the survey (men <70 years, 33% who received radiation therapy vs. 11% who underwent surgery alone; men ≥70 years, 27% who received radiation therapy vs. 12% who underwent surgery alone).
therapy, however, were more likely to report problems with bowel function, especially frequent bowel movements (10% vs. 3%). As in the results of the surgical patient survey, about 24% of radiation patients reported additional subsequent treatment of known or suspected cancer persistence or recurrence within 3 years of primary therapy.

Sildenafil citrate may be effective in the management of sexual dysfunction after radiation therapy in some men. In a randomized placebo-controlled crossover design study (RTOG-0215) of 60 men who had undergone radiation therapy for clinically localized prostate cancer, and who reported erectile dysfunction that began after their radiation therapy, 55% reported successful intercourse after sildenafil versus 18% after placebo ($P < 0.001$).

A prospective community-based cohort of men aged 55 to 74 years treated with radical prostatectomy ($n = 1156$) or EBRT ($n = 435$) attempted to compare acute and chronic complications of the two treatment strategies after adjusting for baseline differences in patient characteristics and underlying health. Regarding acute treatment-related morbidity, radical prostatectomy was associated with higher rates of cardiopulmonary complications (5.5% vs. 1.9%) and the need for treatment of urinary strictures (17.4% vs. 7.2%). Radiation therapy was associated with more acute rectal proctitis (18.7% vs. 1.6%). With regard to chronic treatment-related morbidity, radical prostatectomy was associated with more urinary incontinence (9.6% vs. 3.5%) and impotence (80% vs. 62%). Radiation therapy was associated with slightly greater declines in bowel function.

Radiation is also known to be carcinogenic. EBRT for prostate cancer is associated with an increased risk of both bladder and rectal cancer. Brachytherapy is associated with bladder cancer.

**Cryotherapy Complications**

Impotence is common in the reported case series, ranging from about 47% to 100%. Other major complications include incontinence, urethral sloughing, urinary fistula or stricture, and bladder neck obstruction.

**Hormone Therapy Complications**

Several different hormonal approaches can benefit men in various stages of prostate cancer. These approaches include bilateral orchiectomy, estrogen therapy, LHRH agonists, antiandrogens, ketoconazole, and aminoglutethimide.

Benefits of bilateral orchiectomy include ease of the procedure, compliance, its immediacy in lowering testosterone levels, and low cost. Disadvantages include psychologic effects, loss of libido, impotence, hot flashes, and osteoporosis.

Estrogens at a dose of 3 mg per day of diethylstilbestrol will achieve castrate levels of testosterone. Like orchiectomy, estrogens may cause loss of libido and impotence. Gynecomastia may be prevented by low-dose radiation therapy to the breasts. Estrogen is seldom used today.
because of the risk of serious side effects, including myocardial infarction, cerebrovascular
accident, and pulmonary embolism.

LHRH agonists such as leuprolide, goserelin, and buserelin will lower testosterone to castrate
levels. Like orchiectomy and estrogens, LHRH agonists cause impotence, hot flashes, and loss of
libido. Tumor flare reactions may occur transiently but can be prevented by antiandrogens or by
short-term estrogens at low dose for several weeks.

The pure antiandrogen flutamide may cause diarrhea, breast tenderness, and nausea. Case reports
show fatal and nonfatal liver toxic effects. Bicalutamide may cause nausea, breast tenderness,
hot flashes, loss of libido, and impotence. The steroidal antiandrogen megestrol acetate
suppresses androgen production incompletely and is generally not used as initial therapy.

Long-term use of ketoconazole can result in impotence, pruritus, nail changes, and adrenal
insufficiency. Aminoglutethimide commonly causes sedation and skin rashes. A national
Medicare survey of men who had undergone radical prostatectomy for prostate cancer showed a
decrease in all seven health-related quality-of-life measures (impact of cancer and treatment,
concern regarding body image, mental health, general health, activity, worries about cancer and
dying, and energy) in men who had received androgen depletion therapy (either medically or
surgically induced) versus those who had not. Additional studies that evaluate the effects of
various hormone therapies on quality of life are required.

Androgen deprivation therapy also can cause osteoporosis and bone fractures. In a population-
based sample of 50,613 Medicare patients aged 66 years or older followed for a median of 5.1
years, men who had been treated with either a gonadotropin-releasing hormone (GnRH) or
orchietomy had a 19.4% bone fracture rate compared to 12.6% in men who had not received
hormone deprivation therapy. The effect was similar in men whether or not they had metastatic
bone disease. A small nonblinded study with short follow-up suggests that the bisphosphonate
pamidronate can prevent bone loss in men receiving a GnRH agonist for prostate cancer. Forty-seven prostate cancer patients (41 evaluable) with locally advanced prostate cancer, but
with no known bone metastases, were randomly assigned to receive 3-monthly depot leuprolide
with or without pamidronate (60 mg intravenously). No bone fractures were reported in either
group. The use of surrogate endpoints and unblinded assessment of endpoints makes it difficult
to know with certainty whether pamidronate use would prevent fractures.

