Clinical basics

Prostate cancer: 7. Radiation therapy for localized disease

Padraig Warde, MB; Charles Catton, MD; Mary K. Gospodarowicz, MD

The case

A 65-year-old man visits his general practitioner for his annual physical examination. On rectal examination the physician discovers a small nodule in the right lobe of his prostate gland. The patient has had no urinary symptoms and is in excellent general health. Sexual function is normal. He has no family history of prostate cancer; his father died of a stroke at age 86 years. The prostate-specific antigen level is elevated (9.3 ng/mL), and transrectal ultrasound-guided biopsy of the nodule reveals adenocarcinoma of the prostate, with a Gleason score of 7. Systematic biopsies of the left lobe yield normal results. At a follow-up visit he tells his physician, "I have been doing some research, and it appears I should have treatment. However, what is less clear is what form of therapy this should take — surgery or radiation treatment. If radiation, should it be external or interstitial? Please tell me what you can about the state of the art with respect to radiation therapy."

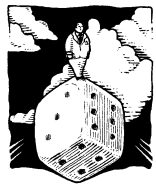
Localized prostate cancer can be treated using potentially curative approaches (e.g., radical prostatectomy and radiation therapy) or palliative approaches with immediate or delayed hormone therapy. Observation or "watchful waiting" is, in essence, a form of delayed therapy, because the disease usually requires treatment in the future. However, in the medical community, there is a lack of consensus regarding the best treatment for patients with localized prostate cancer,[1] especially in terms of the choice between radical prostatectomy and radiation therapy.

This lack of consensus stems from the excellent long-term survival rates among patients with localized disease regardless of treatment approach. No direct comparison of the outcomes of patients treated with surgery and those with radiation therapy in a prospective randomized trial is available. The choice of therapy is made by the patient after consultation with a urologist and radiation oncologist; taken into account are the extent of the disease, the tumour grade, the prostate-specific antigen (PSA) level, comorbid conditions and the patient's preference.

Two radiotherapeutic interventions are available to treat localized prostate cancer: external beam radiation therapy and interstitial brachytherapy. The former uses high-energy linear accelerators and remains the most common approach in most centres. In interstitial brachytherapy, radioactive sources are placed in direct contact with the tumour in the prostate gland as a temporary or permanent implant. The development of improved technology for placement of these implants has recently renewed interest in this approach.[2]

This 13-part series was made possible in part by an unrestricted educational grant from ZENECA Pharma

This 13-part series was made possible in part by an unrestricted educational grant from Pharmacia & Upjohn Inc.



Education

Éducation

The authors are with the Department of Radiation Oncology, University of Toronto and Princess Margaret Hospital, Toronto, Ont.

This article has been peer reviewed.

The members of the Prostate Cancer Alliance of Canada, an umbrella group formed to carry out the recommendations of the 1997 National Prostate Cancer Forum, are pleased to support the intent to inform both health care professionals and lay people about the detection, diagnosis and treatment of prostate cancer through this 13-part series. The list of members of the Alliance appears at the end of this article.

Series editors: *Dr. Neill A. Iscoe, Medical Oncologist, Toronto–Sunnybrook Regional Cancer Centre, and Dr. Michael Jewett, Professor and Chairman, Division of Urology, University of Toronto, Toronto, Ont.*

CMAJ 1998;159:1381-8

External beam radiation therapy

Longitudinal multicentre studies have documented excellent long-term overall survival rates among patients with localized prostate cancer treated with external beam radiation therapy. In one study[3] involving 690 patients with clinically localized disease (T1/T2 N0),[4] the 10-year survival rate was 60%. This rate is similar to the 10-year cause-specific survival rate of 75% reported in an age-matched cohort.[3] Similar results have been reported from many other centres (Table 1).[3,5–8]

Although these results are encouraging, overall survival may not be the most appropriate measure of treatment efficacy in older men with other competing causes of death. Also, cause-specific survival rates can often be misleading, because the exact cause of death in elderly people is often difficult to ascertain. The definition of failure following radiation therapy depends on the endpoint measured. For most types of cancer, local recurrence or distant metastasis is regarded as evidence of failure. However, for prostate cancer, a tumour marker, PSA, has refined our ability to detect progressive disease. The currently accepted definition of biochemical recurrence is 3 consecutive rising PSA values after reaching a nadir.[9] With the use of PSA testing to assess treatment outcome, biochemical failure is observed earlier and more frequently than clinical failure. In a cohort of 504 men treated with radiation therapy, the biochemical disease-free survival rate at 10 years was only 40%.[10] Similar results have been reported by others,[3,6] which indicates that, on the basis of a biochemical definition of cure, less than half of the patients treated with radiation therapy in the past have been cured of prostate cancer.

