

# Radiation Therapy for Prostate Cancer: External Beam, Brachytherapy, and Salvage

Scott L. Sailer, MD

Radiation is a viable curative treatment option for localized prostate carcinoma. It can be used as primary therapy and can also be used to cure patients who have failed surgery or are at high risk of recurrence after prostatectomy. For locally advanced tumors, radiation is the preferred treatment and, based on randomized trials, should be combined with hormonal therapy for optimal results. Watchful waiting is another option for patients with low-risk disease.

## Radiation as Primary Therapy

Radiation can be delivered using external beam radiation therapy, brachytherapy (permanent or temporary implantation of the prostate with radioactive seeds), or a combination of these methods. There are no randomized trials comparing the various radiation techniques to each other or to radical prostatectomy, so comparisons of outcomes after various treatments is based on retrospective reviews. Risk groups have been developed to categorize the aggressiveness of prostate carcinomas so that patient cohorts who have similar prostate cancers can be compared. One of the more popular risk-group categorizations has been developed by D'Amico et al.<sup>1,2</sup> (see Table 1).

These risk groups can be used to compare patients treated at different institutions with different techniques, but as always, there are pitfalls with retrospective reviews arising from patient selection and unknown bias. Patients treated with radiation tend to be older, have more advanced local disease, have higher prostate-specific antigen (PSA) levels, and have higher Gleason scores.<sup>a</sup> Because of this bias, outcomes after radiation will be inferior to surgery unless there is an attempt to compare patients with similar prostate cancers. Risk-group stratification is a simple way to adjust for this bias, but is obviously not as rigorous as randomized trial data. Another difficulty that limits retrospective comparisons is that both surgical and radiation techniques have improved over the past ten-to-15 years, so there is no long-term follow-up of prostate cancer patients treated with modern techniques.

Nevertheless, retrospective comparisons using appropriate risk groups are the best datasets available during patient counseling. Kupelian et al.<sup>3</sup> reported results for 2,507 patients treated with external beam radiation (greater than or equal to 72 Gy), surgery, brachytherapy, or a combination of brachytherapy and external beam from 1990 to 1998 (see Table 2). The data are not “clean” in that a fraction of patients in each treatment group also received

hormonal therapy. For some patients receiving radiation, hormonal therapy can improve survival, but at a minimum, patients treated with hormonal therapy will have a delay in PSA recurrence. Hormone use was limited to six months in this study, so the impact of hormonal therapy should be minimal. The patients in the intermediate- and high-risk

**Table 1.**  
**Risk Groups for Clinically Localized Prostate Carcinoma<sup>1,2</sup>**

Risk Group	Characteristics	Expected ten-year PSA failure-free survival
Low	PSA < 10 and Gleason score < 6 and 1992 AJCC stage T1c, T2a	80-85%
Intermediate	PSA > 10 and < 20 or Gleason score = 7 or 1992 AJCC stage T2b	50-60%
High	PSA > 20 or Gleason score > 8 or 1992 AJCC stage T2c, T3	30-40%

American Joint Committee on Cancer (AJCC).

a The Gleason scoring system grades prostate cancer patterns from 1 (well-differentiated malignancy) to 5 (poorly differentiated malignancy). For more information see page 123 of Dr. Culley Carson's article in this issue of the Journal.

Scott L. Sailer, MD, is in private practice at Wake Radiology Oncology in Cary, NC. Dr. Sailer can be reached at ssailer@wakeradiology.com or 300 Ashville Avenue, Suite 110, Cary, NC 27511. Telephone: 919-854-4588.

group were primarily intermediate risk. There were no T3 patients (patients with tumors that had spread outside the prostate capsule), 27% of patients had a PSA level greater than 20, and 19% had a Gleason score greater than 7. D'Amico has also reported outcomes for surgery and radiation based on risk groups.<sup>1</sup> No patients received hormonal therapy (see Table 3). These retrospective series show that the results after surgery and radiation are similar at five years. There is also little difference between brachytherapy and external beam radiation. Of note, even within the same risk group, the outcome after surgery is better at the Hospital of the University of Pennsylvania in Philadelphia than it is at Brigham and Women's Hospital in Boston (see Table 3), implying selection of more favorable patients at the University of Pennsylvania even within similar risk groups (assuming surgery is equivalent at the two institutions). While some patients in these series have been followed for ten years, the number of patients followed for ten years is too small to provide reliable data. With additional follow-up, long-term comparisons within these databases will be possible.

