Complete Summary

GUIDELINE TITLE

Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases.

BIBLIOGRAPHIC SOURCE(S)

Supportive Care Guidelines Group. Radiotherapy fractionation for the palliation of uncomplicated painful bone metastases [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2003 Mar. 22 p. (Practice guideline; no. 13-2). [48 references]

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Bone metastases

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Treatment

CLINICAL SPECIALTY

Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To provide recommendations for the preferred dose-fractionation of localized radiotherapy for the treatment of uncomplicated painful bone metastases
- To evaluate the expected response rate and duration of pain relief

TARGET POPULATION

Adult patients with single or multiple radiographically confirmed bone metastases of any histology corresponding to painful areas in previously non-irradiated areas without pathologic fractures or spinal cord/cauda equina compression. It does not apply to the management of malignant primary bone tumour.

INTERVENTIONS AND PRACTICES CONSIDERED

Radiotherapy (single and multiple fractions)

MAJOR OUTCOMES CONSIDERED

- Pain relief (primary outcome considered)
- Complete and overall response, including duration of response
- Quality of life
- Analgesic consumption
- Remineralization
- Adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Two independent literature searches were conducted. The first was a search of PubMed (National Library of Medicine) for the years 1980 to 2000 with no language restrictions, using the search terms "bone", "metastasis" or "metastases", "radiation" or "radiotherapy", and "fraction". Citations listed in the PubMed output were evaluated for eligibility for the systematic review of the evidence as were those marked "Related" to the eligible papers.

The second search was conducted to complement the results of the search described above. In addition to several randomized controlled trials (RCTs), the original literature search had found five systematic reviews, the most recent of which covered the literature up to August 1998. For this practice guideline report, a second search of MEDLINE, CANCERLIT, and the Cochrane Library (2002, Issue 4) was conducted to find randomized trials published between January 1998 and December 2002 using MeSH headings (radiotherapy, radiotherapy dosage, dose fractionation, bone neoplasms/sc [Secondary], explode Clinical Trials, clinical trial [publication type]), and text words (bon:, osseous, metasta:, radiotherapy, irradiation, radiation, pain, analgesi:, trial, and study) without language restrictions.

Proceedings of the meetings of the American Society for Therapeutic Radiology and Oncology (ASTRO) (2001-2002) and the Canadian Association of Radiation Oncologists (2000), as well as reference lists of papers and review articles, were scanned for additional citations. The Physician Data Query (PDQ) clinical trials database on the Internet (http://www.cancer.gov/search/clinical_trials/) was searched for reports of ongoing randomized trials. The Canadian Medical Association Infobase (http://www.cma.ca/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/) and other web sites were searched for existing evidence-based practice guidelines prior to the development of this guideline report.

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they met all of the following criteria:

1. They were published reports of either a systematic review of radiotherapy dose fractionation studies or full or abstract reports of results from randomized controlled trials comparing two or more dose-fractionation schedules for localized radiotherapy of painful bone metastases.
2. The article reported data on pain relief for each intervention group.

Exclusion Criteria

Studies of hemi-body radiotherapy or systemic radiotherapy with radionuclides were excluded. Letters and editorials were not considered.

NUMBER OF SOURCE DOCUMENTS

Five reviews and eighteen randomized trials

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

There were some variations in patient population, treatment technique and pain/analgesic scoring method, and measured outcomes among the trials. A summary of these methodologic variations is provided in Appendices 1-3 in the original guideline document. The studies comparing single against multifraction regimens were the most homogeneous group, and a meta-analysis of these trials was performed based on published response data except for one study, which was reported in abstract form. Additional data from this study (the Canadian Bone Mets study) was obtained from the investigators by personal communication. No unpublished data was solicited from investigators of other trials.

Pain relief, expressed as a response rate, was the primary outcome for the randomized trials reported here. To estimate the overall effect of radiotherapy on pain relief, complete and/or overall response rates were abstracted from the published reports of individual randomized controlled trials (RCTs) and pooled by intention-to-treat using the Review Manager software (RevMan 4.1) provided by the Cochrane Collaboration (Metaview© Update Software). For some studies, response rates by intention-to-treat were recalculated using the number of randomized patients as denominator, because these trials did not report response rates by intention-to-treat. Some studies included responses to repeat irradiation in the reported response rates. Pooled response comparisons are expressed as relative risks (also known as risk ratios) with 95% confidence intervals (CI), where a relative risk (RR) for response as the event >1.0 indicates that single fraction radiotherapy improved pain compared with multifraction radiotherapy. Conversely, a relative risk <1.0 suggests that patients in the multifraction group experienced better response to treatment. Sensitivity analysis was done with evaluated patients as the denominators (i.e., not intention-to-treat). An attempt to explore the effect of dose response, incorporating results from multifraction studies, was done by calculating the biological equivalent doses (BED) for all fractionation schedules using an alpha/beta ratio of 10. Any trial that employed treatment arms above and below a specific BED cut-off was pooled with other trials with similar BED treatment arms. The meta-analysis portion of this practice guideline report has been published.

