

Cancer Care Ontario Practice Guidelines Initiative

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The Role of Neoadjuvant Chemotherapy in the Treatment of Locally Advanced Squamous Cell Carcinoma of the Head and Neck (excluding nasopharynx)

Practice Guideline Report # 5-1

ORIGINAL GUIDELINE: February 15, 1996
MOST RECENT LITERATURE SEARCH: February 2003
NEW EVIDENCE ADDED TO THE GUIDELINE REPORT: February 2003

New evidence found by update searches since the completion of the original guideline is consistent with the original recommendation. A qualifying statement has been added.

SUMMARY

Guideline Question

What is the role of neoadjuvant chemotherapy in the treatment of patients with locally advanced squamous cell carcinoma of the head and neck region (excluding nasopharynx)?

Target Population

These recommendations apply to adult patients with locally advanced squamous cell carcinoma of the head and neck (excluding nasopharynx).

Recommendations

Key Recommendations

- Neoadjuvant chemotherapy should not be used in the routine management of patients with locally advanced squamous cell carcinoma of the head and neck if the main objective is improved survival.

Update

Qualifying Statement

- Since the initial release of this guideline, it has become common practice to use neoadjuvant chemotherapy in a combined modality approach with radiation to preserve organ function to achieve enhanced quality of life in patients with otherwise resectable disease. The randomized trials demonstrate that when neoadjuvant chemotherapy is combined with radiotherapy, organ function can be preserved in a substantial proportion of otherwise resectable patients with improved quality of life. However, there is a trend for reduced survival which is not significant. Preliminary results from a large organ preservation trial indicate that with no differences in overall survival, neoadjuvant chemotherapy with radiotherapy produces similar outcomes as radiotherapy alone. Neither treatment was as effective as concomitant chemotherapy and radiation in terms of laryngectomy preservation rate and loco-regional control.

Methods

The literature was searched using MEDLINE (through January 2003), CANCELIT (through October 2002), the Cochrane Library (Issue 4, 2002), the Physician Data Query (PDQ) database, clinical trial and practice guideline Internet sites, abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1999-2002), the American Society for Therapeutic Radiology and Oncology (1999-2002) and the European Society for Medical Oncology (1998, 2000). Article bibliographies and personal files were also searched to November 2002.

Evidence was selected and reviewed by one member of the Cancer Care Ontario Practice Guidelines Initiative's (CCOPGI) Head and Neck Cancer Disease Site Group (DSG) and methodologists. This practice guideline has been reviewed and approved by the Head and Neck cancer DSG, which comprises medical and radiation oncologists, surgeons, and epidemiologists and one 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 CCOPGI 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 published meta-analyses and 23 randomized trials were reviewed in the original guideline report. The Head and Neck Cancer Disease Site Group pooled data from 23 trials included in the original guideline report. The results indicated no survival benefit with NAC. When 19 studies of NAC involving 2915 patients were analyzed, the odds ratio (OR) was 1.07 (95% CI, 0.89 to 1.29) tending to favour the control. Other published meta-analyses are consistent with these results.
- The updated literature search identified three additional published meta-analyses, twelve new or updated reports of randomized trials and one quality of life report.
- A meta-analysis using individual patient data from 31 randomized trials (5269 patients) demonstrated no significant survival benefit for neoadjuvant chemotherapy compared with locoregional treatment alone (hazard ratio, 0.95; 95% CI, 0.88 to 1.01; $p=0.10$). However, a subgroup analysis of 15 trials (2487 patients) detected significantly improved survival with neoadjuvant chemotherapy using fluorouracil plus either cisplatin or carboplatin (hazard ratio, 0.88; 95% CI, 0.79 to 0.97; $p<0.05$). Individual patient data from three trials of larynx-preservation versus surgery were pooled in a separate analysis (602 patients). The hazard ratio for death was not-significant in favour of surgery over larynx preservation (HR = 1.19, 95% CI, 0.97 to 1.46; $p=0.10$) favouring surgery.

Prepared by the Head and Neck Cancer Disease Site Group

For further information about this practice-guideline-in-progress report, please contact Dr. D. Ian Hodson, Chair, Head and Neck Cancer Disease Site Group, Hamilton Regional Cancer Centre, 699 Concession Street, Hamilton ON, L8V 5C2; TEL (905) 387-9712; FAX (905) 575-6326.

