CME

# What's a man to do?

## *Treatment options for localized prostate cancer*

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**ABSTRACT**

**OBJECTIVE** To describe treatments for localized prostate cancer: surgery, external radiation therapy, and brachytherapy; watchful waiting might also be appropriate. Patients trying to decide about treatment ask family physicians for advice. This article sets out a framework to aid patients (and physicians) in the decision.

**QUALITY OF EVIDENCE** Only two randomized studies comparing different treatments were identified. Because of the paucity of level I or II evidence, suggestions in this review are largely based on expert opinion and consensus statements.

**MAIN MESSAGE** Risk-grouping and nomograms are useful for assessing treatments and estimating outcomes of treatment. Where treatments are equivalent, decisions can be based on perception of toxicity and convenience. Effects on patients' lives and on sexual, urinary, and bowel function vary by treatment modality.

**CONCLUSION** Men with low-risk prostate cancer should decide on treatment based on their perception of how treatment will affect their lives. Men with higher-risk cancers might accept adverse effects on their quality of life in return for longer survival.

**RÉSUMÉ**

**OBJECTIF** Décrire les différents traitements du cancer prostatique localisé: chirurgie, radiothérapie externe et brachythérapie; dans certains cas, une simple surveillance pourrait suffire. Les patients consultent leur médecin de famille sur le choix du traitement. Cet article propose une stratégie susceptible d'aider le patient (et le médecin) dans cette décision.

**QUALITÉ DES PREUVES** Seulement deux études randomisées comparant différents traitements ont été repérées. Vu le très petit nombre de preuves de niveaux I et II, les suggestions proposées ici reposent surtout sur l'opinion d'experts et sur des déclarations consensuelles.

**PRINCIPAL MESSAGE** L'utilisation de nomogrammes et le regroupement des patients par niveau de risque facilitent l'évaluation des différents traitements et de leurs résultats éventuels. Devant des traitements équivalents, le patient choisira selon son niveau de tolérance aux effets toxiques ou des raisons de commodité. Les effets sur la vie du patient et sur ses fonctions sexuelles, urinaires et intestinales varient selon les traitements.

**CONCLUSION** Dans les cancers prostatiques peu sévères, les effets escomptés du traitement sur la vie du patient devraient diriger le choix. Dans les cancers plus sévères, le patient pourrait accepter une baisse de sa qualité de vie en retour d'une survie prolongée.

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Many men with localized prostate cancer face a difficult choice between several equally effective, but very different, treatments or perhaps no treatment at all. Treatments can lead to urinary incontinence, sexual impotence, and other unwanted side effects. Family physicians can consult a urologist or oncologist for advice before patients embark on treatment. This review sets out a framework for decision making and describes recent advances in radiotherapy. It does not explore decision making per se, nor does it review surgical options in detail.

The correct treatment depends on which treatment is appropriate for the stage and grade of cancer, which treatment gives the best control, and which treatment has the fewest adverse effects and is least toxic. Each patient will rank the importance of these factors differently, and many men these days choose to take an active part in making the decision.[1]

## Quality of evidence

MEDLINE was searched for articles published during the last 7 years using the headings "exp.prostate neoplasms," "radiotherapy.tw," "prostatectomy.tw," "watchful waiting.tw," and "brachytherapy.tw." Of 3987 articles found, 140 reported randomized trials; only two described a direct comparison between treatments. Because of the paucity of level I and II evidence, suggestions in this review are largely based on expert opinion and statements of consensus groups.

## Risk grouping

In 2000, the Canadian Genitourinary Radiation Group agreed on a standard definition of risk grouping and guidelines for radiation therapy for prostate cancer.[2] The guidelines, which have since been adopted by the wider urology community,[3] are based on T stage,[4] initial prostate-specific antigen (PSA) level, and Gleason score.

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The T stage varies from T1 (impalpable tumour detected from biopsy or transurethral resection only) through T2 (palpable nodule confined to less than half a lobe [T2a], more than half a lobe [T2b], or both lobes [T2c]) to extracapsular extension (T3a) or seminal vesicle involvement (T3b). More advanced cancers (T4) (involving adjacent structures, or metastatic) are outside the scope of this review.

Gleason score is a numeric score assigned by a pathologist to describe the major and minor forms of histologic differentiation. It is quoted as two scores, each out of 5, totaling 10 (eg, 3 + 4 = 7/10). **Table 1** outlines risk groups and treatments suitable for each group.

