Clinical basics

# Prostate cancer: 10. Palliative care

**Neill A. Iscoe, MD; Eduardo Bruera, MD; Richard C. Choo, MD**

*Education*

*Éducation*

**Dr. Iscoe is Medical Oncologist, Toronto-Sunnybrook Regional Cancer Centre, and Adjunct Scientist, Institute for Clinical Evaluative Sciences, and is also affiliated with the Program in Clinical Epidemiology and Health Services Research, Sunnybrook and Women's College Health Sciences Centre Unit, University of Toronto, Toronto, Ont. Dr. Bruera is Professor of Oncology, Alberta Cancer Foundation in Palliative Medicine, University of Alberta, and Grey Nuns Community Hospital, Edmonton, Alta. Dr. Choo is Radiation Oncologist, Toronto-Sunnybrook Regional Cancer Centre and Department of Radiation Oncology, University of Toronto, Toronto, Ont.**

**The case**

A 72-year-old man with no significant illnesses apart from his prostate cancer visits his urologist for follow-up. His prostate cancer was diagnosed 6 years earlier and was treated with radical local therapy. He was well for 3 years, then experienced relapse with bone metastases and pain. Treatment consisted of bilateral orchidectomy, and his symptoms were controlled for 24 months. As the disease progressed, anti-androgen therapy was started. However, over the past 6 months, the symptoms and level of disease, as indicated by prostate-specific antigen, have been increasing, despite withdrawal of the anti-androgen, spot irradiation and a regimen of cytotoxic chemotherapy. The patient is aware that he cannot be cured but wants to ask his physician about complementary therapies, such as green tea and Essiac, and he wants to know what more can be done for him.

The issues raised by the patient described in the case are understandable and altogether too common. He is aware that his prostate cancer cannot be cured with currently available treatments and is asking for care that will relieve his discomfort while he explores other, less conventional, forms of treatment. In this article we provide an overview of complementary therapies (sometimes called unconventional or alternative therapies) and describe the current role of radiation therapy and palliative care in relation to the problems commonly encountered by men with progressive prostate cancer.

## Complementary therapy

This particular patient has asked about green tea and Essiac, although he could have easily asked questions related to mind–body therapies, various diets or nutritional supplements, therapies that purport to augment the immune system and a host of other manoeuvres. The range of interventions is further confused by the terms used to describe them: unconventional, unorthodox, unproven, alternative and complementary. Although an Office of Technology Assessment report[1] to the United States Congress referred to these therapies as "unconventional," most proponents prefer the term "complementary," because they are often (although not uniformly) used to complement standard medical care.

What physicians must realize is that this approach to care is exceedingly common. Although no accurate Canadian data are available, recent figures from the United States suggest that expenditures on these interventions increased substantially between 1990 and 1997 and that patients there now spend in excess of $21 billion annually on unconventional therapies for all disorders.[2] Patients seek complementary therapies for many reasons, including their need to assert some control over their situation, their belief system (which may differ from the physician's) and their need to examine their lives in

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.

*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* 1999;160:365-71

See related article page 351



© 1999 Canadian Medical Association

the context of a life-threatening illness. Although the reasons why a patient seeks complementary therapies are of immense importance in understanding the patient's needs, they are not the subject of this chapter.

No one can dismiss a patient's desire to try anything that might provide greater disease control and comfort. Given the myriad of options from which patients may choose and the potential for unscrupulous people to take advantage of vulnerable patients, how is a practitioner to guide the patient in making an informed choice, if that is what he is determined to do?

These therapies may be promoted by physicians who have graduated from reputable medical schools as well as those with no such training. Although this may be a cause for concern, the common feature of these therapies is that they have not been assessed by standard investigative methods. For some, such as homeopathic therapy, in which a noxious substance is administered in infinitely small dilutions, the underlying premise of the therapy defies the standard laws of physics. For others, the premise is either outside the accepted notions of biology or based on ideas that cannot be tested. Some therapies are based on a product whose composition is known only to its manufacturer and which has not been subjected to any inquiry into its physical or chemical nature.