Recurrent Prostate Cancer

In prostate cancer, the selection of further treatment depends on many factors, including previous
treatment, site of recurrence, coexistent illnesses, and individual patient considerations.
Definitive radiation therapy can be given to patients who fail only locally following
prostatectomy. An occasional patient can be salvaged with prostatectomy after a
local recurrence following definitive radiation therapy. In patients who fail and are untreated
with local salvage therapy, prolonged disease control is often possible with hormonal therapy,
with median cancer-specific survival of 6 years after local failure. Cryosurgical ablation of
recurrence following radiation therapy is associated frequently with elevated prostate-specific
antigen (PSA) and a high complication rate. This technique is still undergoing clinical
Some relapsing patients who initially received locoregional therapy with surgery or radiation therapy will then fail with disseminated disease and are managed with hormonal therapy. The management of these patients with stage IV disease is discussed in the preceding section. Palliative radiation therapy for bone pain can be very useful. Because of the poor prognosis in prostate cancer patients with relapsing or progressive disease after hormonal therapy, clinical trials are appropriate. These include phase I and phase II trials of new chemotherapeutic or biologic agents.

There is a history of successful salvage of local failure with LDR and HDR brachytherapy. Several salvage brachytherapy series actually report salvage rates in excess of 80%. In the Beyer series, the 80% success rate was seen with permanent brachytherapy salvage of selected patients with low Gleason scores, PSA less than 10 ng/mL and a relatively long interval to recurrence. The UCSF HDR series had a 89% salvage success rate even including higher risk localized recurrences, though the median follow-up in that series remained less than 2 years at the time of reporting and so requires longer-term confirmation.

Due to the previously-described prostate SBRT capability to accomplish a substantial degree of HDR dosimetry replicating, SBRT also emerges as an intriguing potential salvage method for post-radiotherapy local relapse patients. Such an approach has been employed under an IRB-approved clinical trial initiated at our own center, using a fractionation scheme of 34 Gy/5 fractions, with HDR-like intraprostatic dose escalation, such that the estimated uniform dose (EUD) within the prostate is approximately 42 Gy/5 fractions.

The result of this trial is still preliminary, currently limited to 17 patients with a median follow-up of 12 months (range 3-36), yet the result is encouraging. The PSA nadir has not been reached, with a median one year PSA level of 0.65 ng/mL (from a median pre-salvage PSA level of 3.1 ng/mL) and 88% of patients with a stable or decreasing PSA level at their last follow-up. Toxicity greater than grade 1 (CTCAE v 3.0) has been limited to the GU domain, with 2/17 patients having chronic grade 2 GU toxicity and 1/17 patients having acute and chronic grade 3 GU toxicity. The data suggest that the risk of > grade 2 GU toxicity may be higher in patients with preexisting toxicity from their initial radiotherapy course, such that it seems prudent to exercise particular caution in this patient population when contemplating “salvage” prostate SBRT.

Another series of salvage SBRT for relapsed prostate cancer was reported by a group from Milan. This series describes a mixture of patients treated with SBRT salvage for post-radiotherapy local prostate relapse, for post-radical prostatectomy prostate bed local relapse, isolated lymph node relapse and solitary distant metastatic foci. Over half of the patients in this series received concomitant androgen suppressive therapy, making the specific SBRT contribution more difficult to ascertain. Nonetheless, some findings are noteworthy: Of 15 patients treated for post-RT prostate recurrence to a salvage SBRT dose of 30 Gy/5 fractions, 10 remained controlled at a median 30 months of follow-up, while 11 of 16 isolated lymph node recurrence SBRT salvage patients remained controlled at last follow-up. The majority of subsequent clinical relapses occurred at new sites, with relapse in SBRT target volume sites comprising only a minority of them. As observed in our own series, the incidence of grade 2 or higher toxicity was low and more prevalent in the GU domain. They concluded that stereotactic
radiotherapy is a feasible approach for isolated recurrent primary, lymph node, or metastatic prostate cancer, offering excellent in-field tumor control and a low toxicity profile.