Various strategies to improve treatment results have been proposed, including reducing tumour bulk before radiation therapy with the use of neoadjuvant hormone therapy and increasing the radiation dose to the primary tumour (Table 2). Adding hormone therapy is a more attractive option than increasing the radiation dose, because of the potential to improve local control (without the increased risk of complications from radiation therapy) and to eradicate occult metastatic disease.

Hormone therapy

Neoadjuvant hormone therapy is given *before* definitive treatment such as surgery or radiation therapy; adjuvant hormone therapy is given *after* definitive treatment. Both strategies are used in the management of patients with localized prostate cancer. The mechanisms of action of neoadjuvant hormone therapy include the following:

- It reduces the number of tumour cells, specifically clonogens (tumour stem cells that have the capacity to divide indefinitely), thus making it easier for radiation therapy to eradicate them.
- When combined with radiation therapy it may enhance tumour cell kill in the prostate through a common mechanism of cell death such as apoptosis (an intrinsic cell suicide program under complex genetic regulation).
- It improves the nutritional and oxygenation status of the tumour, thereby increasing the number of cancer cells killed by each fraction of radiation.[11]

In patients with locally advanced prostate cancer (stage T3 or T4) the role of neoadjuvant and adjuvant hormone therapy has been assessed in prospective randomized trials, and combining radiation therapy with hormone therapy was shown to improve local control and survival. The European Organization for Research and Treatment of Cancer Radiotherapy Group[12] recently reported the results of a study of 415 patients randomly chosen to receive external beam radiation therapy either alone or with 3 years of adjuvant luteinizing hormone-releasing hormone therapy. With a median follow-up of 45 months the overall 5-year survival rate was 79% in the combined treatment group, as compared with 62% in the radiation only group (p = 0.001). Improvement was also seen in disease-free survival and local tumour control. The 5-year PSA progression-free rate was 81% in the combined treatment group and 43% in the radiation only group.

Table 1: Overall and cause-specific survival rates among patients with early-stage (T1 or T2) prostate cancer who underwent external beam radiation therapy

			5-year survival rate, %		10-year survival rate, %	
Study	No. of patients	Tumour stage	Overall	Cause specific	Overall	Cause specific
Duncan et al[5]	70	T1	83.8	93	57.8	79
	341	T2	81.8	92	53.6	66
Perez et al[6]	48	T1b	85	78	70	60
	252	T2	82	76	65	56
Shipley et al[7]	126	T2	85	–	–	–
Zagars et al[8]	32	T1b	74	90	68	
	82	T2	93	89	70	85

This trial confirmed the superiority of combined treatment in locally advanced disease. Other studies, such as the Radiation Therapy Oncology Group (RTOG) trial 86-10, have shown some benefit with neoadjuvant hormone therapy in terms of local control and disease-free survival in locally advanced prostate cancer.[13,14] However, no improvement in overall survival has been shown in any study of neoadjuvant hormone therapy. The timing and duration of neoadjuvant and adjuvant hormone therapy in locally advanced prostate cancer remain unclear and are being addressed in ongoing trials.

Current studies are addressing the role of neoadjuvant and adjuvant hormone therapy in patients with early stage prostate cancer (T1 and T2). At present the routine use of neoadjuvant or adjuvant hormone therapy in these patients is considered experimental. Neoadjuvant treatment, usually chemotherapy, in other cancers has not been shown to be of benefit. Neoadjuvant treatment could potentially be detrimental by delaying definitive therapy or by stimulating repopulation of surviving tumour cells, making subsequent radiation therapy less effective. However, these largely theoretical concerns have not been supported by clinical data.

