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Use of Strontium⁸⁹ in Patients with Endocrine-Refractory Carcinoma of the Prostate Metastatic to Bone Practice Guideline Report # 3-6

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ORIGINAL GUIDELINE: November 23, 1997

UPDATE: October 2001

This summary integrates the original practice guideline with the most current information (labeled NEW).

Part 1: Strontium⁸⁹ treatment for hormone refractory prostate cancer skeletal metastases: multiple painful sites of disease

Guideline Question

What is the role of Strontium⁸⁹ in effective palliation of patients with stage D endocrine-refractory prostate cancer and multiple sites of painful bony metastases?

Target Population

These recommendations apply to adult patients with stage D endocrine-refractory prostate cancer and multiple sites of painful bony metastases.

Recommendations

- Strontium⁸⁹ is recommended for use in patients with endocrine-refractory carcinoma of the prostate who have multiple uncontrolled painful sites of metastases on both sides of the diaphragm, not adequately controlled with conventional analgesic therapy and in whom the use of multiple single fields of external beam radiation is not possible.
- Strontium⁸⁹ has proven efficacy in the palliation of hormone-refractory painful bony metastases from prostate cancer.
- Strontium⁸⁹ has not been shown to lengthen the average duration of patient survival. There is limited evidence to determine its relative efficacy compared to wide-field irradiation. Specific indications, recommendations for administration, and the need for further data about the treatment are summarized in the report.

Indications for strontium⁸⁹ therapy in this clinical setting

All of the following are required:

1. Established diagnosis of prostate cancer metastatic to bone
2. Metastatic disease refractory to hormone therapy
3. Progressive sites of pain poorly controlled with conventional narcotics
4. Painful sites of disease on both sides of the diaphragm (otherwise, hemibody radiation is equally efficacious)

5. Patient or tumour factors (number of involved sites, location of involved sites, or level of pain control) are relative contraindications to the use of multiple single fields of radiation as an alternative
6. No evidence of impending spinal cord compression
7. Adequate bone marrow reserve
8. Painful bony lesions concentrate radionuclide on diagnostic scan

Methods

Entries to MEDLINE (1985 through September 2001), CANCERLIT (1985 through August 2001) and Cochrane Library (1985 through 2001, Issue 3) databases have been searched for evidence relevant to this practice guideline. The most recent literature search was performed in October 2001. No new evidence has emerged from review and updating activities.

Evidence was selected and reviewed by three members of the Practice Guidelines Initiative's (PGI) Genitourinary Cancer Disease Site Group (GU DSG) and methodologists. This practice guideline has been reviewed and approved by the GU DSG, which comprises medical oncologists, radiation oncologists, urologists, a pathologist, and a community representative.

External Review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC). The Practice Guideline Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Key Evidence

Three randomized controlled trials were available for evaluation. One randomized study compared the use of strontium⁸⁹ to conventional radiation (either hemibody or local field irradiation as determined prior to randomization), and the other two compared strontium⁸⁹ to placebo.

One of two studies comparing strontium⁸⁹ to placebo demonstrated the palliative efficacy of the intervention ($p < 0.01$), while the other showed no benefit. A third study comparing the efficacy of strontium⁸⁹ with conventional radiation concluded that all treatments provided equally effective pain relief, and that improvement was sustained for at least three months in similar proportions of patients. The median duration of patient survival was neither clinically nor statistically different between groups in this study.

The use of strontium⁸⁹ may cause bone marrow suppression, but clinically significant sequelae are uncommon. The use of strontium⁸⁹ may preclude further systemic chemotherapy and/or eligibility for clinical trials of systemic therapy. Symptoms other than those due to bone marrow suppression are rare.

Future Research

- At present, many factors related to cost (such as need for hospitalization, expensive analgesics, further radiotherapy, and so on) have not been evaluated in a prospective analysis. Further information is also required regarding validated palliative outcome measures in studies enrolling larger numbers of patients, before a full cost-effectiveness analysis can be considered.

Part 2: Strontium⁸⁹ treatment for hormone-refractory prostate cancer skeletal metastases: adjunctive strontium⁸⁹ for patients receiving local radiotherapy

Guideline Question

What is the role of strontium⁸⁹ in effectively palliating patients with stage D hormone-refractory prostate cancer receiving local radiotherapy for isolated painful bony metastases?

Target Population

These recommendations apply to adult patients with stage D hormone-refractory prostate cancer receiving local radiotherapy for isolated painful bony metastases.