Even among patients with metastatic hormone-refractory prostate cancer, some heterogeneity is found in prognosis and in retained hormone sensitivity. In such patients who have symptomatic bone disease, several factors are associated with worsened prognosis: poor performance status, elevated alkaline phosphatase, abnormal serum creatinine, and short (<1 year) previous response to hormone therapy. The absolute level of PSA at the initiation of therapy in relapsed or hormone-refractory patients has not been shown to be of prognostic significance. Some patients whose disease has progressed on combined androgen blockade can respond to a variety of second-line hormonal therapies. Aminoglutethimide, hydrocortisone, flutamide withdrawal, progesterone, ketoconazole, and combinations of these therapies have produced PSA responses in 14% to 60% of patients treated and have also produced clinical responses of 0% to 25% when assessed. The duration of these PSA responses has been in the range of 2 to 4 months.

Survival rates are similar whether ketoconazole plus hydrocortisone is initiated at the same time as anti-androgen (e.g., flutamide, bicalutamide, or nilutamide) withdrawal or when PSA has risen after an initial trial of anti-androgen withdrawal as seen in the CLB-9583 trial, for example. Data on whether PSA changes while on chemotherapy are predictive of survival are conflicting.

Patients treated with either luteinizing hormone agonists or estrogens as primary therapy are generally maintained with castrate levels of testosterone. One study from the Eastern Cooperative Oncology Group showed that a superior survival resulted when patients were maintained on primary androgen deprivation; however, another study from the Southwest Oncology Group did not show an advantage to continued androgen blockade.

Painful bone metastases can be a major problem for patients with prostate cancer. Many strategies have been studied for palliation, including pain medication, radiation therapy, corticosteroids, bone-seeking radionuclides, gallium nitrate, and bisphosphonates. External-beam radiation therapy (EBRT) for palliation of bone pain can be very useful. A single fraction of 8 Gy has been shown to have similar benefits on bone pain relief and quality of life as multiple fractions (3 Gy × 10) as seen in the RTOG-9714 trial, for example. Also, the use of radioisotopes such as strontium chloride Sr 89 has been shown to be effective as palliative treatment of some patients with osteoblastic metastases. When this isotope is given alone, it decreased bone pain in 80% of patients treated and is similar to responses with local or hemibody radiation therapy. When used as an adjunct to EBRT, strontium chloride Sr 89 was shown to slow disease progression and to reduce analgesic requirements, compared with EBRT alone.

A multicenter randomized trial of a single intravenous dose of strontium chloride Sr 89 (150 MBq: 4 mCi) versus palliative EBRT in men with painful bone metastases from prostate cancer despite hormone treatment showed similar subjective pain response rates: 34.7% versus 33.3%, respectively. Overall survival was better in the EBRT group than in the strontium chloride Sr 89 group ($P = .046$; median survival 11.0 vs. 7.2 months). No statistically significant differences in time-to-subjective progression or in progression-free survival were seen.

Low-dose prednisone may palliate symptoms in some patients. In a randomized comparison of prednisone (5 mg 4 times per day) with flutamide (250 mg 3 times per day) in patients with
disease progression after androgen ablative therapy (castration or luteinizing hormone-releasing hormone [LHRH] agonist), prednisone and flutamide produced similar survival, symptomatic response, PSA response, and time to progression; however, there were statistically significant differences in pain, nausea and vomiting, and diarrhea in patients who received prednisone. Ongoing clinical trials continue to explore the value of chemotherapy for these patients.

A randomized trial showed improved pain control in hormone-resistant patients treated with mitoxantrone plus prednisone compared with those treated with prednisone alone. Differences in overall survival (OS) or measured global quality of life between the two treatments were not statistically significant.

In randomized trials of men with hormone-refractory prostate cancer, regimens of docetaxel given every 3 weeks have produced better OS (at 21–33 months) than mitoxantrone.

In a randomized trial of patients with hormone-refractory prostate cancer, docetaxel (75 mg/M² every 3 weeks) and docetaxel (30 mg weekly for 5 out of every 6 weeks) were compared with mitoxantrone (12 mg/M² every 3 weeks). All patients received oral prednisone (5 mg twice per day). Patients in the docetaxel arms also received high-dose dexamethasone pretreatment for each docetaxel administration (8 mg were given at 12 hours, 3 hours, and 1 hour prior to the 3-week regimen; 8 mg were given at 1 hour prior to the 5 out-of-every-6 weeks' regimen). OS at 3 years was statistically significantly better in the 3-weekly docetaxel arm (18.6%) than in the mitoxantrone arm (13.5%, hazard ratio [HR] for death = 0.79; 95% confidence interval [CI], 0.67–0.93). The OS rate for the 5 out-of-every-6 weeks' docetaxel regimen was 16.8%, which was not statistically significantly better than mitoxantrone. Quality of life was also superior in the docetaxel arms compared with mitoxantrone ($P = .009$).