Teaching points

- The chances of long-term survival for patients with localized prostate cancer are excellent regardless of treatment.
- There is no clear difference in outcome between radiation therapy and surgery for patients with localized prostate cancer; the choice will depend on the extent of the disease, comorbid conditions and patient preference.
- External beam radiation therapy results in high overall survival rates, but less than half of patients undergoing conventional treatment are likely to be "cured."

Increasing the radiation dose

Another strategy for improving the effect of external beam radiation therapy is to increase the radiation dose using conformal techniques. Advances in computer technology have allowed the development of 3-dimensional conformal radiation therapy and the delivery of high-precision radiation therapy. Currently, satisfactory techniques are available to deliver radiotherapy in a manner that molds the spatial distribution of the dose to the precise 3-dimensional configuration of the prostate. These techniques also minimize the exposure to radiation of the surrounding structures.

Retrospective studies have suggested that doses of 70 Gy or more improve local tumour control and biochemical freedom from relapse.[15] Increasing the radiation dose can be done safely provided the distribution of radiation between the prostate and surrounding normal tissues (particularly the bladder and rectum) is optimized using conformal techniques.

When these conformal techniques were used in a consecutive series of 202 patients with early stage (T1c) prostate cancer[16] the 5-year rate for biochemical freedom from relapse was 97% among patients with pretreatment PSA levels of less than 10 ng/mL and 88% among those with pretreatment levels of 10–20 ng/mL. Less than 1% of patients had severe rectal or urinary sequelae, and 61% maintained sexual potency. However, chronic rectal bleeding can occur after escalated-dose radiation therapy; it may require ongoing treatment and can significantly affect a patient's quality of life.[17] Similar data on biochemical freedom from disease have been reported from other centres using dose-escalation protocols, and overall these results are comparable to those from recent reports of nerve-sparing radical prostatectomy.[18,19]

An even more refined delivery method is intensity-modulated radiation therapy. This form of treatment involves the production of a conformal radiation field by a moving multileaf collimator and accelerator gantry. During treatment, a nonuniform radiation dose is delivered to the patient from various entry points, allowing for a uniform dose distribution within the tumour while preventing exposure of normal tissues to a high dose. This technique is now being introduced into clinical practice, and early results are promising for the treatment of localized prostate cancer.[20]

Although the initial experience with dose-escalation radiation therapy provides reasons for optimism, the long-term benefits for patients with localized prostate cancer await assessment in phase III randomized trials. The Radiation Therapy Oncology Group is currently embarking on such a study.

Interstitial brachytherapy

Interstitial brachytherapy using iodine 125 was exten-

Table 2: Potential strategies to improve results of radiation therapy for localized prostate cancer

Aim	Examples of techniques
Improvement of dose distribution between tumour and normal tissue	Conformal radiotherapy; proton therapy; brachytherapy
Reduction of tumour volume	Neoadjuvant hormone therapy
Improvement in nutritional and oxygenation status of tumour	Neoadjuvant hormone therapy
Biological modification	Altered fractionation; use of radiosensitizers; neutron therapy

sively used in the management of localized prostate cancer in the late 1970s and early 1980s. The initial results were excellent, and serious side effects were rare. In particular, impotence rates were believed to be much lower than those seen with external beam radiation therapy. However, the long-term results were disappointing, and the technique was abandoned. In retrospect, the poor results were likely related to imprecise implantation techniques. Accurate placement of radioactive sources is required to deliver a uniform radiation dose to the whole prostate gland. Early treatments relied on free-hand placement of the radioactive sources, which resulted in dose distributions that were not homogeneous because of less than ideal positioning of the radioactive sources.[21]

Teaching points

- Results of external beam radiation therapy may be improved by increasing the dose using conformal techniques or by using neoadjuvant hormone therapy.
- Interstitial brachytherapy — placement of a radioactive source in the prostate in direct contact with the tumour — is a reasonable alternative to surgery or external beam radiation therapy in patients with early-stage, low-grade disease.

Recently, the use of transrectal ultrasonography and CT scanning to direct transperineal implantation has resulted in much improved clinical outcomes.[22] These techniques allow for a more uniform placement of the radioactive sources and, consequently, improved dose distribution.