**Table 1. Potentially suitable treatments (not ranked) for localized prostate cancer stratified by risk group:** *Treatment options in parentheses would be infrequently used.*

| RISK LEVEL | RISK FACTORS | | | RECOMMENDED TREATMENTS |
|---|---|---|---|---|
| | STAGE | GLEASON SCORE | PSA LEVEL | |
| Low: all risk factors at these levels or below | ≤T2a | 2–6 | ≤10 | Watchful waiting<br>Radical prostatectomy<br>Brachytherapy implant<br>External RT |
| Intermediate: all risk factors at these levels if patient is not low risk | T2b–T2c | ≤7 | >10–≤20 | External RT<br>Radical prostatectomy<br>(Brachytherapy implant and hormones)<br>(Watchful waiting) |
| High: any risk factors at these levels | ≥T3a | ≥8 | >20 | Hormones and external RT<br>Hormones and prostatectomy<br>Hormones only |

*PSA—prostate-specific antigen, RT—radiation therapy.*

## Outcomes of treatment

A randomized trial of watchful waiting versus radical prostatectomy published in 2002[5] followed 695 men with localized (generally low- to intermediate-risk) prostate cancer diagnosed in Scandinavia before PSA screening was in use. After a median of 6.2 years' follow up, development of metastatic disease was 17% in the watchful waiting arm and 11% in the treatment arm. Overall survival of the

two groups at 6.2 years was similar (87.3% and 89%). Whether a significant difference in survival will emerge with longer follow up is uncertain.

In a parallel report,[6] no overall difference in quality of life was seen in the two groups. There were differences in erectile dysfunction and urinary leakage (both worse in the surgery arm) and urinary obstruction (worse in the watchful waiting arm). Canadian practice differs from Scandinavian in that tumours diagnosed here are at an earlier stage (due to physician awareness and PSA screening). Results might not, therefore, be applicable to our practices because earlier diagnosis would give an additional 5 to 6 years' lead time and thus reduce any improvement in mortality that might otherwise appear after more extended follow up.

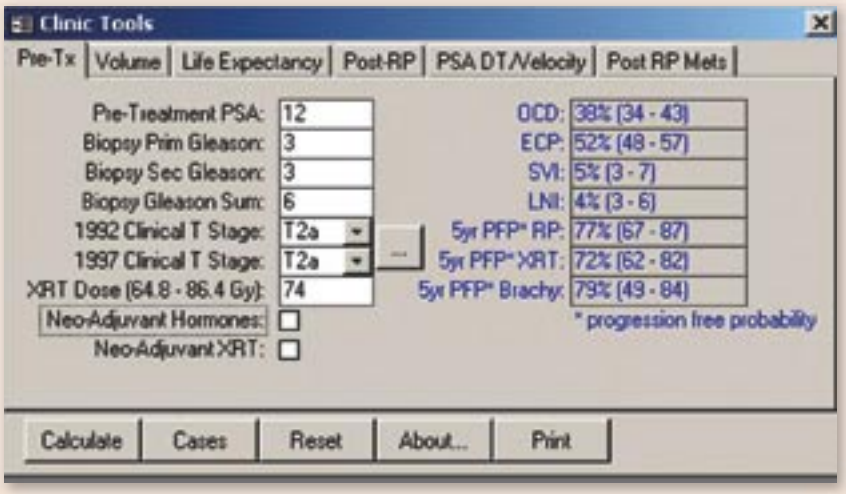
The second randomized study compared surgery and radiation therapy, both combined with androgen deprivation.[7] It reported worse outcomes with radiation therapy than surgery. The study has been criticized for taking more than 4 years to accrue just 100 patients from six institutions in Japan. Slow accrual, low patient numbers, and the relative scarcity of prostate cancer in Japan raise questions regarding treating physicians' experience and patient selection. Results are, therefore, probably unreliable.

Other trials of surgery, radiation, or watchful waiting have not accrued enough patients and have been closed prematurely without reporting results. A new study, SPIRIT,[8] just begun in North America, is a randomized comparison of radical prostatectomy and brachytherapy in 1980 men with low-risk cancer. Results are not expected until at least 2010.