In another randomized trial of patients with hormone-refractory prostate cancer, a 3-week regimen of estramustine (280 mg orally 3 times a day for days 1 to 5, plus daily warfarin and 325 mg of aspirin to prevent vascular thrombosis), and docetaxel (60 mg/M² intravenously on day 2, preceded by dexamethasone [20 mg times 3 starting the night before]) was compared with mitoxantrone (12 mg/M² intravenously every 3 weeks) plus prednisone (5 mg daily). After a median follow-up of 32 months, median OS was 17.5 months in the estramustine arm versus 15.6 months in the mitoxantrone arm ($P = .02$; HR for death = 0.80; 95% CI, 0.67–0.97). Global quality of life and pain palliation measures were similar in the two treatment arms.

Other chemotherapy regimens reported to produce subjective improvement in symptoms and reduction in PSA level include the following:

- Paclitaxel.
- Estramustine/etoposide.
- Estramustine/vinblastine.
- Estramustine/paclitaxel.

One study suggests that patients whose tumors exhibit neuroendocrine differentiation are more responsive to chemotherapy.
VII. SRS Literature Review

This section reviews the existing data on SRS treatment for carcinoma of the prostate. SRS is at times called stereotactic body radiation therapy, and is defined as a high dose of radiation per treatment with a small number of total treatments (up to a maximum of five). High dose radiation (HDR) therapy, such as SRS uses sophisticated image guidance to deliver a potent ablative dose to cancerous tissues while minimizing the risk to normal tissue. For prostate cancer, the critical structures at risk are the bladder, rectum and small bowel. Escalation of dose in prostate radiotherapy using conventional techniques is limited by rectal tolerance. As stated earlier in the section on treatment, a randomized controlled trial has demonstrated less recurrence with higher doses of radiation therapy delivered with conformal techniques as compared to conventional doses. In this study, 393 patients with stage T1b through T2b prostate cancer and PSA levels less than 15 ng/ml received EBRT with either 70.2 Gy (low dose) or 79.2 Gy (high dose). The study found that patients who had received the higher dose of radiation had a lower risk of biochemical failure.

There may be inherent biologic advantages of high dose rate radiation over low dose rate irradiation in the prostate specifically in terms of improved tissue tolerance. A low α/β ratio for prostate cancer indicates that a hypofractionated treatment regime delivered via radiosurgical techniques may be more effective than conventional EBRT. Both dose escalation and hypofractionation (defined as the use of large does-per-fraction sizes or fewer but larger fractions) for the prostate appear to be beneficial due to the unique biologic nature of prostate cancer. In addition, SRS treatment appears theoretically similar to high dose rate (HDR) brachytherapy in terms of dosimetric and biological considerations in the treatment of prostate carcinoma. In lieu of Phase 1 studies with SRS, several studies which have shown that dose escalation can increase the chances of freedom from biochemical recurrence for early stage prostate cancer treated with primary radiation.

As early as 2003, a group from Stanford University published on the rationale and technical feasibility of treatment with SRS for localized prostate cancer. In this study, inverse planning of SRS was used to design a course of therapy for localized prostate cancer and compare the conformal isodose curves and does volume histograms with an optimized Intensity-Modulated Radiotherapy (IMRT) plan that was actually delivered to the patient. The study found that SRS produced superior dose volume histograms while sparing normal tissues such as the rectum and the bladder.

There have also been reports from France on the use of SRS for prostate carcinoma as it is considered to be a technical improvement of already validated treatment that is comparable to HDR brachytherapy. A paper published by Hannoun-Levi et al. discussed the biologic rationale for hypofractionated treatment, does escalation and brachtherpay boost to deliver a prostate boost after pelvic or peri-prostatic area radiation.

Another study by Fuller et al. demonstrated that the radiation dose distributions of SRS approximate those obtained with HDR brachytherapy. This study tested the ability to approximate the dose (38 Gy), fractionation (4 fractions) and distribution of HDR brachytherapy with SRS for prostate cancer. Ten patients were treated with SRS and compared to HDR.
brachytherapy treatment. This study compared the planning target volume coverage, intraprostatic dose escalation and radiation exposure of normal tissue. It was found that SRS could be delivered with a similar pattern of dose escalation as HDR brachytherapy, with minimal toxicity in patients treated with these HDR-like dose distributions. Maximum follow up was limited to 12 months and PSA was found to decrease by 86% from baseline to a nadir of 0.95 ng/mL. Acute toxicity was primarily urologic and was self limited and manageable.