The radiation dose delivered by brachytherapy using ^{125}I implants is substantially greater than that delivered by external beam radiation therapy. Recent studies involving patients with a PSA level of less than 10 ng/mL showed results similar to those achieved with external beam dose-escalation protocols, with more than 85% of patients biochemically free of disease at 3 years.[22,23]

The morbidity profile of brachytherapy in terms of acute reactions is favourable. Treatment involves an outpatient procedure with minimal intraoperative complications. Symptoms of increased frequency of urination and urgency are common but are usually mild and self-limiting. Few patients require temporary catheterization to alleviate bladder outlet obstruction.

However, late treatment complications are of greater concern. A recent report of 92 patients documented persistent moderately severe urinary symptoms 2 years after implantation in 14 patients and radiation-induced rectal ulceration in 5 patients.[24] The incidence of complications was considerably lower among those who had not had transurethral resection of the prostate in the past. Preliminary data on impotence in men managed with seed implantation indicate preservation of erectile function in the majority of patients.[25]

To improve these techniques further, newer isotopes, including palladium 103 and iridium 192, have recently been introduced into clinical practice. ^{103}Pd has a higher dose rate than ^{125}I and, although the clinical significance of this is controversial, mathematical models suggest that ^{125}I would be better in the treatment of slower growing tumours and ^{103}Pd would be more effective in rapidly growing tumours.[2] Currently, ^{125}I is used primarily for well- to moderately differentiated tumours (Gleason score 2–6), and ^{103}Pd is used in patients with poorly differentiated tumours (Gleason score 7–10). ^{192}Ir is used in temporary seed implantation and, because of a significant high-energy gamma radiation component, requires sophisticated shielding for medical personnel. In contrast, both ^{103}Pd and ^{125}I produce only low-energy gamma radiation, and protection for medical personnel and patients' families is relatively easy. There is general agreement that the optimal candidates for permanent seed implantation are patients with stage T1 or T2 tumours with low-grade disease (Gleason score ≤ 6) and a PSA level of 10 ng/mL or less. Comparison of treatment outcomes with surgery and external beam radiation therapy would suggest that brachytherapy is as efficacious in terms of PSA progression-free survival in this group of patients.[26] However, long-term results with brachytherapy are not available, and randomized clinical trials are necessary to delineate its role in prostate cancer management.

Complications of external beam radiation therapy

As with any curative cancer therapy, radiation therapy commonly results in minor complications but rarely in major ones. Unlike surgery, though, this treatment does not require admission to hospital, and there are few contraindications to its use. Side effects may occur as acute reactions during and immediately after radiation treatment and as late reactions that may become apparent within several months or even 3 to 10 years after treatment.

Acute reactions

Acute reactions are due to specific injury of mucosal epithelium within the irradiated volume and to nonspecific factors such as fatigue. The onset of symptoms (Table 3) depends on the number of weeks over which the

radiation is given and on the turnover rate of epithelial cells. For conventional prostatic irradiation given over 6–7 weeks, symptoms usually develop 2–3 weeks after treatment starts, peak at 5–6 weeks and begin to subside toward the completion of treatment, when re-epithelialization begins.

The severity of the reaction depends on the total radiation dose given and the time over which it is given, the volume of mucosa in the treatment area and the patient's inherent sensitivity to radiation. The tissues commonly at risk are in the prostate itself, at the base of the bladder and in the anterior rectal wall; they may also include the small bowel if prophylactic nodal irradiation is used.

In a series of 914 patients treated with curative radiation therapy 24% experienced genitourinary symptoms and 43% had gastrointestinal side effects.[27] Most of the reactions were minor. Severe acute genitourinary or gastrointestinal sequelae that require a halt in therapy are uncommon; such effects were identified in 2.5% of all treated patients in another large series.[6]

Teaching points

- Radiation therapy commonly results in minor side effects but rarely in major ones. Unlike surgery, though, this treatment does not require admission to hospital, and there are few contraindications to its use.
- Common acute reactions to radiation therapy are fatigue, frequent and urgent urination, rectal tenesmus and diarrhea. These often begin a few weeks after treatment starts, but they subside after the completion of treatment.
- Late reactions, resulting from connective-tissue injury, develop months to years after therapy but occur in less than 2% of patients.

