Complete Summary

GUIDELINE TITLE

The role of postoperative chemoradiotherapy for advanced squamous cell carcinoma of the head and neck.

BIBLIOGRAPHIC SOURCE(S)

Head and Neck Disease Site Group. Winquist E, Oliver T, Gilbert R. The role of postoperative chemoradiotherapy for advanced squamous cell carcinoma of the head and neck. Toronto (ON): Cancer Care Ontario (CCO); 2004 Dec. 20 p. (Evidence-based series; no. 5-10). [13 references]

GUIDELINE STATUS

This is the current release of the guideline.

The Guideline will expand over time 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.

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SCOPE

DISEASE/CONDITION(S)

Advanced squamous cell carcinoma of the head and neck

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Oncology
Otolaryngology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the role of postoperative concurrent chemotherapy and radiotherapy for patients with advanced (Stage III or IV) squamous cell carcinoma of the head and neck

TARGET POPULATION

Adult patients scheduled to receive adjuvant therapy after definitive surgery for advanced (Stage III or IV) squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx, who are also considered at a high-risk of cancer recurrence by the treating oncologist because of one or more of the following tumour characteristics:

- Microscopically involved mucosal margins of resection
- Histological evidence of metastases in two or more regional lymph nodes (pN2-N3)
- Extracapsular extension of nodal disease
- pT3-T4 tumours with negative surgical margins (except pT3 larynx)
- Oral cavity or oropharynx cancers with level IV or V pathological nodal involvement
- Perineural involvement
- Microvascular tumour emboli

INTERVENTIONS AND PRACTICES CONSIDERED

Treatment

Postoperative adjuvant concurrent chemoradiotherapy

MAJOR OUTCOMES CONSIDERED

- Locoregional control
- Distant metastases
- Progression-free, disease-free, and overall survival
- Adverse events
- Quality of life

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

The literature was searched using MEDLINE (OVID: 1966 through September 2004), EMBASE (OVID:1980 through September 2004), the Cochrane Library (OVID: Issue 2, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse. In addition, the proceedings of the meetings of the American Society of Clinical Oncology (1997-2004), the American Society for Therapeutic Radiology and Oncology (1992-2003), the European Society of Therapeutic Radiology and Oncology (2000, 2002), and the European Society for Medical Oncology (1998, 2000, 2002) were searched for relevant abstracts. Article bibliographies and personal files were also searched to September 2004 for evidence relevant to this practice guideline report.

The literature search of the electronic databases combined disease specific terms (head and neck neoplasms/ or carcinoma, squamous cell/ or head and neck cancer.mp.) with treatment specific terms in the postoperative setting (drug therapy/ or chemotherapy/ or radiochemotherapy.mp. or chemoradiotherapy.mp.) and search specific terms for the following study designs: practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials.

Inclusion Criteria

Articles were selected for inclusion in the systematic review of the evidence if they were published reports or published abstracts of randomized controlled trials that:

- Included patients with newly diagnosed locally advanced squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx
- Compared any combination of postoperative concurrent chemoradiotherapy versus the identical postoperative radiotherapy regimen alone
- Reported results for the outcomes of interest: locoregional control, distant metastases, progression-free survival, disease-free survival, overall survival, adverse events, and aspects related to quality of life

Practice guidelines, meta-analyses, or systematic reviews explicitly based on randomized trials related to the guideline question were also eligible for inclusion in the systematic review of the evidence.

Exclusion Criteria

Articles were excluded from the systematic review of the evidence if they were any of the following:

- Papers published in a language other than English.

NUMBER OF SOURCE DOCUMENTS

Four randomized controlled trials were eligible for inclusion and review.

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

Combining results across trials provides added power for detecting the efficacy of the treatment and improves the reliability or confidence of the point estimate. Where appropriate, data on outcomes of interest are pooled across trials using a clinically relevant event or time-point. Data are pooled using Review Manager 4.0.3 (Metaview© Update Software), which is available through the Cochrane Collaboration (www.cochrane.org). The random effects model is generally used over the fixed effects model as the more conservative estimate of effect. Results are expressed as the Risk Ratio (RR) with 95% confidence intervals (CI), where a RR less than 1.0 favours the experimental treatment and a RR greater than 1.0 favours control. The number of patients needed to treat for one additional patient to benefit (NNT) is calculated using the inverse of the risk difference.

Where appropriate, sensitivity analyses are conducted to determine whether particular study characteristics influence the estimate of treatment effect. In the event of multiple treatment arms, the treatment arms are categorized as separate trials, comparing each treatment arm with the same control arm.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

From the data it was clear that there were significant loco-regional control and survival benefits associated with the addition of chemotherapy to post-operative radiation. The main considerations for use however were not the control nor the survival benefits, but the appropriate patient population for this treatment, the

patient's ability to tolerate high doses of cisplatin, and the concern over possible increases in severe late effects.

The four randomized trials identified in the search of the literature involved only patients who were considered to be at a high risk of recurrence. While the presence of some indicators such as perineural involvement or vascular tumor emboli alone may not necessarily indicate a high risk of recurrence, those prognostic indicators were included as part of the eligibility criteria in one of the larger randomized trials. On that basis, those prognostic indicators were included as part of the target population of patients deemed at a higher risk of recurrence. It is relatively rare that a patient would present with only perineural involvement or vascular tumor emboli; however, it would be expected that the treating clinician would weigh individual patient circumstances in applying high-risk recurrence criteria to specific patients. Patients in these trials also had good to excellent performance status and the vast majority were less than 70 years of age. This should be kept in mind when considering the addition of chemotherapy to post-operative radiotherapy.