Madsen et al. studied the feasibility and toxicity of hypofractionated SRS using a conventional linear accelerator. Forty patients aged 50 to 82 years with low risk disease and Gleason scores less than 6 and PSA levels less that 10 ng/ml were treated with five fractions of 6.7 Gy for a total of 33.5 Gy. At a median follow-up of 41 months, five patients died from non-prostate related illness and a median PSA nadir was observed at 18 months. They observed a 70% biochemical freedom from relapse, two Grade 3 genitourinary (GU) toxicities, and no long-term gastrointestinal (GI) toxicity. The authors concluded that it may be possible to achieve a lower PSA nadir and lower rates of biochemical relapse with dose escalation while still maintaining an acceptable level of toxicity.

Since this initial SBRT result, only a few additional publications to date have reported on gantry based SBRT delivery. In 2008, Tang et al. reported on treatment of 30 patients with 35 Gy delivered in 5 fractions once a week over 29 days. They postulated that the hypothesized slow doubling time of prostate cancer should ameliorate any potential detrimental effect on tumor control with the weekly schedule. Preliminary results with 6 month follow-up reported no Grade 3 toxicities; longer term results have not been published. More recently Boike et al. reported on a Phase 1 SBRT study using Trilogy (Varian Medical Systems Inc., Palo Alto, CA), Synergy (Elekta AB, Stockholm) or TomoTherapy (Accuray Incorporated, Sunnyvale, CA) for delivery. In this dose escalation study, three groups of 15 patients each received either 45 Gy, 47.5 Gy or 50 Gy (the highest SBRT dose reported to date) delivered in 5 fractions every other day. A rectal balloon was used to push the posterior and lateral rectal walls away from the planning target volume (PTV) and to stabilize the prostate. Fiducial markers and either megavoltage or kilovoltage CT were used for daily set-up, but intrafraction guidance was not used. A 3 mm expansion of the clinical target volume (CTV) was used to create the PTV. At a median follow-up of 30, 18 and 12 months for the three groups, no PSA failures were noted. The mean PSA was 0.2 ng/ml at 30 months. Overall, genitourinary (GU) Grade 2 and Grade 3 toxicity occurred in 31% and 4% of patients, respectively, and one Grade 4 GU toxicity occurred. Rectal Grade 2 and Grade 3 toxicity was found in 18% and 2% of patients, respectively.

Another approach to gantry-based SBRT delivery was reported at ASTRO 2011 by Mantz et al. who used Trilogy with a Calypso system for daily patient set-up followed by cone beam CT to verify and check for deformation. Calypso was then further used to track intrafraction prostate motion. Eighty low-risk patients, none of which had a prostate larger than 60 cc, received 40 Gy delivered in 5 every other day fractions. At a median follow-up of 36 months, no biochemical failures were seen. The mean PSA at 3 years was 0.30 ng/ml down from 7.2 ng/ml before treatment. At 18 months, the mean EPIC scores for bowel, urinary and sexual function were lower than baseline but the changes were not significant changes from baseline.
Cyberknife SBRT

The Stanford group recently published interim results of a Phase II prospective clinical trial of SRS with CK for localized prostate cancer. In this study, 41 low-risk prostate cancer patients received 36.25 Gy in five fractions of 7.25 Gy each.\textsuperscript{197} The early (<3 months) and late (>6 months) urinary and rectal toxicities were assessed using validated quality of life questionnaires as well as PSA patterns. The median follow-up time was 33 months. There were no Grade 4 acute or late rectal/urinary complications. There were 2 patients who had late grade 3 urinary toxicity but none who had grade 3 rectal complications. It was found that there was a reduced rate of severe rectal toxicities with every-other-day treatment as compared to five consecutive days treatment regimen (0\% vs. 38\%, \(p = 0.0035\)). Of the 32 patients with 12 months minimum follow-up, 25 patients (78\%) achieved a PSA nadir \(\leq 0.4\) ng/mL. In addition, PSA decline to progressively lower nadirs up to 3 years after treatment was observed. In this study the authors concluded that the early and late toxicity profile and PSA response for prostate SRS are highly encouraging. Continued accrual and follow-up will be necessary to confirm durable biochemical control rates and low toxicity profiles.