Recommendations

- Strontium⁸⁹ is not recommended for routine use as an adjunct to local radiotherapy in this clinical setting.
- Strontium⁸⁹ is known to temporarily reduce analgesic intake and to modestly delay the need for treatment of sites of new pain, when used as an adjunct to local field radiotherapy and when compared to placebo adjunct therapy. The clinical significance of these benefits is not certain.
- Strontium⁸⁹ has not been shown to lengthen the average duration of patient survival in this setting and there is no evidence to determine its relative efficacy compared with wide-field irradiation. The need for further data about the treatment is summarized in the report.

Methods

Entries to MEDLINE (1985 through September 2001), CANCELIT (1985 through August 2001) and Cochrane Library (1985 through to Issue 3, 2001) databases have been searched for evidence relevant to this practice guideline. The most recent literature search was performed in October 2001. No new evidence has emerged from review and updating activities.

Evidence was selected and reviewed by three members of the Practice Guidelines Initiative's (PGI) Genitourinary Cancer Disease Site Group (GU DSG) and methodologists. This practice guideline has been reviewed and approved by the GU DSG, which comprises medical oncologists, radiation oncologists, urologists, a pathologist, and a community representative.

External Review by Ontario practitioners was obtained through a mailed survey. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee (PGCC). The Practice Guideline Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Key Evidence

One randomized controlled trial was available for evaluation. This study compared the use of strontium⁸⁹ to placebo injection as adjunctive treatment of patients receiving local radiotherapy for painful bony metastases from prostate cancer.

The randomized trial demonstrated that patients receiving strontium⁸⁹ had fewer analgesic requirements, fewer sites of new pain, and less need for additional local-field radiotherapy than patients receiving placebo. All of these differences were statistically significant. Differences in relief of pain at the index site and the duration of survival were neither statistically nor clinically significant.

The use of strontium⁸⁹ may cause bone marrow suppression, but clinically significant sequelae are uncommon. The use of strontium⁸⁹ may preclude further systemic chemotherapy and/or eligibility for clinical trials of systemic therapy. Symptoms other than those due to bone marrow suppression are rare.

Future Research

- At present, many factors related to cost (such as need for hospitalization, expensive analgesics, further radiotherapy, and so on) have not been evaluated in a prospective analysis. Further information is also required regarding validated palliative outcome measures in studies enrolling larger numbers of patients, before a full cost-effectiveness analysis can be considered.

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*The Practice Guidelines Initiative is sponsored by:
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PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care. The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹ The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

- ¹ Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

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FULL REPORT

Original guideline information and new information that has emerged from review and updating activities is labeled ORIGINAL and UPDATE, respectively.

I. QUESTION

This practice guideline addresses the role of strontium⁸⁹ in the management of patients with endocrine-refractory carcinoma of the prostate metastatic to bone. Two distinct clinical situations are considered. First, the role of strontium⁸⁹ in the management of patients with multiple painful bony metastases is evaluated. Second, the role of strontium⁸⁹ in the management of patients with isolated painful metastases as an adjunct to the use of involved-field radiation is considered. The two clinical situations constitute different patient populations, thus the recommendations for one clinical situation cannot be extrapolated to the other. Therefore, the abstract, interpretive summary and evidence-based recommendation of this report are divided into two parts.

The practice guideline is not structured to be an exhaustive review of the literature relating to strontium⁸⁹ therapy; however, such reviews are available (1,2). Rather, the report will focus on the literature relating to the therapeutic indications for strontium⁸⁹ in patients with metastatic prostate cancer. The guideline is intended to address the efficacy of strontium⁸⁹ in the aforementioned clinical circumstances. This guideline does not attempt to address the efficacy of alternative strategies used in the management of endocrine-refractory prostate cancer.

II. CHOICE OF TOPIC AND RATIONALE

In patients with adenocarcinoma of the prostate refractory to endocrine therapy, the palliation of painful osseous metastases constitutes a substantial proportion of clinical practice (3). While hormone therapy remains the preferred treatment in patients with responsive disease, strontium⁸⁹ has been evaluated in phase III studies in patients with endocrine-refractory disease.

Strontium⁸⁹ is an injectable non-sealed radionuclide with a potential role in the management of patients with painful bony metastases. It has a physical half-life of 50.5 days and decays with the emission of beta particles (maximum energy 1.5 MeV) and a range in tissue of 0.8 cm. Strontium⁸⁹ is preferentially taken up and retained by sites of osteoblastic metastases (4) and is “washed out” of healthy bone with a biological half-life of 14 days (5). The differential distribution and retention of the nuclide results in a therapeutic advantage by targeting delivery of radiation to metastatic sites. This selective distribution also reduces the potential for marked hematological toxicity such as that seen with (and limiting) the use of phosphorus³².