With few good-quality randomized studies comparing treatments, evidence of benefit must be drawn from elsewhere. Single-institution reports are particularly prone to bias, which can be minimized by using nomograms. Nomograms are based on results from several thousand patients, typically from several series. To date, there are at least 42 nomograms, of which 17 have been validated.[9] A comparison between clinicians and 22 nomograms showed that nomograms predicted outcome better than clinicians in 13 cases. "Modification" of a nomogram's output by a urologist worsened its predictive ability.[10]

The most widely used nomogram is the Prostogram.[11] It is freely available at **www.nomograms.org.** Typical output from this nomogram is shown in **Figure 1**

**Figure 1. Output from Prostogram nomogram for a patient with typical presenting features:** *This patient has a palpable nodule confined to one lobe (T2a), a PSA score of 12, and a Gleason score of 3+3 = 6. Left-hand columns are the input of prognostic factors; right-hand columns are the output from the nomogram.*




*5yr PFP RP (XRT) and (Brachy)—percentage of men with no evidence of recurrent cancer as defined by rising PSA level after 5 years with each of radical prostatectomy, external radiation therapy, and brachytherapy (with confidence intervals); ECP—chance that patient would have extracapsular extension of tumour; LNI—chance that patient would have lymph node involvement; OCD—chance that patient would have organ-confined disease; SVI—chance that patient would have seminal vesicle involvement.*

and can be used to indicate the likely relative success of treatments. A criticism of the Prostogram is that it does not model the effect of adjuvant hormone therapy, which substantially improves outcomes with higher-risk tumours.

Toxicity is also important to most men, some of whom choose quality rather than quantity of life.[12] When assessing toxicity, it is important to go by patients' assessments rather than physicians' assessments, which would give erroneous results.[13]

## Watchful waiting

For men with limited life expectancy (eg, less than 10 years) or with particularly small or low-grade cancers, watchful waiting might be appropriate. Watchful waiting implies ongoing follow up and reevaluation for subsequent treatment should the disease progress; it is probably better called "delayed intervention." Several studies of the natural history of untreated prostate cancer have been published; the one by Albertsen et al is probably the best.[14] It shows that a 70- to 75-year-old man with Gleason score 5 prostate cancer untreated until metastasis has an 8% risk of dying of prostate cancer within 10 years, compared with an overall mortality risk of 80%. Men with higher Gleason scores have a much higher risk of dying of prostate cancer; most trials show that Gleason score is the most important prognostic factor for death. A Canadian study of the feasibility of watchful waiting[15] has shown that more than half the men ended up being treated within 4 years. Those with Gleason 7 cancers were more likely to require intervention than those with lower-grade tumours (23% vs 16%). Men with faster-rising PSA levels are also more likely to be treated than those with slow PSA doubling times.[16] In general, watchful waiting is reserved for those with low-risk prostate cancers and shorter life expectancy.

## Surgery

Radical prostatectomy is regarded as the criterion standard of treatment. Retropubic prostatectomy typically takes 2 to 3 hours to perform and requires 3 to 5 days in hospital. Because surgeons have been more selective in choosing elderly patients for surgery and because surgical technique has advanced, hospital stays are now shorter, and fewer men end up incontinent.[17] Perineal prostatectomy is used less often than retropubic prostatectomy, due to concern about total tumour clearance with bulkier tumours, but it does promise shorter hospital stays.[18]

Recent developments include nerve-sparing surgery. With early-stage tumours, surgeons attempt to leave the bundle of nerves that runs alongside the prostate intact. They usually attempt to do this only on the side of the prostate with negative biopsy results. In experienced hands, this surgery can reduce risk of impotence from about 75% to about 40%.

Laparoscopic surgery is being introduced gradually. The main benefit is that hospital stays could be reduced to 2 days, and recovery is faster. This technique is difficult to master, however, and takes a relatively long time to learn. Operating times for physicians new to the procedure can be long. Patients considering surgery should ask to be referred to a busy surgeon who performs at least 30 radical prostatectomies a year, as there is emerging evidence that complications of surgery are related to surgeons' experience.[19,20]

## Advances in external beam radiation

External beam radiation therapy (EBRT) is a mainstay of treatment for most men, comprising about 50% of all "curative" treatment options.[21] Many men are too elderly or have too-advanced cancers to have surgery; others choose radiation on the basis of reduced toxicity and equivalent outcomes.

The technique of EBRT has changed considerably in the last decade with the introduction of computed tomographic planning and then true three-dimensional physics planning. Intensity-modulated radiation therapy, a new type of conformal radiation therapy, is being evaluated. Technical changes have led to decreased toxicity[22] and promise improved tumour control if radiation doses are increased.[23] Using PSA levels to detect occult cancer after therapy has also changed our understanding of the effectiveness of competing treatments, of how to identify high-risk men who will do poorly

with standard therapy, and of who could benefit from new approaches.