Secondary outcomes evaluated by these trials included analgesic use, quality of life, time to response, duration of response, retreatment with radiotherapy for bone pain, and adverse effects.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The Supportive Care Guidelines Group discussed the first draft of this practice guideline report in March 2001. They agreed that a review of the evidence suggested that there was no real difference in response between a single fraction and multiple fractions of radiation. The group discussed the inclusion of the Canadian study that had been published only in abstract form and concluded that it would be appropriate to include it because it contributed to the overall picture. They also debated the merits of including the three, non-English papers reporting randomized controlled trials (RCTs) that were found by the literature search. It was pointed out that, without a search of databases likely to include the bulk of the non-English literature, these may constitute a biased sample of that subset of the evidence. Translations of these papers were available, and a decision was made to include them. The final issue discussed concerned whether or not data from the randomized trials should be pooled in a meta-analysis. The Cochrane review group had decided not to pool response rates for their systematic review because of some variation among studies in definitions of response and the difficulties with inclusion of systemic radiotherapy trials. However, the Supportive Care Guidelines Group felt that these differences were not substantial enough to preclude pooling the group of studies that compared single fraction with multifraction localized radiotherapy. Since some of the studies reported outcomes including response to re-irradiation, the role of re-irradiation should be considered when applying results of study patients to general radiation oncology practice.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Practitioner feedback was obtained through a mailed survey of 95 radiation oncologists across Ontario. The survey consisted of items evaluating the methods,

results, and interpretive summary used to inform the draft recommendation and whether the draft recommendation should be approved as a practice guideline. Written comments were invited. The practitioner feedback survey was mailed out on October 9, 2002. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Supportive Care Guidelines Group reviewed the results of the survey.

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Supportive Care Guidelines Group and the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

For patients where the treatment objective is pain relief, a single 8 Gy treatment, prescribed to the appropriate target volume, is recommended as the standard dose-fractionation schedule for the treatment of symptomatic and uncomplicated bone metastases.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The literature search identified no evidence-based practice guidelines, five reviews and 18 randomized studies. Of the five reviews identified, four were systematic reviews of radiotherapy for painful bone metastases.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Based on intention-to-treat principle, meta-analysis of published data from eight randomized trials of single fraction versus multifraction radiotherapy for the treatment of uncomplicated painful bone metastases did not detect a significant difference in response rate (pain reduction or control) between a single fraction of 8 Gy prescribed to the appropriate target depth and fractionated radiotherapy. Pooled complete response rates were 33% with single fraction and 32% with multifraction (relative risk, 1.03; 95% confidence interval, 0.94 to 1.13, p=0.5) and overall response rates were 62% and 59% respectively (relative risk, 1.05; 95% confidence interval, 1.00 to 1.11, p=0.04).
- The majority of patients enrolled in the studies were breast, prostate, and lung cancer patients. Other less common epithelial and non-epithelial tumours

were often included, but relative efficacy of dose-fractionation schedules cannot be determined in such subgroups.
- Median duration of response was 12 to 24 weeks, with no significant difference between fractionation schedules within individual trials.
- No significant difference in quality of life after radiotherapy (in the few studies assessed), analgesic consumption, or acute adverse effects (vomiting and tiredness) was detected between single- and multiple-fractionation schedules.
- One study showed greater remineralization following fractionated radiotherapy (30 Gy/10 fractions) than single fraction (8 Gy). The implication of this finding on prevention of pathologic fracture is unclear.

POTENTIAL HARMS

- There is no evidence to suggest that fractionated regimens result in fewer cases of acute nausea and vomiting compared with single fraction treatment. Nausea and vomiting are better controlled by prophylactic anti-emetics, as demonstrated in the Canadian study. Complete emesis control was superior with single fraction radiotherapy using prophylactic ondansetron, 8 mg twice a day (BID) x 3 days, compared with 2000 cGy/5 fractions without prophylactic anti-emetic (53% *emesis-free* after single fraction + prophylactic ondansetron versus 35% *emesis-free* for multiple fractionation without prophylaxis). Vomiting was equally common (30%) in either treatment arm in a subgroup of patients evaluated (n=124) for nausea/vomiting in the Bone Pain Trial study.
- Observed re-irradiation rates were higher with single fraction treatment (11-25%) than with multiple-fraction treatment (3-12%). Indications for re-irradiation were not described.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- "*Standard*" refers to what is applicable to the majority of patients, with a preference for patient convenience and ease of administration, without compromising treatment efficacy or morbidity.
- The recommendation does not apply to lesions previously irradiated, or lesions causing cord compression or pathologic fractures, because such patients were mostly excluded from clinical trials examining fractionation schedules.
- Prophylactic anti-emetic agents should be considered when a significant proportion of the gastrointestinal tract is in the irradiated volume.
- Patients and referring physicians should be advised that repeat irradiation to the treated area may be possible.
- There is insufficient evidence at this time to make a dose-fractionation recommendation for other treatment indications, such as long term disease control for patients with solitary bone metastasis, prevention/treatment of cord compression, prevention/treatment of pathologic fractures, and treatment of soft tissue masses associated with bony disease.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult these guidelines is expected to use independent medical judgement in the context of individual clinical circumstances or seek out the supervision of a qualified

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IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

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ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Mar 14

GUIDELINE DEVELOPER(S)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Supportive Care Guidelines Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of members, please visit the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Supportive Care Guidelines Group disclosed potential conflict of interest information.

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GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

- Radiotherapy Fractionation for the Palliation of Uncomplicated Painful Bone Metastases. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available from the Cancer Care Ontario Web site.
- 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.

PATIENT RESOURCES

None available

NGC STATUS

This summary was updated on July 30, 2003. The updated information was verified by the guideline developer on September 2, 2003.

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