Late reactions

Late reactions (Table 4) result from connective-tissue injury that develops months to years after therapy. Typically, progressive microvascular injury produces subepithelial telangiectasia and fibrosis in the submucosal layer and muscular layer of the organ wall, which in turn leads to a more fragile mucosa that has a tendency to minor bleeding, along with a degree of chronic functional change. This fibrosis rarely disrupts the microvasculature to the point where chronic mucosal ulceration and necrosis may result. The severity of a late reaction depends mainly on the total radiation dose given, the size of the daily radiation fraction given and the amount of sensitive normal tissue in the treatment volume. The severity of an acute reaction does not predict the severity of any late reaction that might occur. Severe late reactions often improve over time, but unlike acute reactions they may never completely resolve. Modern treatment techniques are designed to minimize the risk of severe late reactions.

The risk of a late reaction becoming permanent is of greater concern to patients than the risk of developing an acute reaction. Fortunately, apart from sexual impotence, severe late genitourinary and gastrointestinal complications rarely follow conventional curative radiation therapy for prostate cancer. A large multicentre study has identified that severe late complications occur in less than 2% of patients.[28]

Risks of late reactions

Our understanding of the risks of complications from prostatic radiation therapy is based on data collected retrospectively and prospectively using toxicity grading systems like the Radiation Therapy Oncology Group toxicity score,[29] which grades treatment-related side effects from the physician's perspective. Grading tools that determine the impact of treatment-related side effects on quality of life from the patient's perspective are now in use, but data from them are limited.[28]

The combined results of large series of curative treatment in a total of 2216 men with prostate cancer showed that the risk of proctitis with rectal bleeding after radiation therapy ranged from 2.6% to 14.9% and persisted for more than 6 months in less than 3% of patients.[30] The risk of persistent diarrhea requiring medication was 2.1%. Similarly, cystitis with hematuria occurred in 2.6%–10.8% of treated patients and persisted for more than 6 months in less than 3%. Urethral stricture or bladder neck contracture that could not be corrected by simple endoscopic procedures was reported in 1.1% of cases. Urinary incontinence, a rare complication of prostatic radiation therapy, was reported in only 0.9% of cases. A history of transurethral resection of the prostate before or after radiation therapy may be a major risk factor for this complication.[30]

A dry ejaculate is a common late side effect of mucosal

Table 3: Symptoms of acute complications of radiation therapy for localized prostate cancer

Common
Fatigue
Frequency, urgency, dysuria, nocturia
Rectal tenesmus, mucous discharge and frequent, pellet-like stools
Diarrhea
Uncommon
Urinary retention due to prostatic edema (usually an exacerbation of pre-existing bladder outlet obstruction)
Rectal bleeding

injury due to prostatic irradiation. Permanent sexual impotence is also a common side effect and is of more significance to patients. The actual risk of impotence secondary to prostatic irradiation is not precisely known, because the causes are multifactorial among the predominantly elderly men with prostate cancer who undergo radiation therapy. It is widely accepted that about 50% of all previously potent men will become impotent within 5 years after curative prostatic irradiation.[27] The risk of impotence is higher among older men with borderline pretreatment erectile function than among younger and healthier men.

Leg and genital edema are rare complications and are usually related to a previous pelvic node dissection. Radionecrosis of pelvic bones is a serious but extremely rare complication and is almost never seen with modern treatment techniques unless an error in treatment prescription or radiation delivery has occurred.

Minimizing the risk of complications

Careful treatment planning and modern delivery systems will minimize the risk of serious radiation injuries.[31] To reduce the risk of incontinence or stricture, transurethral resection of the bladder neck should be avoided in patients who are about to undergo or who have received prostatic irradiation.

Patients with large-volume glands who require a larger radiation volume are at higher risk of moderate or severe acute and late rectal injury.[32] Patients with pre-existing symptoms of bladder outlet obstruction are more likely to have increased obstructive symptoms after radiation therapy. In both cases, reduction of prostate bulk with hormone therapy may lessen the risk of severe complications.