III. METHODS

Guideline Development

This guideline report was developed out of the Practice Guidelines Initiative (PGI), using the methodology of the Practice Guidelines Development Cycle by Browman et al (1u). Evidence was selected and reviewed by three members of the PGI’s Genitourinary Cancer Disease Site Group (GU DSG) and methodologists. The guideline is a convenient and up-to-date source of the best available evidence on use of strontium⁸⁹ with endocrine-refractory prostate cancer metastatic to bone developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. It is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information.

Guideline History

This practice guideline report was originally completed on November 23, 1997 and published in *Cancer Prevention & Control* 1998;2(2):79-87. The guideline was reviewed monthly from June 1998 to December 1999, quarterly through 2000, and most recently in October 2001. Original guideline information and new information that has emerged from review and updating activities is labeled ORIGINAL and UPDATE, respectively, in this report.

Literature Search Strategy

Original: November 1997

MEDLINE and CANCERLIT searches were done for the years 1985-April 1997. The search terms included "prostatic neoplasms", "strontium89", "metastron", "89sr:", "89stron:", and "sr89". Selected bibliographies were reviewed to identify papers not included in the computerized databases. The PDQ database was searched to identify active registered trials in stage D prostate cancer.

Update: October 2001

The original literature search has been updated using MEDLINE (through September 2001), CANCERLIT (through August 2001), the Cochrane Library (Issue 3, 2001).

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were randomized controlled trials which used strontium⁸⁹ for stage D endocrine-refractory prostate cancer metastatic to bone. Outcomes of interest included markers of successful palliation (e.g., change in analgesic requirements, functional status, quality of life evaluation), time to further radiotherapy, patient survival and treatment toxicity.

IV. RESULTS

Literature Search Results

Original: November 1997

Four randomized trials were identified from 40 articles and ten abstracts found by the literature search. Two trials compared strontium⁸⁹ with placebo, one compared strontium⁸⁹ with conventional radiotherapy and the fourth trial evaluated strontium⁸⁹ as an adjunctive therapy with involved field radiotherapy. The principal findings of these trials are summarized below and in Table 1. For clarity, please refer to Table 1 while reviewing the text of this report. The remaining articles included ten review articles, five retrospective case series, one cost analysis, three phase II studies, three articles published in languages other than English, and 14 other papers, most of which were pharmaco-kinetic and dose-distribution studies. One systematic review was published in 1995, which did not provide pooled estimates of effects (6).

Update: October 2001

There is no additional evidence on this topic at this time.

Outcomes

Palliative Efficacy of Strontium⁸⁹ Compared with Placebo in Patients with Multiple Sites of Painful Osseous Metastases and Endocrine-Refractory Disease

Original: November 1997

Two randomized trials evaluated the palliative efficacy of strontium⁸⁹ compared with placebo (7,8). In one trial, strontium⁸⁹ treatment was associated with improvement in outcomes for palliation compared with placebo (7); the other trial detected no such effect but suffered from methodologic flaws (8).

Lewington and colleagues completed a double-blind crossover comparison of strontium⁸⁹ with placebo (stable strontium) in a European study of 32 patients (7). Changes in general condition, mobility, analgesic use and pain were measured five weeks after therapy in 26 evaluable patients. These four measures were combined to give a composite response score. Only data from the first treatment period of the study (i.e., before crossover) are reported. Summary statistics were not reported but the authors stated that average response score in the strontium⁸⁹ group was higher than in the placebo group ($p < 0.01$). Four of 12 patients on active treatment and none on placebo were pain free at five weeks.

Buchali and colleagues reported a double-blind comparison of strontium⁸⁹ with placebo in 49 patients (8). Treatment allocation was blinded for at least one year after therapy. Palliation was rated by patients' subjective reports for 41 who required analgesic therapy. Seven of 19 patients (37%) receiving strontium⁸⁹ reported relief of pain one to three years after therapy compared with 11 of 22 patients (50%) receiving placebo. This difference was not statistically significant. When treatment groups were combined and examined across strata, relief of pain was reported in a significantly higher proportion of patients with a disease history of less than one year (14 of 21) compared to a disease history of more than one year (4 of 20, $p < 0.01$). Both groups included patients with endocrine-sensitive disease. The interpretation of the palliative benefit of strontium⁸⁹ in this study is limited by the small number of patients and consequent limited study power, by the long interval between treatment and evaluation, and by the limited information provided about the subjective assessment scale used. The authors found significant differences in actuarial survival at two years (46% versus 4%; $p < 0.05$) in favour of the group receiving strontium⁸⁹. This effect of treatment on survival retained significance in a multivariate model, but the authors appear to have excluded ten patients who died of disease in the first three months (thus excluding all those who did not complete treatment), and included patients with endocrine-responsive disease. These methodologic details limit the interpretation of the observed survival differences.

Update: October 2001

There is no additional evidence on this topic at this time.