How then does one advise desperate patients about the likelihood of a given intervention doing more harm than good? Although randomized controlled trials (RCTs), ideally of a double-blind nature, are the "gold standard" of assessment, the profession must acknowledge that many frequently used *conventional* therapies have not been subjected to this standard. Therefore, the presence or absence of an RCT should not be the sole criterion on which a decision is based. It may be useful to examine both the criteria for evaluating an intervention and those for attributing causation (i.e., the likelihood that exposure to a particular event will produce a given outcome) (Table 1).[3,4] Explaining these criteria to patients or their families in simple terms will probably give them the tools they need to make their own assessments. The essence of these recommendations is that patients should behave like consumers in this domain and should request from the prospective practitioner documentation that has been subjected to external scrutiny in support of the therapy in question.

For example, let us examine the situation in which a patient asks about second-line cytotoxic chemotherapy for prostate cancer and the use of a hypothetical unconventional therapy called etatsorp. Second-line cytotoxic chemotherapy has not been assessed in the treatment of prostate cancer, but it has been evaluated for other malignant diseases, for which defined response patterns and toxicity profiles are reported. Those promoting etatsorp claim that it relieves pain and controls the cancer by enhancing the immune system. The claimants suggest that these effects occur in all cancers to some extent, but that this agent is particularly effective in prostate cancer. The proponents argue that etatsorp is most useful when the burden of disease is small and, therefore, that patients should use it as soon as possible after diagnosis. Although personal testimonials are offered, there is no standard medical documentation of these cases.

With reference to the criteria in Table 1, it is apparent that neither cytotoxic chemotherapy nor etatsorp has been subjected to trials assessing their activity in the management of patients with prostate cancer; similarly, there have been no RCTs to compare their effectiveness with that of other therapies or best supportive care. RCTs of the cytotoxic agent are foreseeable, and claims that RCTs for complementary therapies are impossible — because each patient is unique — are invalid.[5] Therefore, the patient's decision about using these methods must be based on inference and beliefs rather than on evidence.

In this example the criteria related to causation are most helpful in decision-making. Is there a biological rationale for the therapy, and are there analogous situations in which the agent has been objectively evaluated and its activity or efficacy documented? In the case of standard chemotherapy there is a biological basis for believing that the therapy has the *potential* to produce a response. However, second-line chemotherapy invariably has less activity against malignant disease than first-line therapy, and first-line chemotherapy in prostate cancer has limited activity. Therefore, although there may be a biological basis supporting this therapy, in reality there should be little optimism that it will be effective for patients with prostate cancer.

In the hypothetical example, etatsorp is purported to

**Table 1: Criteria for evaluating reports of an intervention and attributing causation***

| |
|---|
| **Evaluating reports of an intervention** |
| Were subjects assigned randomly to receive the intervention? |
| Were all clinically important outcomes reported? |
| Were the study patients similar to your own? |
| Were both clinical and statistical significance considered? |
| Is the intervention feasible in your practice? |
| Were all patients accounted for at the end of the study? |
| **Attributing causation** |
| Is there a true experiment in humans? |
| Is the association strong? |
| Is the association consistent between studies of the same question? |
| Is the temporal relationship correct? |
| Is there a dose–response relationship? |
| Is the association epidemiologically sensible? |
| Does the association make sense biologically? |
| Is the association specific? |
| Is the association analogous to a previously proven causal association? |

*Adapted from *CMAJ* with permission.[3,4]

be an enhancer of the immune system. The extent to which this statement is supported by documented objective and, perhaps, reproducible in-vivo or in-vitro evidence is critical in determining its potential merit. It must also be determined whether an objective benefit has been noted in clinical situations sufficiently analogous to our patient's to provide a foundation for considering the treatment. Unfortunately, because most complementary therapies are developed outside the usual investigational models, the background information to support or refute the premise is seldom available. Perhaps more distressing is the same dearth of information at the clinical level.

As physicians, we should warn this man that complementary therapies can be expensive, that imported compounds may not be produced under safe and acceptable conditions, and that other countries may not require labelling even though the compounds contain powerful agents.

Therefore, the advice to this patient should be that the only reason to pursue either cytotoxic therapy or etatsorp therapy is a *belief* that the treatment will work, since there is no evidence in favour of the use of either. Whatever transpires, the physician should continue to provide support and comfort to the patient and his family through this difficult time.

## Palliative radiotherapy

Radiotherapy has been a mainstay in the palliation of symptomatic metastatic prostate cancer and is most often used for palliation of painful metastatic bone lesions. Other medical problems amenable to palliative radiotherapy include compression of the spinal cord or a nerve root, hematuria, ureteric obstruction, and perineal discomfort caused by the local progression of prostate cancer and symptomatic metastatic lymphadenopathy.