Friedland et al. recently reported on the results of a cohort of 112 patients treated with CK SRS for early stage prostate cancer between February 2005 and December 2006.\textsuperscript{198} Patients with localized, biopsy-proven adenocarcinoma of the prostate were treated with SRS. The mean initial PSA was 6.0, and the mean initial prostate volume was 46.3cc. Implanted gold fiducials were used for image-guided targeting and tracking. Patients received 35 to 36 Gy administered in five fractions to the prostate and the proximal seminal vesicles, as identified on CT and MRI scans. At a median follow-up of 24 months, the mean PSA value was 0.78 ng/ml. Two patients developed biopsy-confirmed local relapse and one patient developed distant metastases. The acute side effects were mild and resolved shortly after treatment. A single Grade 3 rectal complication of rectal bleeding was reported. In terms of potency, 82\% of patients who were sexually potent before treatment maintained erectile function post-treatment. Additional follow-up is on going for late toxicity and long-term PSA outcomes.

Katz et al. published the largest CyberKnife SBRT series to date with treatment of 304 prostate cancer patients\textsuperscript{199} A small minority of patients received hormone ablative therapy that was discontinued prior to treatment. The first 50 patients, most of whom were low risk, received a total dose of 35 Gy delivered in 5 fractions. Homogeneous treatment plans were created on CT fused with MRI, using 5-mm margins to the PTV, 3 mm posteriorly. All patients received 1500 mg of Amifostine (MedImmune, LLC Gaithersburg, MD) intrarectally 15minutes prior to each fraction. At a median 30 months follow-up, there were no biochemical failures and the median PSA was 0.22 ng/ml with 97\% of patients obtaining a PSA below 1.0 ng/ml. Toxicity was mild with no Grade 3 toxicity and only 2\% of patients exhibiting late Grade 2 urinary toxicity. The subsequent 254 patients (166 low-, 76 intermediate-, and 12-high-risk patients) received daily doses of 7.25 Gy delivered in 5 daily fractions. Treatment plans were similar to the first 50 patients except that the GTV included the proximal seminal vesicles if the patient was intermediate- or high-risk. At a median 17 months follow-up, there was one local failure in the high-risk group and 2 distant failures for both the low- and high-risk groups. A PSA bounce was observed in 19\% of patients. Urinary toxicity was slightly higher than in the 35 Gy group. Overall potency preservation was 87\% at 2 years and the mean EPIC sexual score dropped by
20%. The authors concluded that patients reported as good, if not better, QOL scores as with other forms of radiation therapy. In a recent update at ASTRO 2011, Katz et al. reported 97%, 93% and 75% 4-year actuarial freedom from biochemical failure rates in the low-, intermediate- and high-risk patients, respectively. At an overall median follow-up of 48 months the median PSA was 0.2 ng/ml, 0.1 ng/ml and 0.1 ng/ml at 36, 48 and 60 months, respectively. There was more urinary toxicity in the higher dose group with 10% late Grade 2 and 2% late Grade 3 toxicity (differences were not statistically significant). Potency was retained in 78% of patients.

The first results with a median 5-years follow-up were published by Freeman and King who pooled 41 low-risk patients who received 35-36.25 Gy delivered in 5 fractions. Late GU toxicity consisted of 25% grade 1, 7% grade 2 and 2.5% grade 3. Late GI toxicity was 13.5% for grade 1 and 2.5% for grade 2. The 5-year actuarial freedom from biochemical failure was 93%. In support of these results, several other recent CyberKnife SBRT studies report on treatment of fifty or fewer patients. Jabbari et al. treated 20 low-risk patients with a total dose of 38 Gy delivered in 4 fractions using an HDR-like dose distribution. An excellent PSA response was seen at a median of 18 months follow-up with 2 Grade 3 urinary toxicities. At ASTRO 2011, Fuller et al. reported on 49 low-and intermediate-risk patients treated with 38 Gy delivered in 4 fractions using an HDR-like dose distribution with 2 mm margins everywhere except posteriorly where no margin was used. Acute urinary toxicity was mild. At a median follow-up of 48 months, late GU toxicity consisted of 18% Grade 2 and 4% Grade 3. An updated toxicity analysis of this series presented at the ARO forum in 2012, revealed a statistically significant correlation between presenting AUA symptom score and development of grade 2 or higher GU toxicity – a “brachythrapy-like” correlation. Late rectal toxicity was extremely low, presumably due to the very tight posterior margins. The median PSA was 0.4 ng/ml, 0.2 ng/ml and 0.1 ng/ml at 24, 36 and 48 months, respectively. The 4-year actuarial freedom from biochemical failure rate was 95%. An updated analysis of this series presented at the ARO forum in 2012 revealed a further decrease in the median 5-year PSA nadir value, to 0.055 ng/mL, confirming a full 5 years to final PSA nadir following “HDR-like” SBRT fractionation to 35 Gy. Bolzicco et al. treated 46 low and low-intermediate risk patients with a total dose of 35 Gy delivered in 5 fractions. At a median follow-up of 20 months, no biochemical failures occurred and low toxicity was observed. Both Aluwini et al. and Townsend et al. published feasibility studies showing mild and transient early toxicity following delivery of 38 Gy in 4 fractions or 35-37.5 Gy in 5 fractions, respectively. Kang et al. reported excellent results on 44 intermediate and high-risk patients receiving 32-36 Gy in 4 fractions in combination with up to two years of hormone ablative therapy. At a median 40 months follow-up, the intermediate-risk patients had no failures and the high-risk patients had a 90% freedom from biochemical failure rate. Another multi-institutional Phase 1 trial by McBride et al reported on delivery of 36.25-37.5 Gy in five fractions for 45 low-risk patients. At a median follow-up of 44 months no biochemical failures occurred with toxicities consisting of one Grade 3 urinary and 2 Grade 3 rectal late toxicities.