Palliative Benefit of Strontium⁸⁹ Compared with Conventional Radiotherapy in Patients with Multiple Sites of Painful Osseous Metastases and Endocrine-Refractory Disease

Original: November 1997

One randomized trial addressed the use of strontium⁸⁹ compared with conventional radiotherapy in patients with wide-spread symptomatic metastases (5). Previous studies using retrospective analyses, historic controls, or phase II evaluations (9-11) to evaluate strontium⁸⁹ in this setting will not be discussed further given the limited value of this evidence in formulating a treatment guideline.

Quilty and colleagues stratified patients with painful metastases by their suitability for either local or hemibody radiotherapy as judged by the treating physician (5). Patients were then randomly allocated within each stratum to external radiation therapy or to strontium⁸⁹ therapy. The primary study outcome was pain relief expressed as an improvement in type and/or severity of pain compared to baseline using Likert scales. Analgesic intake, the appearance of new pain sites, requirements for supplementary radiotherapy, and the general

condition and mobility of the patient were also measured at each follow-up. An overall palliation score was assigned at 12 weeks from baseline or at the time of treatment failure in patients who crossed over into the alternative treatment group. This score was determined using the same method as the study by Lewington et al and was based on four components (general condition, mobility, analgesic intake, and pain at original sites) (7).

1) In patients randomized between hemibody radiation and strontium⁸⁹, there was no observed difference in pain relief at index sites at final assessment (67% for hemibody radiation versus 70% for strontium⁸⁹, p=NS) or in the proportion of patients with sustained improvement after three months (64% with hemibody treatment, 66% with strontium, p=NS). Seventy-four percent of patients receiving strontium⁸⁹ were free of new pain sites at the final assessment compared with 52% in the hemibody radiotherapy group (p<0.05). Radiotherapy to a new site was required in six patients after hemibody therapy and in nine patients after strontium⁸⁹; this difference was not statistically significant.

2) In patients randomized between involved field radiation and strontium⁸⁹, some pain relief at index sites was seen in both arms (67% for local radiotherapy v. 65% for strontium⁸⁹), with sustained relief after three months in similar proportions (61% versus 66% respectively). More patients in the strontium⁸⁹ group (64%) than in the local radiotherapy group (42%) were free of new pain sites at the final assessment (p<0.05). Radiotherapy to a new site was required in 12 of 48 patients after involved field radiation and in two of 63 after strontium⁸⁹ (p<0.01).

There were no statistically significant differences between either hemibody radiation and placebo, or between local radiation and placebo in the other outcomes measured (i.e., the number of patients with “substantial” or “dramatic” improvement in overall score, the number requiring a reduction in analgesic intake of 50% or more, or survival). Pooling the data across the hemibody and local radiotherapy groups, the median survival was 28 weeks after placebo and 33 weeks after strontium⁸⁹.

The trial was generally well designed and reported, providing sufficient detail regarding the patient characteristics, treatment, evaluation and exclusions. The method of palliative assessment was not validated. The relatively small number of patients within strata raises the possibility of a type II error with respect to some of the observed differences.

Update: October 2001

There is no additional evidence on this topic at this time.

Palliative Benefit of Adjunctive Strontium⁸⁹ in Patients Receiving Involved Field Radiotherapy

Original: November 1997

Only one randomized trial has been done in this area. Porter and colleagues evaluated the role of strontium⁸⁹ in patients receiving external beam radiotherapy for pain relief (12). Since this patient population generally has multiple known or clinically occult metastases, the trial was designed to evaluate the role of strontium⁸⁹ in treating less symptomatic disease beyond the index site.

This was a placebo-controlled double-blind study of 126 endocrine-refractory patients. Strontium⁸⁹ was administered as a single dose any time between the last day of radiation and seven days after completion of radiation. Three months after treatment, 59% of the strontium⁸⁹ patients and 34% of the placebo patients were free of new painful metastases, with a significantly lower (p<0.002) number of new painful sites per patient in the strontium⁸⁹ group (mean = 0.59) than in the placebo group (mean = 1.21). There was no statistically significant difference between the strontium⁸⁹ and placebo groups in the proportion of patients with partial or complete pain relief at index sites. The proportion of patients with reduced analgesic intake varied over the six-month follow-up, but more patients in the strontium⁸⁹ group than in the placebo group had reduced analgesic intake at each of the monthly assessments. Analysis of