The two larger randomized trials employed high doses of cisplatin (100 mg/m2) once every three weeks for three cycles. At that dose, acute toxicities were high and compliance to the full course of chemotherapy was less than two thirds of the patient population in each of the trials. Quality of life was also not assessed in any of the randomized trials.

Even with no statistically significant differences in late effects reported in any of the randomized trials, the late effects with chemotherapy, especially pharangeal stricture and dysphagia were of concern to members of the Disease Site Group (DSG), and to practitioners who provided comments during practitioner feedback. While the alternative of withholding a treatment that improves control and survival at the expense of adverse events is not being suggested, it is clear that the addition of chemotherapy to postoperative radiotherapy does come at a cost. Clinicians and patients alike should be aware of the potential trade-off between improved control and survival, and the increased toxicity and potential long terms effects associated with chemotherapy as part of a post-operative adjuvant treatment approach.

In light of the overall evidence with input from Ontario practitioners and the Practice Guidelines Coordinating Committee, the Head and Neck Cancer Disease Site Group generated recommendations on the use of post-operative radiochemotherapy for patients at a high risk of recurrence.

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 91 practitioners in Ontario (12 medical oncologists, 24 radiation oncologists, and 55 surgeons). The survey consisted of 21 items evaluating the methods, results, and interpretive summary used to inform the draft recommendations outlined 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 practice guideline report was circulated to 15 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Nine of the 15 members returned ballots. All nine PGCC members approved the practice guideline report as written. One member requested minor modifications to the format of the document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

- Postoperative adjuvant chemoradiotherapy is recommended as an effective treatment approach to improve control and survival outcomes for those patients at a high risk of recurrence who are willing and deemed able to tolerate the addition of chemotherapy to radiotherapy.
- The recommended postoperative adjuvant chemoradiotherapy regimen is 100mg/m^2 of cisplatin administered every 21 days for three cycles concurrently with standard doses of conventionally fractionated radiotherapy.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are supported by randomized controlled trials.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

- Three trials reported statistically significant improvements in locoregional control with radiochemotherapy when compared with radiotherapy alone. Rates of locoregional recurrence were significantly less for patients who received radiochemotherapy versus those who received radiotherapy alone

(relative risk=0.59; 95% confidence interval, 0.47 to 0.75; p=0.00001). The relative risk of 0.59 indicates a 41% relative reduction in the risk of locoregional recurrence occurring when chemotherapy is added to radiotherapy. In absolute terms, this result translates into a 12.5% improvement (number needed to treat=8; 95% confidence interval, 6 to 14) in locoregional control in favour of radiochemotherapy.
- Three trials reported statically significant improvements in overall survival favouring radiochemotherapy versus radiotherapy alone. Pooled data across all trials confirm this treatment effect (relative risk=0.80; 95% confidence interval, 0.71 to 0.90; p=0.0002). The relative risk of 0.80 indicates a 20% relative reduction in the risk of death when chemotherapy is added to radiotherapy. With a number needed to treat of eight (95% confidence interval, 6 to 17), this result translates into a 12.5% absolute improvement in overall survival in favour of radiochemotherapy.

POTENTIAL HARMS

Table 3 in the original guideline document outlines some of the commonly reported adverse events related to treatment. Statistical comparisons were not consistently reported; however, as can be expected, acute adverse events were more common with radiochemotherapy than with radiotherapy alone. The most common grade 3/4 adverse events were mucositis or dysphagia, followed by various hematological events and nausea and vomiting. The late toxicity profile of that treatment approach was not well documented.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Chemoradiotherapy is associated with more acute toxicity than radiotherapy alone; specifically, more frequent and severe mucositis or dysphagia, nausea and vomiting, weight loss, and hematological toxicity. The late toxicity profile of this treatment approach is not well documented and remains a concern.
- Quality of life was not assessed in any of the randomized trials.
- The majority of patients studied in the randomized trials of adjuvant chemoradiotherapy were less than 70 years of age, all with good to excellent functional status.
- All of the trials employed at least 54 Gy of conventionally fractionated radiotherapy. In the two larger trials, radiotherapy to the primary target volume was 54 or 60 Gy with an additional boost to high-risk sites to 66 Gy.
- Care has been taken in the preparation of the information contained in this document. Nonetheless, any person seeking to apply or consult the practice guideline is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or warranties of any kind whatsoever regarding their content or use or application and disclaims any responsibility for their application or use in any way.

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

BIBLIOGRAPHIC SOURCE(S)

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ADAPTATION

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

DATE RELEASED

2004 Dec

GUIDELINE DEVELOPER(S)

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

GUIDELINE DEVELOPER COMMENT

The Program in Evidence-based Care (PEBC), is a project supported 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

Provincial Head and Neck Cancer Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of past and present members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the disease site group disclosed potential conflict of interest information. The author(s) declare that they have no competing interests.

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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

The following are available:

- The role of postoperative chemoradiotherapy for advanced squamous cell carcinoma of the head and neck. Summary. Toronto (ON): Cancer Care Ontario (CCO). Electronic copies: Available in Portable Document Format (PDF) 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 NGC summary was completed by ECRI on August 12, 2005. The information was verified by the guideline developer on September 13, 2005.

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