**SBRT as a Boost for Higher Risk Disease**

For intermediate- and high-risk disease there is a significant risk of extraprostatic involvement, yet the localized nature of HDR or LDR implants limits their ability to adequately treat microscopic disease outside the capsule. Consequently, researchers have used brachytherapy as a boost within the prostate following EBRT or IMRT delivery of 45-50 Gy to the prostate and
surrounding tissues. As noted earlier, HDR brachytherapy as a boost to EBRT or IMRT can achieve 5-8 year freedom from biochemical failure rates of 85-90% and 68-73% for intermediate- and high-risk disease, respectively. This boost strategy has been employed in three published SBRT studies all of which have used the CyberKnife for the SBRT boost. Jabbari et al. treated 18 patients with intermediate- and high-risk disease with an SBRT boost of 19.5 Gy delivered in 2 fractions after 45-50 Gy IMRT pelvic radiation therapy. In addition to the boost these patients received hormone ablative therapy for up to two years. Two patients had late Grade 3 GU toxicity. Oermann et al. reported on early results following treatment of 24 intermediate- and high-risk patients with an SBRT boost of 19.5 Gy delivered in 3 fractions following 50.4 Gy IMRT. At 6 months follow-up the median PSA dropped to 1.5 ng/ml and the EPIC scores returned to baseline. Katz et al. treated 73 patients (41 intermediate- and 32 high-risk patients) with an SBRT boost of 18-21 Gy in 3 fractions 2 weeks after delivery of 4-field EBRT to 45 Gy in 25 fractions. Amifostine was used as a rectal radioprotection prior to the CyberKnife boost and 36 patients received ADT for a mean 4.8 months prior to SBRT. At a median 33 months follow-up, the freedom from biochemical failure rate was 89.5% and 78% for the intermediate- and high-risk patients, respectively. Two high-risk and no intermediate-risk patients failed locally. A PSA nadir of less than 0.5 ng/ml was obtained for 71.8% of patients. Toxicity was mild with no late Grade 3 rectal and 1 Grade 3 late urinary complications. The three boost dose schemes of 18 Gy, 19.5 Gy and 21 Gy yielded no difference in efficacy or toxicity and there was no difference in outcomes with or without hormone ablation. These outcomes are similar to those reported with HDR brachytherapy as a boost at the same follow-up interval. A recent update (Katz et al. ESTRO 2012) at a median 60 months follow-up shows no additional toxicity and a 5-year actuarial freedom from biochemical failure of 87.5% and 73% for intermediate- and high-risk patients. These results suggest the efficacy of SBRT boost will continue to be equivalent to HDR brachytherapy however, additional follow-up is needed to confirm this.

In the case of high-risk patients, pelvic node coverage is the primary rationale for using boost rather than monotherapy. A recent randomized trial has examined the use of whole pelvic XRT to treat the lymph nodes. This study failed to show a benefit in treating the lymph nodes to prophylactic doses for high-risk patients. Further questioning the need for pelvic node coverage, excellent 5-year freedom from biochemical failure rates of 68% and 70% have been obtained for high-risk patients using both conventional and moderate hypofractionation without pelvic radiation, respectively. Furthermore, in an editorial, Nguyen et al. state that the lack of evidence supporting whole pelvic treatment suggests it should not be offered routinely in the clinic. This raises the question as to whether such treatment should be recommended for use in conjunction with SBRT for higher-risk patients. Published SBRT outcomes for high-risk patients suggest pelvic treatment is not necessary.