For patients with intermediate- and high-risk prostate cancers,

*“...both surgical and radiation techniques have improved over the past ten-to-15 years, so there is no long-term follow-up of prostate cancer patients treated with modern techniques.”*

however, comparing surgery to radiation alone no longer reflects clinical practice. There are randomized data that support the use of hormonal therapy in patients with intermediate- and high-risk prostate carcinoma who are treated with radiation.<sup>4-6</sup> Several studies have shown a statistically significant survival advantage from the addition of hormonal therapy to radiation (see Table 4). Patients in the D'Amico et al. study<sup>5</sup> had slightly less severe prostate cancer compared to the other two studies, although many of the patients would still be considered high risk. The optimal duration of hormonal therapy when combined with radiation is not known, but higher-risk patients are probably

best treated with two-to-three years of hormonal therapy.

Over a five-to-ten-year time frame, the outcome after radiation or surgery is similar, based on the above retrospective reviews of patients stratified by risk groups. Outcome beyond ten years is less certain. On theoretical grounds, surgery should have a slight advantage over radiation because, if a prostate cancer is truly localized to the prostate gland (without

extracapsular spread or occult distant metastasis), surgical removal of the gland should be permanently curative. Surgery is not always successful in clinically localized, low-risk tumors, however, because of inadequate surgical technique or tumor biology, which often leads to early dissemination or extracapsular spread. If the “horse is out of the barn,” no local therapy is curative, although radiation probably has an advantage if there is only local

**Table 2.**  
**PSA Failure-Free Survival for Stage T1-T2 Prostate Carcinomas at the Cleveland Clinic and Memorial Sloan Kettering at Mercy Hospital, 2003<sup>3</sup>**

Five-year PSA failure-free survival				
Treatment	Number	Low risk	Intermediate and high risk	Percent with hormonal therapy (duration < 6 months)
Radical Prostatectomy	1,034	90%	70% <sup>+</sup>	17%
External Beam Radiation (> 72 Gy)	301	92%	75% <sup>*</sup>	39%
Permanent Implant	950	90%	75% <sup>++</sup>	24%
External Beam and Implant	222	92%	75% <sup>**</sup>	36%

+ 21% Gleason score > 7, 26% PSA > 20

\* 22% Gleason score > 7, 35% PSA > 20

++ 12% Gleason score > 7, 21% PSA > 20

\*\* 22% Gleason score > 7, 35% PSA > 20

**Table 3.**  
**PSA Failure-Free Survival after Surgery or Radiation<sup>1</sup>**

Five-year PSA failure-free survival				
Treatment	Number	Low risk	Intermediate risk	High risk
Radical Prostatectomy <sup>*</sup>	1027	90%	71%	40%
Radical Prostatectomy <sup>+</sup>	1100	85%	55%	30%
External Beam Radiation <sup>^</sup>	473	90%	61%	42%

\* Hospital of the University of Pennsylvania, Philadelphia

+ Brigham and Women's Hospital, Boston

^ Joint Center for Radiation Therapy, Boston

**Table 4.**  
**Randomized Trials Evaluating Hormonal Therapy in Intermediate and High-Risk Prostate Carcinoma**

Study	Number	Duration of hormones	Five-year survival	
			Radiation alone	Radiation and hormones
D'Amico <sup>5</sup>	206	6 months	78%	88%
Hanks <sup>6*</sup>	361	2 years	71%	81%
Bolla <sup>4</sup>	415	3 years	62%	78%

\* Gleason score 8-10 only

## Radiation Modality

For patients choosing brachytherapy, the most important consideration is the experience of the brachytherapy center. The quality of the prostate implant as judged by dosimetric parameters increases with the number of implants performed. If appropriately proctored, however, treatment is likely satisfactory at less-experienced centers.

For external beam radiation, newer techniques that allow greater doses of

extension of disease, since radiation delivers a margin of effective dose around the prostate gland and seminal vesicles.

In contrast, the long-term efficacy of radiation, if a cancer is truly localized to the gland, is less certain based on a number of theoretical arguments. Although atrophied, the prostate is still present after radiation, and new cancers may develop ten-to-20 years after initial treatment. Second, there is variability in the sensitivity of prostate cancer cells to radiation. Finally, radiation kills clonogenic (replicating) cells in a random fashion. A given dose of radiation theoretically kills a fixed fraction of clonogenic cells, and with repeated doses of radiation, the fraction of surviving cells approaches, but never reaches, zero:

$$\text{survival fraction} = e^{-(\text{constant} * \text{radiation dose})}$$

For a given survival fraction, the chance of cure is mathematically described by the tumor control probability. If the surviving fraction is 0, the tumor control probability is 100%:

$$\text{tumor control probability} = e^{-(\text{surviving fraction} * \text{number of clonogens})}$$

Although the above is supported by laboratory work, tumor control probability *in vivo* is also dependent on host factors that are not well characterized. Radiation can definitely cure many prostate cancers, but if a large number of similar, truly localized tumors are radiated, there will likely be a few that are not cured because of the random nature of radiation killing, variability in radiation sensitivity, and variability in host factors. These tumors would have been cured with adequate surgical resection.