the entire follow-up period showed more patients in the strontium⁸⁹ group had stopped taking analgesics ($p < 0.05$), with the largest difference observed at three months (17% for strontium⁸⁹ versus 2% for placebo). Data abstracted from the Kaplan-Meier curves for time to first requirement for further radiotherapy showed that the probability of patients receiving further radiotherapy two years after study treatment was 0.40 in those receiving strontium⁸⁹ and 0.63 in those receiving placebo. There was a significant difference favouring strontium⁸⁹ ($p = 0.006$) in the time from treatment to further radiotherapy (median = 35.3 weeks for strontium⁸⁹ and 20.3 weeks for placebo). Overall quality of life, measured by questionnaire, was significantly better in the strontium⁸⁹ group compared to placebo ($p = 0.006$). Significant benefit was seen in two subscales, pain in the previous 24 hours and physical activity ($p < 0.05$). No difference was observed in survival duration between groups (median = 27 weeks for strontium⁸⁹ versus 34 weeks for placebo). The treatment was reasonably well tolerated with grade IV hematological toxicity observed in seven patients (10%) receiving strontium⁸⁹ and in one receiving placebo (2%).

The study was reasonably well described with respect to its methodology. The Radiation Therapy Oncology Group (RTOG) analgesic and pain scoring system was utilized. The quality of life instrument used was not described and no reference was made to its validation.

Update: October 2001

There is no additional evidence on this topic at this time.

V. INTERPRETIVE SUMMARY

Original: November 1997

Part 1: Strontium⁸⁹ treatment for patients with skeletal metastases from hormone-refractory prostate cancer: multiple painful sites of disease

One placebo-controlled study (7) detected some palliative benefit for strontium⁸⁹, whereas another study demonstrated similar palliative efficacy of strontium⁸⁹ and hemibody radiotherapy (5). The power of these studies was somewhat limited, and the palliative assessment technique has not been used by other investigators. Nonetheless, strontium⁸⁹ was as efficacious as hemibody radiotherapy and was superior to involved field radiotherapy (in patients allocated to this stratum) with respect to the need for further radiation. The treatment is well tolerated and all studies show that serious sequelae are uncommon and are limited to haematological consequences. The use of strontium⁸⁹ may preclude further systemic chemotherapy and/or eligibility for clinical trials of systemic therapy. Strontium⁸⁹ does not appear to prolong patient survival in this clinical setting.

Part 2: Strontium⁸⁹ treatment for patients with isolated painful skeletal metastases from hormone-refractory prostate cancer: adjunctive strontium⁸⁹ for patients receiving local radiotherapy

The findings of Porter and colleagues indicate that the use of strontium⁸⁹ in addition to involved field radiation is safe and seems to delay the need for further radiotherapy but the benefits to patient quality of life are not well established (12). There is no improvement in patient survival. The dose of strontium⁸⁹ used in this trial was substantially higher than that in other trials in the usual clinical setting (Table 1), and the possible role of wide-field radiation as an alternative adjunctive strategy has not been evaluated. There is thus insufficient evidence to recommend the routine use of strontium⁸⁹ in this clinical setting. The group consensus process supporting this interpretation is found in section VII below.

Recommendations for administration

Strontium⁸⁹ therapy has potential toxicities and may be harmful if given in inappropriate clinical circumstances. It must be used in the appropriate context and only after an evaluation of

the patient's overall status, previous therapy, and possible future treatments. For example, patients who have already received wide-field radiotherapy or myelosuppressive chemotherapy may be at high risk of serious hematological toxicity despite relatively normal hematological indices. The use of strontium⁸⁹ should be restricted to oncologists with expertise in the overall management of the prostate cancer patient (and the overall management plan for the individual patient being considered for treatment). A radiation oncologist should be involved in the decision to employ strontium⁸⁹.

Alternatives to strontium⁸⁹

The therapeutic role of strontium⁸⁹ should be considered in the context of alternative management strategies for patients with painful osseous metastases including step-wise use of analgesic therapy, involved-field radiotherapy, wide-field radiotherapy, and other supportive palliative measures (3,13).

Future Research

Strontium⁸⁹ and wide-field radiotherapy appear to be similar in their ability to palliate patients according to the one phase III trial available (6). Strontium⁸⁹ appears to be at least as well tolerated as wide-field radiotherapy. Strontium⁸⁹ appears to have some palliative benefits when used as an adjunct, with few major toxicities. At present, many factors related to cost (such as need for hospitalization, expensive analgesics, further radiotherapy, and so on) have not been evaluated in a prospective analysis. Further information is also required regarding validated palliative outcome measures in studies enrolling larger numbers of patients, before a full cost-effectiveness analysis can be considered.