Although no good-quality randomized studies have compared external radiation with surgery, single-institution comparisons have shown no difference.[24] In theory, EBRT might be expected to provide greater tumour control when a high risk of microscopic tumour extension beyond the prostate exists (intermediate- and high-risk cancers) because radiation can safely be given to the pelvic lymph nodes and periprostatic region to sterilize tumour microdeposits. A synergistic benefit of hormones with radiation (but not with surgery) has been demonstrated.[25] No additional benefit of radiation over surgery would be expected where risk of microscopic extraprostatic extension is small (low-risk cancers).

Several randomized studies[26-29] have shown that high-risk patients benefit from adjuvant (during and after radiation) and neoadjuvant (before radiation) hormone therapy (**Table 1**). These patients now routinely have 2 to 3 years of hormone therapy in conjunction with radiation, and some intermediate-risk patients are also offered hormones. Typically, hormones are used for 3 to 6 months before treatment and for 6 to 36 months after treatment. Exact duration depends on risk versus toxicity of prolonged hormone therapy and potential benefit. All patients should be assessed by a radiation oncologist before initiation of hormone therapy because use will change clinical assessment and thus affect radiation planning.

The EBRT technique starts with a computed tomography scan to outline the prostate and adjacent structures. A radiation oncologist works with a physicist for the next several days to formulate a treatment plan that will conform the radiation closely to the prostate with a margin of 0.5 to 1.5 cm at the circumference. Some high-risk patients will receive part of the treatment to the pelvic lymph nodes; during 6 to 8 weeks, most will receive a total of 66 to 76 Gy in 33 to 38 daily treatments to the prostate (and possibly the seminal vesicle). All treatments are given on an outpatient basis.

Acute toxicity is generally minimal; malaise is common, as are irritative urinary tract and bowel side effects. Typically, men require a steroid-based anorectal preparation or suppositories for 1 to 2 weeks for radiation proctitis. Also common is nocturia and urinary frequency, which can be treated with α-blockers. Incidence of more severe toxicity is <4%. Most men can return to work 1 to 2 weeks after completion of treatment; some motivated men continue working throughout therapy.

Incidence of severe late toxicity is <5%; serious late side effects occur in 1% of treated men. Impotence is common: about 50% of those potent before treatment will retain potency. Use of adjuvant hormones does not appear to affect the long-term preservation of potency. Incontinence is very unusual (<1%). Minor changes in bowel function, including urgency, are relatively common (30%); fecal soiling and incontinence are rare. The main toxicities of treatment are shown in **Table 2.**[30-32]

**Table 2. Summary of toxicity by treatment modality:** *Responses from patient questionnaires 2 to 5 years after treatment.*