Based on these theoretical arguments and the lack of long-term randomized or retrospective data, I usually recommend radical prostatectomy for patients with low- and intermediate-risk cancers who are healthy and have a greater than ten-year life expectancy. For patients in poor health or older than 70 years, I will usually recommend radiation, since I am fairly confident that the ten-year results are similar to surgery. The patient with high-risk, localized prostate cancer, however, may be better treated with radiation and hormonal therapy, regardless of age, although there may be a role for surgery and adjuvant radiation in the younger patient.

radiation to be delivered safely should be used. At a minimum, this should include three-dimensional (3D) conformal therapy, which allows more accurate targeting of the prostate and seminal vesicles while avoiding the rectum and bladder. Intensity-modulated radiation therapy (IMRT) should also be considered in patients with intermediate- and high-risk disease. IMRT is an extension of 3D, which modulates the intensity of each radiation beam in a way that allows for dose escalation while minimizing dose to sensitive normal structures. A similar dose escalation with standard 3D techniques results in excess late rectal toxicity.

Image-guided radiation therapy (IGRT) is another new technology that is being introduced into the clinic. Using a variety of techniques, IGRT increases the daily accuracy of tumor localization, which results in lower doses to surrounding normal tissue by allowing a decrease in the margin from the tumor to the edge of the radiation beam.

The choice of radiation modality is partially based on disease characteristics. Treatment with brachytherapy alone is best for patients with low-risk disease as long as the prostate is not too large (greater than 60-70 cc) or too small (less than 30 cc). Hormonal therapy is occasionally used with brachytherapy to decrease the size of the prostate prior to the implant. External beam radiation is used alone for low-risk disease and is combined with hormonal therapy for intermediate- and high-risk disease. Some centers will combine external beam radiation, hormonal therapy, and brachytherapy for patients with intermediate- or high-risk disease. As briefly reviewed above, there are no data to support one type of radiation over another for appropriate patients.

Patient preference and expected side effects also influence treatment choice. Brachytherapy as sole therapy has the distinct advantage of being completed in a single appointment although it requires general or spinal anesthesia, and treatment effects are felt for several months after the implant. External beam radiation typically involves daily treatments for seven-to-eight weeks (35-to-40 treatments). During treatment, brachytherapy tends to result in more urinary symptoms (frequency, burning, and urgency), and external beam radiation tends to cause more rectal symptoms (tenesmus, increased bowel frequency, hemorrhoid discomfort, and diarrhea), although both treatments can result in urinary and rectal symptoms. A small percentage of brachytherapy patients require bladder catheterization during the first few months after implantation, while this rarely occurs

during or after external beam radiation. Both techniques can result in rectal injury, which manifests as rectal bleeding several months to years after treatment. Urinary incontinence is rare with both treatments, although it is more likely following brachytherapy. Sexual dysfunction is probably more frequent after external beam radiation compared to brachytherapy.

## Radiation after Radical Prostatectomy

After prostatectomy, the PSA should become undetectable. If the PSA fails to fall to zero or becomes detectable after initially falling to zero, radiation is often used in a curative attempt to “salvage” the failure. As a local modality, radiation will only be effective if residual disease is confined to the prostate bed or pelvic nodes, although pelvic (nodal) radiation is less frequently used than prostate bed radiation after prostatectomy. Post-prostatectomy radiation is more effective with lower post-prostatectomy PSAs, an initially undetected PSA after surgery, a long disease-free interval prior to PSA failure, and adverse pathologic features, which predict residual local disease (extracapsular extension or positive margin). If a patient’s PSA does not initially decline to zero, he likely had occult metastatic disease at diagnosis and would not benefit from localized radiation, unless the source of the residual PSA is a positive margin and the Gleason score less than 8. A ProstaScint<sup>®</sup> scan<sup>b</sup> is often used to confirm a prostate bed recurrence or, at least, attempt to rule out distant disease, but the low sensitivity and specificity of this examination limits its usefulness. The PSA disease-free survival after salvage radiation for all patients is approximately 25-40% at five-to-ten years after radiation.<sup>7,8</sup> Favorable patients (PSA less than 2.0, Gleason score less than 8, positive surgical margins) may experience PSA disease-free survivals of 60-70%.<sup>8</sup>