### *Skeletal metastatic lesions*

The most common symptom in metastatic prostate cancer is pain from bone lesions, particularly in the spine and pelvis. Palliative radiotherapy is usually indicated unless pain is relieved by well-tolerated analgesics. In general, 80% to 90% of patients obtain some degree of pain relief from palliative radiotherapy. In addition to pain relief, the goals of this treatment include elimination or reduction of the need for narcotics and arrest of local tumour growth that might otherwise lead to compression of the spinal cord or pathologic fracture.

Palliative radiotherapy for bone metastases may consist of local-field radiotherapy, hemibody irradiation or use of systemic radionuclides. Local-field and hemibody treatments are delivered by external-beam irradiation, whereas systemic radionuclide therapy is given intravenously, by means of bone-seeking radioactive isotopes. Factors to be considered in the selection of the radiation modality and the extent of radiation therapy for an individual patient include estimated life expectancy, functional status, bone marrow function, extent and volume of metastatic bone lesions, number of symptomatic sites, presence of visceral metastasis and previous treatments.

#### Local-field radiotherapy

Patients with several metastatic bone lesions, only one

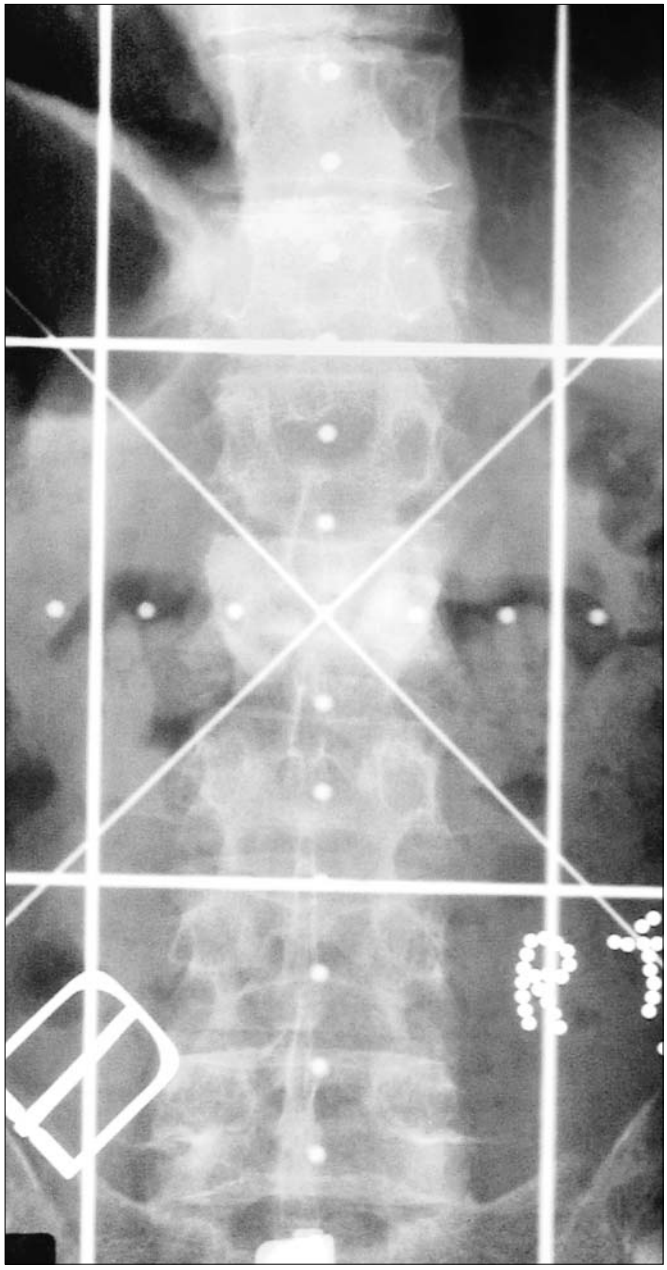

**Fig. 1: Simulation radiograph demonstrating local-field radiotherapy of the spine. The rectangular area delimited by the white lines represents the irradiated volume of tissue.**

or a few of which are symptomatic, can be effectively treated with local-field external-beam irradiation (Fig. 1). Pain flare may occur in some patients at the beginning of radiotherapy. This usually lasts 2–3 days and generally predicts a good palliative response. Pain relief usually begins 1–2 weeks after the start of therapy and invariably is present, if it occurs at all, within 1–3 months. Imaging studies that correlate with the signs and symptoms of bone metastasis aid in designing the radiation field. Local-field irradiation is generally well tolerated and has minimal acute toxic effects and negligible long-term adverse effects.