Update: October 2001

There is no additional evidence on this topic at this time

VI. ONGOING TRIALS

The GU DSG is not aware of any phase III trials currently in progress; however, the protocol of a randomized phase III study evaluating the use of strontium89 in patients with hormone refractory prostate cancer has recently been approved (MDA-ID-00156, NCI-3410). This trial will compare the effectiveness of consolidation therapy with or without strontium89 after induction chemotherapy. Patients will receive one of two induction chemotherapy regimens; the first regimen will consist of doxorubicin, ketoconazole, vinblastine, and estramustine, and the second regimen will consist of estramustine and docetaxel. After induction chemotherapy, patients with a PSA response will be randomized to one of two consolidation treatment arms. Patients in one arm will receive doxorubicin plus strontium89 at the first administration of chemotherapy. Patients in the second arm will receive doxorubicin only. Projected patient accrual for this trial is 680 patients over 34 months. The start date of the trial is currently unknown.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

Original: November 1997

The structured review of the literature was reviewed by a subcommittee of the Genitourinary Cancer Disease Site Group (DSG). The conclusions of the sub-committee were then discussed with the entire DSG and reviewed by the Chair of the PGI Methods Resource Group. Comments were incorporated into the final draft by consensus.

The group reached a unanimous consensus, based on the available literature, on the role of strontium⁸⁹ therapy in patients with multiple painful sites of disease who meet the listed indications for treatment (Practice Guideline, part 1).

The group reached a majority consensus, based on the available literature, on the role of adjunctive strontium⁸⁹ therapy in patients receiving local radiotherapy for isolated painful metastases. The DSG concluded that the demonstrated benefits of adjunctive strontium⁸⁹ (with respect to analgesic intake requirements and the need for future treatments) were of uncertain clinical significance in the absence of valid quality of life data and in the absence of demonstrated benefit in patient survival. The group recommended further comparative study of adjunctive strontium⁸⁹ with adjunctive wide-field radiation including appropriate symptom control, quality of life, and economic evaluations (Practice Guideline, part 2).

Update: October 2001

The information above remains current.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Original: November 1997

This section describes the external review activities undertaken for the original guideline report. For a description of external review activities of the new information presented in the updated sections of this report, please refer to Update below.

Draft Practice Guideline

Based on the evidence contained under the Original subtitles throughout this report, the Genitourinary DSG drafted the following recommendations:

Part 1: Strontium⁸⁹ treatment for hormone refractory prostate cancer skeletal metastases: multiple painful sites of disease

Strontium⁸⁹ is recommended for use in patients with multiple uncontrolled painful sites of metastases on both sides of the diaphragm, not adequately controlled with conventional analgesic therapy and in whom the use of multiple single fields of external beam radiation is not possible. Strontium⁸⁹ has proven efficacy in the palliation of hormone-refractory painful bony metastases. Strontium⁸⁹ has not been shown to lengthen the average duration of patient survival. There is limited evidence to determine its relative efficacy compared to wide-field irradiation. Under specific indications, strontium⁸⁹ is the treatment of choice.

Indications for strontium⁸⁹ therapy in this clinical setting

All of the following are required:

1. Established diagnosis of prostate cancer metastatic to bone
2. Metastatic disease refractory to hormone therapy
3. Progressive sites of pain poorly controlled with conventional narcotics
4. Painful sites of disease on both sides of the diaphragm (otherwise, hemibody radiation is equally efficacious)
5. Patient or tumour factors (number of involved sites, location of involved sites, or level of pain control) are relative contraindications to the use of multiple single fields of radiation as an alternative
6. No evidence of impending spinal cord compression
7. Adequate bone marrow reserve
8. Painful bony lesions concentrate radionuclide on diagnostic scan

Part 2: Strontium⁸⁹ treatment for hormone-refractory prostate cancer skeletal metastases: adjunctive strontium⁸⁹ for patients receiving local radiotherapy

Strontium⁸⁹ is not recommended for routine use as an adjunct to local radiotherapy in this clinical setting. Strontium⁸⁹ is known to temporarily reduce analgesic intake and to modestly delay the need for treatment of sites of new pain, when used as an adjunct to local field radiotherapy and when compared to placebo adjunct therapy. The clinical significance of these

benefits is not certain. Strontium⁸⁹ has not been shown to lengthen the average duration of patient survival in this setting and there is no evidence to determine its relative efficacy compared to wide-field irradiation. The need for further data about the treatment is summarized in the report.

Practitioner Feedback

Based on the evidence contained under the Original subtitles in this report and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods

Practitioner feedback was obtained through a mailed survey of 166 practitioners in Ontario. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendations above should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Genitourinary Disease Site Group.

Results

Key results of the practitioner feedback survey of the original draft guideline report are summarized. Fifty-two percent of the surveys were returned. Seventy-two to ninety-six percent of the respondents agreed or strongly agreed that the methodology and data synthesis used in the development of the report was acceptable. Ninety-six percent of the respondents endorsed the recommendations and 89% agreed the report should be approved as a practice guideline.