Adjuvant radiation for high-risk prostate cancer after radical prostatectomy is rarely used. Adjuvant refers to a situation where all clinically detectable disease has been removed. Most urologists will follow patients with high-risk prostate cancer and only consider radiation if the PSA does not fall to zero or if it becomes detectable, at which time the treatment is considered salvage therapy. The rationale for this “wait-and-see” approach is that not all high-risk patients are destined to fail, failures can be picked up “early” with PSA, and many patients are spared the toxicity of unneeded radiation. Arguments pointing out that PSA becomes detectable only after a million cells are present<sup>9</sup> have not increased the use of adjuvant radiation. Theoretically, radiation is most effective when the tumor burden is smallest. A randomized study of adjuvant radiation showed that the biochemical relapse was reduced from 47% to 26% at five years with the use of radiation.<sup>10</sup>

## Watchful Waiting

For the older patient with low-risk prostate carcinoma, watchful waiting is a reasonable option. This is especially true if the patient has multiple co-morbidities or the Gleason score is less than 6. A group of patients identified from the Connecticut Tumor Registry had data extracted from chart review. For patients with Gleason 2-5 carcinomas who were not treated with local therapy, only 4-11% died from prostate carcinoma.<sup>11</sup> D’Amico showed that for low-risk prostate carcinoma, the risk of dying from prostate cancer after radiation or surgery was 1-2% at ten years, while the risk of dying from other causes was ten-to-30%.<sup>12</sup>

Most radiation oncologists are comfortable following patients without treatment, although this is usually done in conjunction with an urologist. Ideally, these patients should be enrolled in a study so outcomes of watchful waiting can be determined, but this is not usually possible in a community setting. A reasonable approach to watchful waiting is to monitor PSA every three months and consider treatment if the PSA doubling time (velocity) is less than 12 months. If the PSA is fairly stable after one-to-two years, monitoring can be decreased to every six months. While patients initially agree to watchful waiting, many elect to proceed with treatment as their anxiety rises with the rise in their PSA, even if the doubling time is greater than 12 months.

## Summary

Radiation is a curative treatment for prostate cancer that is most appropriate for the older patient or the patient with significant co-morbidities. Younger patients with a greater than ten-year survival are probably best treated with surgery unless the disease is high risk. For all patients, high-risk disease is best treated with hormones and radiation. The long-term superiority of surgery over radiation, however, has not been demonstrated in randomized or retrospective studies, and the recommendation for surgery in the younger, healthy patient with favorable local disease is largely based on theoretical considerations. If chosen for appropriate indications and delivered with appropriate techniques, radiation can be delivered using external beam or brachytherapy with equal efficacy. The choice of radiation treatment is based on tumor characteristics and patient preference. Radiation can be used after prostatectomy to cure patients who are not cured with surgery. Watchful waiting may be appropriate for patients with low-risk disease. **NCMedJ**

---

b ProstaScint<sup>®</sup> scan involves injecting a small amount of radioactive material into the body to determine if and where any prostate cancer cells may be.

## REFERENCES

- 1 D'Amico AV. Combined-modality staging for localized adenocarcinoma of the prostate. *Oncology* 2001;15(8):1049-1059.
- 2 D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280(11):969-974.
- 3 Kupelian PA, Potters L, Khuntia D, et al. Radical prostatectomy, external beam radiotherapy <72 Gy, external beam radiotherapy > or =72 Gy, permanent seed implantation, or combined seeds/external beam radiotherapy for stage T1-T2 prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58(1):25-33.
- 4 Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): A phase III randomised trial. *Lancet* 2002;360(9327):103-106.
- 5 D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCrocce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. *JAMA* 2004;292(7):821-827.
- 6 Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cyoreduction and radiotherapy in locally advanced carcinoma of the prostate: The Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003;21(21):3972-3978.
- 7 Pazona JF, Han M, Hawkins SA, Roehl KA, Catalona WJ. Salvage radiation therapy for prostate-specific antigen progression following radical prostatectomy: 10-year outcome estimates. *J Urol* 2005;174(4 Pt 1):1282-1286.
- 8 Stephenson AJ, Shariat SE, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. *JAMA* 2004;291(11):1325-1332.
- 9 Anscher MS. Adjuvant radiotherapy following radical prostatectomy is more effective and less toxic than salvage radiotherapy for a rising prostate-specific antigen. *Int J Cancer* 2001;96(2):91-93.
- 10 Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: A randomised controlled trial (EORTC trial 22911). *Lancet* 2005;366(9485):572-578.
- 11 Albertsen PC, Hanley JA, Gleason DF, Barry MJ. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA* 1998;280(11):975-980.
- 12 D'Amico AV, Moul J, Carroll PR, Sun L, Lubeck D, Chen MH. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol* 2003;21(11):2163-2172.

# MEN

would rather talk about

*Emotions*

than their prostate.

One in six men will be diagnosed with prostate cancer in his lifetime. The good news is, it's highly treatable, if you find it early. If you're 50 or older, speak with your doctor about getting tested.

Hope. Progress. Answers. / 1-800-ACS-2345 / [www.cancer.org](http://www.cancer.org)