Kang et al. recently reported on 29 high-risk patients treated with CyberKnife SBRT alone to a dose of 34-36 Gy in four fractions in conjunction with ADT. At a median 40 months follow-up, the 5-year freedom from biochemical failure rate was 90.8%. In addition, Katz et al. observed a 4-year freedom from biochemical failure rate of 75% for 12 patients treated with SBRT alone. Also, Katz et al. reported on a pooled analysis of 1100 patients treated at 8 different institutions with CK monotherapy. In this study, patients with low, intermediate and high risk had a five
year actuarial freedom from relapse of 96%, 92% and 80% respectively. The observed control rates in these studies suggest that outcomes for intermediate and high risk disease may be as good, with less toxicity than with SBRT as a boost to pelvic radiotherapy. Confirming this for intermediate risk patients is the Katz study of 304 patients and Meier's analysis of 130 intermediate risk patients who received 40 Gy as per the Accuray homogeneous trial. He reported 99% control at a three year follow-up. Additional data is needed to verify this observation.

A new study by Katz et al. explores the question of optimal dose for lower risk patients through a matched pair analysis of two groups of 41 patients with low or low-intermediate risk. One group received 35 Gy in five daily fractions (EQD1.8 approximately 91 Gy) and one group received 36.25 Gy (EQD1.8 approximately 96 Gy) also in five daily fractions. At a median 48 months follow-up, each group had only one failure yielding a freedom from biochemical failure rate of 97.5%. At 36 and 48 months, the median PSAs were identical between the dose groups at 0.2 ng/ml and 0.1 ng/ml. In the higher dose group, late Grade 2 urinary toxicity was slightly higher than the lower dose group and there was one Grade 3 toxicity in the higher dose group but none in the lower dose group. These differences were not statistically significant, probably due to the small numbers. Despite the small numbers and limited follow-up, these data raise that question as to whether 35 Gy in five fractions (EQD 1.8 90 Gy) is the optimal dose to control lower risk disease with minimal side effects. It is interesting to compare the PSA results achieved by heterogeneous planning to a dose of 38 Gy in 4 fractions to 35 Gy in five fractions given homogeneously. At ASTRO 2011, Fuller et al. using heterogeneous and Katz et al., using homogeneous planning, both reported the exact same median PSA in populations of low- and intermediate-risk patients. Specifically, both reported median PSAs of 0.4, 0.2, and 0.1 ng/ml at 24, 36 and 48 months, respectively. One implication from this observation is that the ultimate radiobiological effect from the two doses may be the same which, if confirmed with longer follow-up and more patients, would further support the concept that 35 Gy in five fractions may be the threshold dose to maximize tumor kill. On the other hand, the Fuller series had a far lower prevalence of androgen suppressive treatment added to the SBRT regimen (21% Katz series versus 2% Fuller series), which suggests a possibility of more “hormone suppression augmented” PSA nadir values in the Katz series. Also, the updated Fuller series revealed further PSA decline at 5-years post-treatment, whereas the Katz 5-year series update did not. Finally, a recently submitted paper from Kupelian et al. (ASCO GU symposium 2013) revealed a slightly higher 5-year biochemical relapse rate at 35 Gy relative to higher dose prostate SBRT regimens. These added factors create at least some degree of uncertainty to the assertion of equivalence of 35 Gy versus higher dose regimens, pending longer-term follow-up and more scientifically rigorous dose-response comparisons.

Finally, Katz et al. recently compared quality of life measures after CK SBRT to surgery, using EPIC scoring over a three year period. The largest differences in QOL occurred in the first 1–6 months after treatment, with larger declines following surgery in urinary and sexual QOL as compared to SBRT, and a larger decline in bowel QOL following SBRT as compared to surgery. Long-term urinary and sexual QOL declines remained clinically significantly lower for surgery patients but not for SBRT patients. This is the first long term follow-up for SBRT to report on quality of life issues and shows a favorable comparison to surgery.
SRS for localized prostate cancer is emerging as an effective non-invasive management strategy. Further studies in the form on multi-institutional Phase II trials are currently underway to show that a potent ablative dose of SRS for prostate cancer is highly therapeutic with low morbidity. There is a currently enrolling clinical trial for SRS treatment of low and intermediate risk prostate cancer emulating HDR brachytherapy dosimetry (NCT00643617). This trial is studying long term biochemical disease free survival and acute and late genitourinary and gastrointestinal toxicity and comparing SRS to HDR monotherapy as reported in the literature. It has been shown that SRS can reproduce the conformality for organ coverage achievable with HDR brachytherapy or IMRT and reported toxicity results, erectile function preservation and early PSA response are all encouraging. Additional follow-up is required to better evaluate potential late toxicity and long-term PSA outcomes.

VIII. Clinical Indications and Guidelines for SRS

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