Several prospective randomized trials and retrospective studies have suggested that high-dose, protracted palliative radiotherapy delivered over a lengthy period of time has no consistent advantage over single-dose or low-dose short-course regimens.[6–11] For a debilitated patient with a short life expectancy, for whom daily trips for fractionated treatment would be burdensome, it is appropriate and expedient to give single-fraction irradiation. On the other hand, a more fractionated higher-dose regimen is generally used for patients with one or a few sites of metastasis who have good functional status and reasonable life expectancy.

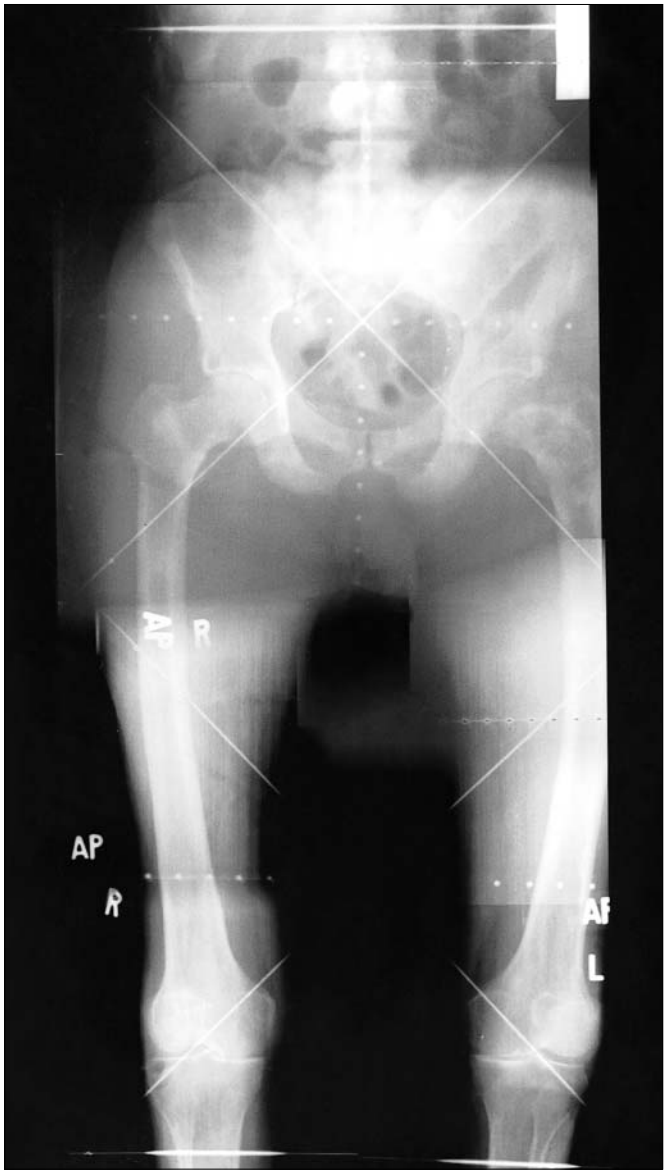


**Fig. 2: Simulation radiograph demonstrating hemibody irradiation to the lower half-body. In this case the area irradiated extends from about the waist to just below the knees.**

## Hemibody irradiation

Hemibody irradiation involves delivering radiation in single or multiple fractions to a large volume of tissue (Fig. 2). It has been used for patients with many painful metastatic bone lesions who have adequate bone marrow function, as an alternative to a series of local-field irradiation doses directed at specific painful sites. Its main purpose is to avoid repeated trips to the hospital for multiple courses of irradiation.

Improved pain control has been reported in up to 80% of patients treated with single-fraction irradiation to the upper or lower half-body.[12–14] Irradiation to the lower or mid-body is generally well tolerated if pretreatment medication is given to minimize nausea and vomiting. Upper half-body irradiation is generally associated with more severe side effects, which often necessitate a day in hospital, hydration, and premedication with antiemetics and corticosteroids.