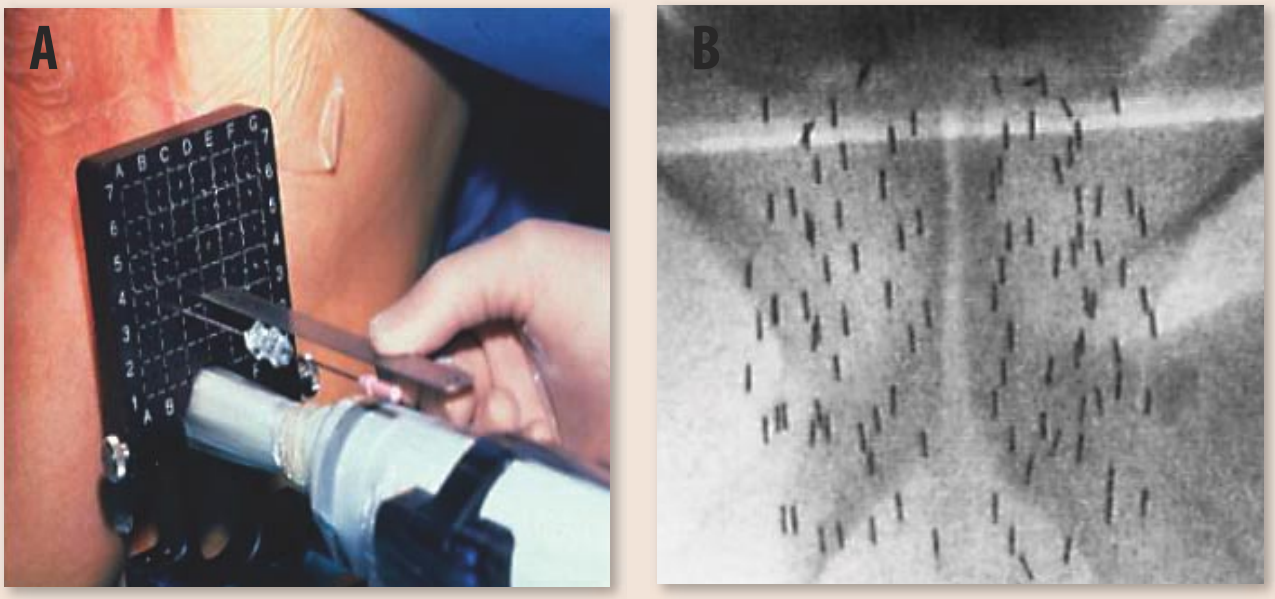
| TOXICITY | PROSTATECTOMY (%) | EXTERNAL BEAM RADIATION THERAPY (%) | BRACHYTHERAPY |
|---|---|---|---|
| **Incontinence** | | | |
| • Frequent drip or leak | 10 | 4 | 10 |
| • Wears pads | 28 | 3 | 18 |
| • Bothered by it | 11 | 2 | NA |
| **Diarrhea** | | | |
| • Any | 21 | 37 | 6 |
| • Perianal wetness | 14 | 22 | <1 |
| • Bothered by it | 3 | 8 | NA |
| **Impotence** | | | |
| • Insufficient for sex | 80 | 61 | 68 |
| • Bothered by it (<60 y) | 59 | 25 | NA |
| • Bothered by it (>60 y) | 53 | 46 | NA |
| **Overall quality of life measure (% of baseline)** | | | |
| • 1 mo after treatment | 85 | 94 | 87 |
| • 1 y after treatment | 101 | 100 | 100 |

*Data from Lee et al,[30] Potosky et al,[31] and Talcott et al.[32]*

## Brachytherapy

The term brachytherapy refers to placement of radioactive sources inside or adjacent to cancerous tumours. Brachytherapy is widely used to treat various types of cancer and predates

**Figure 2. Brachytherapy:** *A) Needle placement is according to predetermined plan aided by a template mounted to a stepping device that also holds a transrectal ultrasound probe. Each of about 25 needles contains 4 to 6 iodine-125 seeds; B) Fluoroscopic x-ray film showing seed location in the prostate, taken at completion of procedure. Note central urethral sparing.*




the more commonly used EBRT by several decades. Brachytherapy for prostate cancer has acquired broad acceptance in the United States during the last few years following development of real-time transrectal ultrasound (TRUS) guidance to accurately position the radioactive "seeds." The procedure, known as "TPIP" (transperineal implantation of the prostate), allows safe delivery of about a 25% higher dose of radiation than is possible with EBRT. Currently, one in four men having curative treatment in British Columbia undergo brachytherapy.[21] That number is expected to increase. In the United States, brachytherapy is now used as often as radical prostatectomy.

Patients currently selected for brachytherapy have earlier-stage tumours (selection criteria are similar to those for choosing operable candidates): cancer should be organ-confined (T1-2) and of low-to-moderate Gleason grade (<7/10), and PSA level should be ≤10.[33] In some provinces, selected patients with low- to intermediate-grade prostate cancer (PSA 10 to 15, Gleason score 7 or lower) are accepted for brachytherapy, but only in combination with hormone therapy or external radiation. Those who have previously had transurethral resection of the prostate are generally unsuitable due to high risk of urinary incontinence subsequent to implant. Large prostate glands (>60 mL) are more difficult to implant and can be treated only if volume can be reduced below 60 mL with neoadjuvant hormone therapy.

A radiation oncologist checks initial eligibility and counsels patients. Patients then have TRUS to assess prostate size and geometry. Then patient and oncologist decide whether to proceed; the procedure follows a few weeks later. During the interval, complex dosimetric planning takes place to determine the exact number and configuration of seeds to be deposited in the prostate.

With patients under anesthetic (usually general), 80 to 120 iodine-125 seeds are inserted with the help of a rigid perineal template and real-time TRUS (**Figure 2**). The procedure lasts about 1 hour, and all men are discharged home at the end of the day when they have successfully voided. The seeds are permanent and gradually lose their radioactivity (half-life of 2 months).