Summary of Main Findings

The main points made in the written comments were:

1. The usefulness of this guideline to community-based urologists. It was suggested that the guideline would be helpful with respect to increasing the knowledge base of urologists, but given that many men with endocrine-refractory carcinoma of the prostate are treated in the province's cancer centres by radiation and medical oncologists, its usefulness to community-based urologists was questioned.
2. A request for discussion of the therapeutic alternatives to strontium⁸⁹.

Modifications/Actions

1. There was an addition made to section I of this report, "Question/Problem". The addition clarifies that the primary intent of this guideline is to address the effectiveness of strontium⁸⁹ in specific clinical circumstances. The guideline does not provide a review of the data of alternative management strategies for men with endocrine-refractory prostate cancer.

Approved Practice Guideline Recommendations

This practice guideline reflects the integration of the draft recommendations in the External Review process and has been approved by the GU DSG and the Practice Guideline Coordinating Committee.

Part 1: Strontium⁸⁹ treatment for hormone refractory prostate cancer skeletal metastases: multiple painful sites of disease

Strontium⁸⁹ is recommended for use in patients with endocrine-refractory carcinoma of the prostate who have multiple uncontrolled painful sites of metastases on both sides of the diaphragm, not adequately controlled with conventional analgesic therapy and in whom the use of multiple single fields of external beam radiation is not possible. Strontium⁸⁹ has proven efficacy in the palliation of hormone-refractory painful bony metastases from prostate cancer.

Strontium⁸⁹ has not been shown to lengthen the average duration of patient survival. There is limited evidence to determine its relative efficacy compared to wide-field irradiation. Specific indications, recommendations for administration, and the need for further data about the treatment are summarized in the report.

Indications for strontium⁸⁹ therapy in this clinical setting

All of the following are required:

1. Established diagnosis of prostate cancer metastatic to bone
2. Metastatic disease refractory to hormone therapy
3. Progressive sites of pain poorly controlled with conventional narcotics
4. Painful sites of disease on both sides of the diaphragm (otherwise, hemibody radiation is equally efficacious)
5. Patient or tumour factors (number of involved sites, location of involved sites, or level of pain control) are relative contraindications to the use of multiple single fields of radiation as an alternative
6. No evidence of impending spinal cord compression
7. Adequate bone marrow reserve
8. Painful bony lesions concentrate radionuclide on diagnostic scan

Part 2: Strontium⁸⁹ treatment for hormone-refractory prostate cancer skeletal metastases: adjunctive strontium⁸⁹ for patients receiving local radiotherapy

Strontium⁸⁹ is not recommended for routine use as an adjunct to local radiotherapy in this clinical setting. Strontium⁸⁹ is known to temporarily reduce analgesic intake and to modestly delay the need for treatment of sites of new pain, when used as an adjunct to local field radiotherapy and when compared to placebo adjunct therapy. The clinical significance of these benefits is not certain. Strontium⁸⁹ has not been shown to lengthen the average duration of patient survival in this setting and there is no evidence to determine its relative efficacy compared with wide-field irradiation. The need for further data about the treatment is summarized in the report.

Update: October 2001

There was no additional evidence to review.

IX. PRACTICE GUIDELINE

This practice guideline reflects the most current information integrating the new evidence with evidence from the original guideline report.

Part 1: Strontium⁸⁹ treatment for hormone refractory prostate cancer skeletal metastases: multiple painful sites of disease

Target Population

These recommendations apply to adult patients with stage D endocrine-refractory prostate cancer and multiple sites of painful bony metastases.

Recommendations

- Strontium⁸⁹ is recommended for use in patients with endocrine-refractory carcinoma of the prostate who have multiple uncontrolled painful sites of metastases on both sides of the diaphragm, not adequately controlled with conventional analgesic therapy and in whom the use of multiple single fields of external beam radiation is not possible.
- Strontium⁸⁹ has proven efficacy in the palliation of hormone-refractory painful bony metastases from prostate cancer.

- Strontium⁸⁹ has not been shown to lengthen the average duration of patient survival. There is limited evidence to determine its relative efficacy compared to wide-field irradiation. Specific indications, recommendations for administration, and the need for further data about the treatment are summarized in the report.

Indications for strontium⁸⁹ therapy in this clinical setting

All of the following are required:

1. Established diagnosis of prostate cancer metastatic to bone
2. Metastatic disease refractory to hormone therapy
3. Progressive sites of pain poorly controlled with conventional narcotics
4. Painful sites of disease on both sides of the diaphragm (otherwise, hemibody radiation is equally efficacious)
5. Patient or tumour factors (number of involved sites, location of involved sites, or level of pain control) are relative contraindications to the use of multiple single fields of radiation as an alternative
6. No evidence of impending spinal cord compression
7. Adequate bone marrow reserve
8. Painful bony lesions concentrate radionuclide on diagnostic scan

Future Research

- At present, many factors related to cost (such as need for hospitalization, expensive analgesics, further radiotherapy, and so on) have not been evaluated in a prospective analysis. Further information is also required regarding validated palliative outcome measures in studies enrolling larger numbers of patients, before a full cost-effectiveness analysis can be considered.