There is no proven method for reducing the risk of erectile dysfunction following radiation therapy, but newer methods of treatment such as 3-dimensional conformal radiation therapy and low-dose rate brachytherapy protect more of the normal rectal and bladder wall from the high-dose radiation and may further reduce the risk of moderate and severe reactions.

Management of complications

Acute reactions

Mild to moderate acute reactions are managed symptomatically. Local measures, including sitz baths, cortisone cream and suppositories, reduce the symptoms of acute

Table 4: Late complications of radiation therapy for localized prostate cancer

Complication	Treatment
Rectum	
Mild: Intermittent, mild rectal bleeding; change in bowel habits not requiring medication	None required
Moderate: Chronic rectal irritation and mucous discharge requiring medication; persistent rectal bleeding	Steroid suppositories or foam retention enemas; sulfasalazine
Severe: Rectal ulceration (very rare)	Defunctioning colostomy
Bladder	
Mild: Mild increase in urinary frequency or nocturia	None required
Moderate: Frequency or nocturia requiring medication; intermittent hematuria	Antispasmodics; coagulation of bleeding telangiectasia
Severe: Contracted bladder with capacity less than 100 mL; chronic hematuria (very rare)	Urinary diversion
Incontinence	
Rare; almost always associated with TURP before or after radiation	Artificial sphincter
Urethral stricture and bladder neck contracture	
Rare; often associated with TURP before radiation	Urethral dilatation
Prostate	
Loss of seminal fluid with scanty or dry ejaculate	None available
Erectile dysfunction	
Incomplete or complete dysfunction in 50% of patients; believed due to microvascular injury to branches of internal pudendal and penile arteries	Medical: Viagra; intracorporeal injection of papavarine Mechanical: vacuum pump; surgical implants
Leg and genital edema	
Rare; almost always associated with prior pelvic node dissection	Compression stockings; compression pump

Note: TURP = transurethral resection of prostate.

treatment-related proctitis. Antispasmodics and urinary analgesics (e.g., phenazopyridine [pyridium]) will treat mild to moderate cystitis and urethritis. Urinary retention is rare and, when present, requires catheterization; radiation therapy can proceed with a catheter in place. Severe bladder or rectal symptoms are extremely uncommon and may require a break in or premature cessation of radiation therapy.

Late reactions

A slight change in bowel or bladder habits or mild intermittent and painless rectal bleeding requires no specific therapy. Such bleeding usually occurs with the passing of stools and its cause must be differentiated from treatment-related proctitis. Proctoscopy of a patient with proctitis will typically demonstrate a friable mucosa with telangiectasia, and these changes are usually most prominent on the anterior rectal wall adjacent to the prostate.

Bleeding from proctitis must not be mistaken for hemorrhoidal bleeding; inappropriate hemorrhoidal surgery after prostatic irradiation leads to poor healing and anal stricture. Coincident hemorrhoids should be managed medically.

Persistent rectal symptoms must be investigated and other causes ruled out. Treatment-related proctitis responds to anti-inflammatory drugs such as cortisone in foam retention enemas twice daily for 2 weeks or sulfasalazine (salazopyrin) for longer-term therapy. The use of short-chain fatty acid enemas in the treatment of proctitis after radiation therapy is currently under investigation and may prove useful.

The development of microscopic or overt hematuria following treatment requires investigation to rule out other causes. Treatment-related cystitis can be diagnosed only using cystoscopy to identify radiation-induced bladder changes. Chronic bladder irritation from radiation-induced cystitis may require long-term therapy with antispasmodics, and persistent hematuria may require coagulation of bleeding telangiectasia. In very severe cases, persistent rectal or bladder symptoms may ultimately require surgical urinary or rectal diversion. Impotence, when present, will become apparent 18 to 60 months after radiation therapy and may be managed with intracorporeal therapy or mechanical aids.