## Systemic radionuclide therapy

Radioactive isotopes, administered intravenously, have been used to palliate pain from widespread metastatic bone lesions. Strontium-89 is the injectable, nonsealed radionuclide most commonly used for hormone-refractory metastatic prostate cancer. Although it is preferentially taken up and retained by sites of osteoblastic metastases, it is washed out of healthy bone, where its biological half-life is 14 days.[15,16] This differential distribution and retention of the nuclide results in preferential delivery of radiation to metastatic sites and therefore therapeutic gain.

On the basis of results from several RCTs,[16–19] strontium-89 is generally recommended for patients with many metastatic bone lesions associated with uncontrolled pain on both sides of the diaphragm, for whom the use of multiple single fields of external-beam radiotherapy is difficult and impractical. In one trial, lessening of pain was observed in 70% of the patients.[16] This agent has also been used in conjunction with local-field radiotherapy for patients with isolated painful metastatic lesions. In this clinical setting, it can delay, by up to 15 weeks, the need for further radiotherapy at new painful sites and can temporarily reduce the intake of analgesics.[19] However, the

clinical significance of these benefits is uncertain. Pain flare occurs in a small proportion of patients and generally lasts 2–4 days. Pain relief usually begins in 2–3 weeks, with maximal relief and nadir blood counts at 6 weeks.

The main side effect of strontium-89 is suppression of bone marrow function. Because a patient may already have a reduced reserve of bone marrow as a result of previous external-beam radiotherapy, myelosuppressive chemotherapy or tumour infiltration of the bone marrow, it is imperative to assess carefully the patient's eligibility for strontium-89 treatment. Systemic radionuclide therapy is not recommended for those with inadequate bone marrow reserves or inadequate renal function, nor for patients whose main symptomatic lesions show inadequate uptake on bone scanning. It is also contraindicated as the sole treatment in patients with fracture or impending fracture and compression of the spinal cord or a nerve root. As strontium-89 is a β emitter and is excreted in the urine, its use in men who are incontinent or who have indwelling catheters poses greater radiation safety concerns and is thus contraindicated.[20] Because strontium-89 must be used in the appropriate context and only after an evaluation of the patient's overall status, previous therapy and possible future treatments, an oncologist with expertise in the overall management of the prostate cancer should be involved in its use.

### *Compression of the spinal cord or a nerve root*

In cases of metastatic disease compromising the integrity of the spinal cord or a nerve root, urgent intervention is required to minimize neurological dysfunction. Pain is the most common presenting symptom and generally precedes neurological deficit. MRI of the spine or myelography with CT at the level where compression is suspected is essential to identify all levels of blockage.

Palliative radiotherapy, either alone or as an adjunct to surgical decompression, is usually indicated for managing compression of the spinal cord or a nerve root. Surgical decompression should be considered in patients with significant pathologic compression of vertebrae, instability of the spine, neurological deterioration during radiotherapy or compression at a previously irradiated site. A short course of fractionated radiotherapy is often effective for relieving pain and reversing neurological dysfunction. In a recent series of 50 patients treated with external-beam radiation, 67% had neurological improvement and 92% experienced pain relief.[21]

The primary determinant of neurological recovery after any form of therapy for spinal cord compression is neurological status and duration of neurological deficit before the intervention. Thus, prompt diagnosis, evaluation and treatment are essential to reverse any existing deficits and to preserve maximum function.

### *Other indications*

Palliative radiotherapy is effective in relieving symptoms secondary to the local progression of prostate cancer, such as hematuria, ureteric obstruction and perineal pain. It is also beneficial for patients with leg edema or back discomfort caused by metastatic pelvic or para-aortic lymphadenopathy. Similarly, any clinical symptoms related to tumour mass effect can be palliated with radiotherapy.

## Symptom control

The patient described at the outset of this article already has bone pain. Although this pain may be relieved by radiation therapy, seldom will such treatment control the symptoms of metastatic bone lesions until death. The management of pain and the control of other symptoms become paramount in caring for this man (Table 2).