The procedure is extremely well tolerated acutely; side effects are limited to anesthetic

effects and surprisingly minor local perineal bruising. During the first few weeks, however, the prostate gland gradually swells and there are acute radiation effects on the urethra that cause frequency and nocturia that can be severe (two thirds of men require medication, and a further 20% have more marked urinary toxicity). About 7% require temporary use of a urinary catheter, usually for only a few days. Most men return to near-baseline urinary function by 3 months; about 10% continue to have severe symptoms after 6 months; and about 5% still have symptoms at 1 year. Some men continue to have ongoing irritative or obstructive urinary symptoms and require use of α-blockers long term.

Transurethral resection of the prostate is used only in exceptional circumstances because it carries a high risk of incontinence after brachytherapy. Unlike EBRT, it has very few side effects on the bowel. About 50% of men potent before the procedure retain potency; risk of urinary incontinence is <2%. Men at particular risk of acute (and probably long-term) urinary toxicity include those with high initial urinary symptom scores, large glands, and diabetes.[34] Radiation protection is an issue only where very close proximity occurs (eg, children should not sit on patients' laps for prolonged periods during the first 3 months). In fact, radiation received by close contact is no greater than normal background radiation.

Brachytherapy appears at least as effective at controlling early-stage low-grade tumours as surgery,[35] is less toxic, and has similar effects on patients' lives.[30] Risk of long-term toxicity and of radiation-induced cancers is unknown, as are the very long-term (>13 years) effects of brachytherapy. It is sensible to be cautious in treating very young men (<50 years) with this technique. Should brachytherapy fail, salvage options are limited because of localized fibrosis.

## Conclusion

For men with low-risk prostate cancer, the choice between surgery and either form of radiation therapy will largely depend on how they think treatment will affect their lives, because tumour control rates are equivalent. Most patients are satisfied with their treatment decisions (81% choosing surgery, 90% choosing radiation).[34] Patients with high-risk prostate cancer have been shown to benefit from a multimodality approach in which hormone therapy is given in addition to EBRT.

**EDITOR'S KEY POINTS**

- Choosing a treatment for prostate cancer should take into account stage and grade of cancer, control rate, and the effect on quality of life. For localized cancer, treatments have similar efficacy: decisions depend more on effect on quality of life.
- For localized cancer, watchful waiting with regular follow up could be appropriate for men older than 75 or with other serious health problems.
- Surgery has been the criterion standard of cure but is complicated by more frequently leading to incontinence and sexual dysfunction. In early cancers, nerve-sparing surgery reduces complications.
- External-beam radiation therapy is the most commonly chosen treatment (50%); it has been improved by computed tomography mapping to reduce side effects. Adjuvant hormone therapy is usually given to high-risk patients.
- Brachytherapy, a refinement of radiation, uses accurately implanted radioactive rods; implantation is guided by ultrasound. Brachytherapy gives a greater local dose of radiation and has fewer side effects.

**POINTS DE REPÈRE DU RÉDACTEUR**

- Dans le cancer de la prostate, le choix du traitement devrait tenir compte du stade et du grade de la tumeur, du degré de contrôle attendu du traitement et des effets sur la qualité de vie. Dans les cancers localisés, tous les traitements ont une efficacité équivalente et la décision dépend davantage des effets sur la qualité de vie.
- Dans les cancers localisés, une simple surveillance avec suivi régulier pourrait suffire pour ceux de plus de 75 ans ou qui ont d'autres problèmes de santé importants.
- La chirurgie constituait la norme de référence en termes de guérison, mais elle entraîne souvent des complications d'incontinence et de dysfonction sexuelle. Dans les cancers débutants, on obtient moins de complications avec une chirurgie qui évite les lésions nerveuses.
- Le traitement le plus utilisé est la radiothérapie externe (50%); la cartographie par tomographie assistée par ordinateur a permis d'améliorer ce traitement et d'en diminuer les effets indésirables. Pour les patients à haut risque, on ajoute habituellement une hormonothérapie d'appoint.
- Dans la brachythérapie, un perfectionnement de la radiothérapie, des aiguilles radioactives sont implantées à des sites précis sous contrôle ultrasonique. Ce traitement permet d'administrer une plus forte dose localement avec moins d'effets indésirables.

Choosing the correct treatment requires assessment by a urologist and radiation oncologist who has the required expertise and input and guidance from patients' family physicians.

## Competing interests

*None declared*

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