Comments

Radiation therapy is an effective treatment option for patients with localized prostate cancer. The Prostate Cancer Clinical Guidelines Panel of the American Urological Association has concluded that outcomes data are inadequate for valid comparison of treatments because of large differences among treatment groups in such significant characteristics as age, tumour grade and pelvic lymph node status.[33] The panel recommended that patients with newly diagnosed, clinically localized prostate cancer should be informed of all available treatment options and that they should take part in formulating the treatment decision. Radiation therapy is contraindicated in patients with inflammatory bowel disease and those previously treated with radiation therapy (e.g., for seminoma).

Patients with early-stage disease (T1b–T2a with a Gleason score of 7 or less and a PSA level of 10 ng/mL or less), such as the man described at the beginning of this article, can be treated successfully with either external beam radiation therapy or interstitial brachytherapy. Patients with more advanced disease (a higher PSA level, larger tumour size or higher Gleason score) should be considered for escalated-dose conformal radiation therapy or combined radiation therapy and hormone therapy.

Large prospective randomized phase III trials should be instituted to address the issue of optimal therapy. It is somewhat disheartening that in 1990 only 1.7% of men with prostate cancer in the United States were enrolled in a clinical trial. Only continued research and properly designed randomized trials will define the optimal management of patients with localized prostate cancer.

References

1. Moore M, O'Sullivan B, Tannock I. How expert physicians would wish to be treated if they had genitourinary cancer. *J Clin Oncol* 1988;6:1736-45.
2. Grimm P, Blasko J, Ragde H, Sylvester J, Clarke C. Does brachytherapy have a role in the treatment of prostate cancer? *Hematol Oncol Clin North Am* 1996;10:653-90.
3. Bagshaw M, Cox R, Hancock S. Control of prostate cancer with radiotherapy: long-term results. *J Urol* 1994;152:1781-5.
4. International Union against Cancer. *TNM classification of malignant tumours*. New York: Wiley-Liss, Inc; 1997.
5. Duncan W, Warde P, Catton C, Munro A, Lakier R, Gadalla T, et al. Carcinoma of the prostate: results of radical radiotherapy (1970–1985). *Int J Radiat Oncol Biol Phys* 1993;26:203-10.
6. Perez C, Hanks G, Leibel S, Zietman A, Fuks Z, Lee W. Localized carcinoma of the prostate (stages T1b, T1c, T2 and T3): review of management with external beam radiation therapy. *Cancer* 1993;72:3156-73.
7. Shipley W, Prout G, Coachman N, McManus P, Healey E. Radiation therapy for localized prostate cancer: experience at the Massachusetts General Hospital (1973–1981). *J Natl Cancer Inst Monogr* 1988;7:67-73.
8. Zagars G, von Eschenbach A, Johnson D, Oswald M. The role of radiation therapy in stages A2 and B adenocarcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1988;14:701-9.
9. American Society for Therapeutic Radiology and Oncology Consensus Panel. Consensus statement: guidelines for PSA following radiation therapy. *Int J Radiat Oncol Biol Phys* 1997;37:1035-41.
10. Zietman A, Coen J, Dallow K, Shipley W. The treatment of prostate cancer by conventional radiation therapy: an analysis of long-term outcome. *Int J Radiat Oncol Biol Phys* 1995;32:287-92.
11. Zietman A, Prince E, Nakfoor B, Shipley W. Neoadjuvant androgen suppression with radiation in the management of locally advanced adenocarcinoma of the prostate: experimental and clinical results. *Urology* 1997;49:74-83.
12. Bolla M, Gonzalez D, Warde P, Dubois J, Mirimanoff R, Storme G, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337:295-300.
13. Pilepich M, Winter K, Roach M, Russell A, Sause W, Rubin P, et al. Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation before and during radiotherapy in locally advanced carcinoma of the prostate [abstract A1185]. *Proc ASCO* 1998;17:308a.