Part 2: Strontium⁸⁹ treatment for hormone-refractory prostate cancer skeletal metastases: adjunctive strontium⁸⁹ for patients receiving local radiotherapy

Target Population

These recommendations apply to adult patients with stage D hormone-refractory prostate cancer receiving local radiotherapy for isolated painful bony metastases.

Recommendations

- Strontium⁸⁹ is not recommended for routine use as an adjunct to local radiotherapy in this clinical setting.
- Strontium⁸⁹ is known to temporarily reduce analgesic intake and to modestly delay the need for treatment of sites of new pain, when used as an adjunct to local field radiotherapy and when compared to placebo adjunct therapy. The clinical significance of these benefits is not certain.
- Strontium⁸⁹ has not been shown to lengthen the average duration of patient survival in this setting and there is no evidence to determine its relative efficacy compared with wide-field irradiation. The need for further data about the treatment is summarized in the report.

Future Research

- At present, many factors related to cost (such as need for hospitalization, expensive analgesics, further radiotherapy, and so on) have not been evaluated in a prospective analysis. Further information is also required regarding validated palliative outcome measures in studies enrolling larger numbers of patients, before a full cost-effectiveness analysis can be considered.

X. JOURNAL REFERENCE

Brundage MD, Crook JM, Lukka H and the Genitourinary Cancer Disease Site Group. Use of Strontium⁸⁹ in Endocrine-Refractory Prostate Cancer Metastatic to Bone. *Cancer Prevention & Control*, 1998; 2(2): 79-87.

XI. ACKNOWLEDGMENTS

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The Genitourinary Cancer Disease Site Group would like to thank Dr. Himu Lukka for taking the lead in updating this practice guideline report.

For a complete list of the Genitourinary Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit our web site at <http://www.cancercare.on.ca/>.

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Original: November 1997

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Update: October 2001

This section includes all references from the review and updating activities.

- 1u. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-512.

Table 1: Randomized controlled trials of strontium⁸⁹.

Authors (Reference #)	Patient Population	Control Treatment	Experimental Treatment	Primary Palliative Outcome	Palliative Findings	Survival Findings	Comments
Lewington 1991 (7)	Endocrine-refractory patients	Placebo N=17	150 MBq wk 1 150 MBq wk 6 (if needed) N=15	Pain Relief (measured by composite response score) at 5 weeks	Significantly higher proportion of strontium ⁸⁹ patients experienced improvement in score	Not addressed	6 of 32 patients unevaluable. Unvalidated pain relief scale.
Buchali 1988 (8)	Endocrine-sensitive and -refractory patients	Placebo N=24	75 MBq each month for 3 months N=25	Pain relief (binary) 1-3 years after treatment	No significant difference in proportion of patients with pain relief	Significantly improved 2-year survival in patients receiving strontium ⁸⁹	10 patients were excluded from the survival analysis.
Quilty 1994 (5) (Stratum I)	Endocrine-refractory patients deemed suitable for local XRT	Involved field XRT N=72	200 MBq N=76	Pain relief 8-12 weeks after treatment	No significant difference in proportion of patients with relief at index sites Significantly more patients free of new pain sites after strontium ⁸⁹ Significantly fewer patients in strontium ⁸⁹ group required XRT	No difference in median survival	37 of 148 patients were unevaluable Unvalidated palliative assessment method
Quilty 1994 (5) (Stratum II)	Endocrine-refractory patients deemed suitable for hemibody XRT	Hemibody XRT (6 Gy upper, 8 Gy lower). N=80	200 MBq N=77	As above	No significant difference in proportion of patients with relief at index sites Significantly more patients free of new pain sites after strontium ⁸⁹	As above	51 of 157 patients were unevaluable Unvalidated palliative assessment method
Porter 1993 (12)	Endocrine-refractory patients deemed suitable for local XRT N=126	Involved field XRT and placebo injection	Involved field XRT and 10.8 mCi (400MBq) injection	Pain from new sites over 6 months following treatment	Significantly fewer new pain sites/patient in strontium ⁸⁹ group No significant differences in relief of pain at index sites Significant differences in favour of strontium ⁸⁹ in need for analgesics, time to further XRT and quality-of-life	No significant difference in median survival	RTOG pain assessment scale Unvalidated quality-of-life scale 2 of 126 patients were unevaluable

RTOG=Radiation Therapy Oncology Group; XRT=Radiotherapy