### *Pain*

This patient has pain because of metastatic bone lesions. Continuous bone pain responds well to opioid analgesics. Most patients will experience good analgesia with a combination of acetaminophen plus codeine or oxycodone. After several weeks or months, this man will likely require stronger opioid agonists such as morphine or hydromorphone (drugs with similar effectiveness and toxicity).[22] The initiation of opioid analgesics represents a major hurdle for some patients, in terms of fears of addiction or uncontrolled pain and the symbolic message that their illness has become serious enough that such agents are necessary. Physicians should be aware of these concerns and address them directly. In particular they should reassure patients that addiction is not an issue and that adequate pain control can be achieved in most cases. Patients should always undergo titration to good pain control with short-acting opioids every 4 hours before being switched over to a maintenance dose of a slow-release opioid preparation. Slow-release preparations of mor-

**Table 2: Symptom control in prostate cancer**

| Symptom | Suggested therapy |
|---|---|
| Pain | Opioid analgesics (oral or subcutaneous)<br>Radiation therapy<br>Bisphosphonates |
| Gastrointestinal symptoms | Megestrol acetate<br>Corticosteroids<br>Metoclopramide<br>Laxatives |
| Delirium | Regular monitoring of cognition<br>Opioid rotation<br>Methadone<br>Haloperidol |

phine (once or twice a day), hydromorphone, codeine, oxycodone and fentanyl (transdermal patches every 3 days) are currently available in Canada. Patients receiving long- or short-acting opioids should have access to extra doses of approximately 10% of the total daily opioid dose for episodes of more severe pain.

Before death, about 80% of patients will require an alternative route of opioid administration for periods ranging from hours to months. The subcutaneous route allows patients to receive analgesia safely and effectively at home as intermittent injections into a butterfly needle every 4 hours from preloaded syringes or low-cost devices such as the Edmonton Injector.[23] A small proportion of patients may require a more expensive device for subcutaneous infusion of opioids.

As previously discussed, radiation therapy can relieve bone pain in 80% to 90% of patients and should be considered for all patients who experience pain in the long bones or for those with a single or predominant painful area.

Bisphosphonates can be administered as an intravenous infusion (pamidronate or clodronate) or as a subcutaneous infusion (clodronate) to decrease generalized bone pain and prevent osteolysis. An infusion every 3–4 weeks over 4 hours can reduce the need for opioid analgesics and radiation therapy and decrease the number of bone fractures.[24,25] The evidence for benefit from bisphosphonates is greater in breast cancer and melanoma. However, at least one study found significant improvement in prostate cancer.[24]

Approximately 20% of patients with metastatic bone lesions have minimal or no pain if they remain completely immobile but experience severe "incidental" pain when they move.[26] In this situation, pain control may be difficult, and patients should be referred to a palliative care or pain specialist.

## *Gastrointestinal symptoms*

The patient described at the beginning of this article will probably experience progressive severe anorexia. Numerous studies have shown that megestrol acetate can be used to treat anorexia, improve food intake, reduce fatigue and produce a sensation of well being. The effects become evident after a period of 1–2 weeks of treatment.[27] Because progestational drugs must be used at doses ranging from 3–5 times the antineoplastic dose (e.g., the dose of megestrol acetate would be 480–800 mg/d), these drugs can be quite expensive. Corticosteroids are also effective appetite stimulants. They are inexpensive and also have antinausea and analgesic effects. However, they do not lead to increased food intake or weight gain, and their effect is short lived (usually less than 4 weeks). The most effective type, dose and route of administration of corticosteroids have not been established. In summary, ambulatory patients with good performance status who complain of profound anorexia could be given a brief course of megestrol acetate. On the other hand, patients whose condition has deteriorated severely and who have severe pain and nausea might benefit from a course of oral or subcutaneous corticosteroids.

Chronic nausea is almost universal in patients with advanced prostate cancer. It results from a combination of autonomic failure with resulting gastroparesis due to advanced cancer, cachexia, opioid therapy, constipation and metabolic abnormalities. Short-acting metoclopramide (10–20 mg every 4 hours) or long-acting metoclopramide (every 12 hours) alone or in combination with corticosteroids and aggressive laxative therapy can be used to control this symptom in most patients.

Finally, constipation is a highly prevalent and underdiagnosed symptom capable of aggravating abdominal pain and causing anorexia, nausea and urinary retention in these patients. All patients with advanced prostate cancer should receive regular oral laxatives, and the frequency and type of bowel movements should be monitored regularly.

## *Delirium*

More than 85% of patients with prostate cancer will experience progressive confusion before death.[28] In these usually elderly patients, the delirium results from many factors. The most frequent reasons are opioid analgesics, psychoactive drugs, sepsis, dehydration, renal failure and other metabolic abnormalities. Brain metastases are rare in patients with prostate cancer.