14. Laverdiere J, Gomez JL, Cusan L, Suburu ER, Diamond P, Lemay M, et al. Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;37:247-52.
15. Pollack A, Zagars G. External beam radiotherapy dose response of prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;39:1011-8.
16. Hanks G, Hanlon A, Pinover W, Al-Saleem T, Schultheiss T. Radiation therapy as treatment for stage T1c prostate cancers. *World J Urol* 1997;15:369-72.
17. Teshima T, Hanks G, Hanlon A, Peter R, Schultheiss T. Rectal bleeding after conformal 3D treatment of prostate cancer: time to occurrence, response to treatment and duration of morbidity. *Int J Radiat Oncol Biol Phys* 1997;39:77-83.
18. Zelefsky MJ, Leibel SA, Gaudin PB, Kutcher GJ, Fleshner NE, Venkatramen ES, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. *Int J Radiat Oncol Biol Phys* 1998; 41:491-500.
19. D'Amico AV, Whittington R, Kaplan I, Beard C, Jiroutek M, Malkowicz SB, et al. Equivalent biochemical failure-free survival after external beam radiation therapy or radical prostatectomy in patients with a pretreatment prostate specific antigen of > 4–20 ng/ml. *Int J Radiat Oncol Biol Phys* 1997;37:1053-8.
20. Reinstein L, Wang X, Burman C, Chen Z, Mohan R, Kutcher G, et al. A feasibility study of automated inverse treatment planning for cancer of the prostate. *Int J Radiat Oncol Biol Phys* 1998;40:207-14.
21. Porter A, Blasko J, Grimm P, Reddy S, Ragde H. Brachytherapy for prostate cancer. *CA Cancer J Clin* 1995;45:165-78.
22. Ragde H, Blasko J, Grimm P, Kenny G, Sylvester J, Hoak D, et al. Brachytherapy for clinically localized prostate cancer: results at 7- and 8-year follow-up. *Semin Surg Oncol* 1997;13:438-43.
23. D'Amico A, Coleman C. Role of interstitial radiotherapy in the management of clinically organ-confined prostate cancer: the jury is still out. *J Clin Oncol* 1996;14:304-15.
24. Wallner K, Roy J, Harrison L. Tumor control and morbidity following transperineal iodine 125 implantation for stage T1/T2 prostatic carcinoma. *J Clin Oncol* 1996;14:449-53.
25. Stock R, Stone N, Iannuzzi C. Sexual potency following interactive ultrasound-guided brachytherapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 1996;35:267-72.
26. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280:969-74.
27. Bagshaw M, Cox R, Ray G. Status of radiation treatment of prostatic cancer at Stanford University. *J Natl Cancer Inst Monogr* 1988;7:47-51.
28. Beard C, Propert K, Reiker P, Clark J, Kaplan I, Kantoff P, et al. Complications after treatment with external beam irradiation in early-stage prostate cancer patients: a prospective multiinstitutional outcomes study. *J Clin Oncol* 1997;15:223-30.
29. Perez C, Brady L, editors. *Principles and practice of radiation oncology*. 2nd ed. Philadelphia: JB Lippincott; 1992. p. 51-5.
30. Shipley W, Zietman A, Hanks G, Coen J, Caplan R, Won M, et al. Treatment related sequelae following external beam radiation for prostate cancer: a review with an update in patients with stages T1 and T2 tumor. *J Urol* 1994;152:1799-805.
31. Perez C, Lee H, Anastasios G, Lockett M. Technical factors affecting morbidity in definitive irradiation for localized carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 1994;28:811-8.
32. Benk V, Adams J, Shipley W, Urie M, McManus P, Efird J, et al. Late rectal bleeding following combined x–ray and proton high dose irradiation for stages T3–T4 prostate cancer. *Int J Radiat Oncol Biol Phys* 1993;26:551-7.
33. Middleton R, Thompson I, Austenfeld M, Cooner W, Correa R, Gibbons R, et al. Prostate Cancer Clinical Guidelines Panel summary report on the management of clinically localized prostate cancer. *J Urol* 1995;154:2144-8.

Reprint requests to: *Dr. Padraig Warde, Department of Radiation Oncology, Princess Margaret Hospital, 610 University Ave., Toronto ON M5G 2M9; fax 416 946-4586; padraig_warde@pmh.toronto.on.ca*

The following organizations are members of the Prostate Cancer Alliance of Canada: Canadian Association for Nurses in Oncology, Canadian Association of Radiation Oncologists, Canadian Cancer Society (National), Canadian Prostate Cancer Network, Canadian Prostate Cancer Research Foundation, Canadian Urology Association, Canadian Uro-Oncology Group and National Cancer Institute of Canada.