Approximately a third of episodes of delirium are fully reversible with simple measures such as opioid rotation (a change in opioid type), hydration, antibiotic therapy or discontinuation of psychoactive drugs.[28]

Opioids should always be considered a potential contributing factor in delirium. This effect is mainly due to the accumulation of active opioid metabolite in patients receiving high doses or undergoing prolonged treatment and in those who have renal failure or dehydration of recent onset. Opioid-induced delirium is frequently associated with generalized myoclonus, agitation, hyperalgesia and tactile hallucinations.[29] Rotation to another opioid allows the active metabolites to be eliminated, usually within 48 hours. The opioid should be used at lower equianalgesic dose and titrated cautiously. Delirium has been observed with all opioid agonists, including morphine, hydromorphone, meperidine, codeine, oxycodone and fentanyl. In patients who present with rapid dose escalation or repeated episodes of opioid-induced delirium, rotation to methadone may be considered. This synthetic agonist has the advantages of extremely low cost and absence of active metabolites. However, the dose ratio be-

tween methadone and other opioids is not well known, and there is the potential for severe toxic effects. Therefore, rotation to methadone should be undertaken only by an experienced palliative care cancer or pain specialist.

Approximately a third of patients with delirium present with severe psychomotor agitation, hallucination or delusional thoughts. In these patients, haloperidol should be administered regularly, by oral or subcutaneous route, for 1 or 2 days while investigation or management of the delirium is implemented. In extreme cases sedation, by continuous subcutaneous infusion of midazolam, may be required.

## Conclusions

For the patient described in the case at the beginning of this article, there may not be a great deal that medicine can do to control his disease generally. This article has focused only on the medical management of selected problems encountered by men with prostate cancer and their families. Depending on individual circumstances, other physicians may be helpful in managing symptomatic problems, for example, orthopedic surgeons for skeletal problems. More important, physicians should not forget others, such as religious leaders, nutritionists, physiotherapists, psychologists and occupational therapists, who may provide valuable advice and comfort for patients. Finally, our experience is that most patients wish to remain at home for as long as possible. The integration of their care in community hospice and palliative care programs at the earliest opportunity will assist in achieving the seamless care desired and will mimimize the potential for the crisis situations that commonly occur when such aspects are not integrated into the patient's care. Much can be done to provide comfort for this man as his disease progresses over the ensuing months. The most important thing to remember is that care not only remains possible, but now assumes even greater importance in the absence of effective therapies that can be directed at his cancer.

## References


1. Office of Technology Assessment. *Unconventional cancer treatments*. Washington: United States Government Printing Office; 1990. Rep no OTA-H-405.
2. Eisenberg DM, Davis RB, Ettner SL, Appel S, Wilkey S, Van Rompay M, et al. Trends in alternative medicine use in the United States, 1990–1997. Results of a follow-up national survey. *JAMA* 1998;280:1569-75.
3. Department of Clinical Epidemiology and Biostatistics, McMaster University Health Sciences Centre. How to read clinical journals: IV. To determine etiology or causation. *CMAJ* 1981;124:985-90.
4. Department of Clinical Epidemiology and Biostatistics, McMaster University Health Sciences Centre. How to read clinical journals: V. To distinguish useful from useless or even harmful therapy. *CMAJ* 1981;124:1156-62.
5. Fontanarosa PB, Lundberg GD. Alternative medicine meets science [editorial]. *JAMA* 1998;280:1618-9.
6. Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol* 1989;1:59-62.
7. Madsen EL. Painful bone metastasis: efficacy of radiotherapy assessed by the patients: a randomized trial comparing 4 Gy × 6 versus 10 Gy × 2. *Int J Radiat Oncol Biol Phys* 1983;9:1775-9.
8. Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986;6:247-55.
9. Tong D, Gillick L, Hendrickson FR. The palliation of symptomatic osseous metastases: final results of the study by the Radiation Therapy Oncology Group. *Cancer* 1982;50:893-9.
10. Blitzer PH. Reanalysis of the RTOG study of the palliation of symptomatic osseous metastasis. *Cancer* 1985;55:1468-72.
11. Arcangeli G, Micheli A, Arcangeli G, Giannarelli D, La Pasta O, Tollis A, et al. The responsiveness of bone metastases to radiotherapy: the effect of site, histology and radiation dose on pain relief. *Radiother Oncol* 1989;14:95-101.
12. Fitzpatrick PJ, Rider WD. Half-body radiotherapy. *Int J Radiat Oncol Biol Phys* 1976;1:197-207.
13. Salazar OM, Rubin P, Hendrickson FR, Poulter C, Zagars G, Feldman MI, et al. Single-dose half-body irradiation for the palliation of multiple bone metastases from solid tumors: a preliminary report. *Int J Radiat Oncol Biol Phys* 1981;7:773-81.
14. Zelefsky MJ, Scher HI, Forman JD, Linares LA, Curley T, Fuks Z. Palliative hemiskeletal irradiation for widespread metastatic prostate cancer: a comparison of single dose and fractionated regimens. *Int J Radiat Oncol Biol Phys* 1989;17:1281-5.
15. Ben-Josef E, Lucas DR, Vasan S, Porter AT. Selective accumulation of strontium-89 in metastatic deposits in bone: radio-histological correlation. *Nucl Med Commun* 1995;16:457-63.
16. Quilty PM, Kirk D, Bolger JJ, Dearnaley DP, Lewington VJ, Mason MD, et al. A comparison of the palliative effects of strontium-89 and external beam radiotherapy in metastatic prostate cancer. *Radiother Oncol* 1994;31:33-40.
17. Lewington VJ, McEwan AJ, Ackery DM, Bayly RJ, Keeling DH, Macleod PM, et al. A prospective, randomized double-blind crossover study to examine the efficacy of strontium-89 in pain palliation in patients with advanced prostate cancer metastatic to bone. *Eur J Cancer* 1991;27:954-8.
18. Buchali K, Correns HJ, Schuerer M, Schnoor D, Lips H, Sydow K. Results of a double blind study of 89-strontium therapy of skeletal metastases of prostatic carcinoma. *Eur J Nucl Med* 1988;14:349-51.
19. Porter AT, McEwan AJ, Powe JE, Reid R, McGowan DG, Lukka H, et al. Results of a randomized phase-III trial to evaluate the efficacy of strontium-89 adjuvant to local field external beam irradiation in the management of endocrine resistant metastatic prostate cancer. *Int J Radiat Oncol Biol Phys* 1993;25:805-13.
20. Porter AT, Ben-Josef E. Strontium 89 in the treatment of bone metastases. In: DeVita VT, Helman S, Rosenberg SA, editors. *Important advances in oncology*. Philadelphia: JB Lippincott; 1995. p. 87-94.
21. Zelefsky JM, Scher HI, Krol G, Portenoy RK, Leibel SA, Fuks ZY. Spinal epidural tumor in patients with prostate cancer. *Cancer* 1992;70:2319-25.
22. Management of cancer pain: clinical practice guidelines. Rockville (MD): Agency for Health Care Policy and Research, Department of Health and Human Services; 1994. AHCPR publ 94-0592.
23. Bruera E, Valasco-Leiva A, Spachynski K, Fainsinger R, Miller MJ, MacEachern T. The use of the Edmonton Injector (EI) for parenteral opioid management of cancer pain: a study of 100 consecutive patients. *J Pain Symptom Manage* 1993;8:525-8.
24. Bloomfield DJ. Should bisphosphonates be part of standard therapy of patients with multiple myeloma and bone metastases from other cancers? An evidence-based review. *J Clin Oncol* 1998;16:1218-26.
25. Ernst DS, Brasher P, Hagen N, Paterson AHG, MacDonald RN, Bruera E. A randomized, controlled trial of intravenous clodronate in patients with metastatic bone disease and pain. *J Pain Symptom Manage* 1997;13:319-26.
26. Bruera E, Schoeller T, Wenk R, MacEachern T, Marcelino S, Suarez-Almazor M, et al. A prospective multi-center assessment of the Edmonton Staging System for cancer pain. *J Pain Symptom Manage* 1995;10:348-55.
27. Fainsinger R. Pharmacological approach to cancer anorexia and cachexia. In: Bruera E, Higginson L, editors. *Cachexia–anorexia in cancer patients*. Oxford: Oxford University Press; 1996. p. 128-40.
28. Pereira J, Hanson J, Bruera E. The frequency and clinical course of cognitive impairment in patients with terminal cancer. *Cancer* 1997;79:835-42.
29. Ripamonti C, Bruera E. CNS adverse effects of opioids in cancer patients. Guidelines for treatment. *Cent Nerv Syst Drugs* 1997;8:21-37.


***Reprint requests to:*** *Dr. Neill A. Iscoe, Toronto–Sunnybrook Regional Cancer Centre, 2075 Bayview Ave., Toronto ON M4N 3M5; neill_iscoe@cancercare.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.