PREAMBLE: About Our Practice Guideline Reports

The Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) 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 CCOPGI 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, community 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

I. QUESTION

Should neoadjuvant chemotherapy (NAC) be offered to patients with locally advanced squamous cell carcinoma of the head and neck region (excluding nasopharynx) with the intent of improving survival?

II. CHOICE OF TOPIC AND RATIONALE

There is controversy regarding the most effective treatment for locally advanced (stages III and IV) squamous cell head and neck cancer (SCHNC). Neither of the conventional treatment modalities, either alone (surgery in resectable cases, nor radiation in resectable or nonresectable cases), or in combination, produce acceptable treatment results. Because chemotherapy is generally associated with impressive tumour response in SCHNC, investigators have tested this modality in an attempt to downstage patients in the hope that surgery and/or radiation might be more effective in improving survival. Despite the disappointing results of neoadjuvant chemotherapy (chemotherapy prior to radiation or surgery) in randomized trials, there is concern that this treatment strategy continues to be practiced. This places an increased burden on patients in terms of side effects of treatment, and possibly on the health care system in terms of costs. Therefore, a practice guideline based on an unbiased explicit review of all the evidence was felt to be an appropriate vehicle for confirming whether our interpretations of the evidence were valid, and for influencing practice.

Recently, it has been suggested that the use of neoadjuvant chemotherapy and the addition of radiation therapy in chemotherapy responders might avoid surgery and its attendant consequences (e.g., loss of voice in patients with advanced, resectable larynx cancer) in a selected group of patients, thereby improving quality of life for some. This strategy of organ preservation is also considered in the guideline.

Carcinoma of the nasopharynx is excluded from consideration in this report because of its distinctive natural history, causes, and responsiveness to therapy compared with other squamous cell tumours of the upper aerodigestive tract. In addition, most studies of SCHNC treat this disease as a separate entity.

III. METHODS

Guideline Development

This guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle (1u). Evidence was selected and reviewed by one member of the CCOPGI's Head and Neck Cancer Disease Site Group (DSG) and methodologists. The guideline is a convenient and up-to-date source of the best available evidence on neoadjuvant chemotherapy in locally advanced squamous cell carcinoma of the head and neck (excluding nasopharynx), 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 CCOPGI 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.

Literature Search Strategy

Initially, a MEDLINE search was done for the years 1980 to June 1994 using the subject heading "head and neck neoplasms" in combination with the text words "chemotherapy" or "neoadjuvant" or "adjuvant" and the publication type "randomized controlled trials". Abstracts were excluded from the original report of December, 1994. The same search terms were used when the guideline was first

updated in February, 1996. "Meta-analysis" and "clinical trials" were added as publication types. A CANCELRIT database search was also done. Abstracts published in 1994 and 1995 were included because of empirical evidence suggesting serious biases favouring experimental treatments where systematic reviews excluded abstracts (1). The citation lists of all retrieved articles were further searched to identify additional studies. The search was restricted to English language publications.

Update

The literature was searched using MEDLINE (through January 2003), CANCELRIT (through October 2002), the Cochrane Library (Issue 4 2002), the Physician Data Query (PDQ) database, clinical trial and practice guideline Internet sites, abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1999-2002), the American Society for Therapeutic Radiology and Oncology (1999-2002) and the European Society for Medical Oncology (1998, 2000). Article bibliographies and personal files were also searched to November 2002.

Inclusion Criteria

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

1. Randomized controlled trials of neoadjuvant chemotherapy prior to local treatment with conventional radiation and/or surgery versus local treatment alone as the control.
2. Abstracts published in 1994 or later were included if the data could be extracted for analysis.

Exclusion Criteria

Trials were excluded if they concerned recurrent or metastatic disease, patients had been previously treated, nasopharynx cancer was an important fraction of the population studied, chemotherapy was not the first modality used, the control arm did not use conventional radiotherapy with or without surgery, chemotherapy was used either with alternating or concurrently with radiation, intra-arterial chemotherapy was used, or publications did not present data in an analyzable form.

Synthesizing the Evidence

To estimate the overall effect on survival of neoadjuvant chemotherapy versus conventional local therapy, the results of the randomized trials using meta-analysis were pooled according to software provided by Dr. Joseph Lau, Tufts New England Medical Centre, Boston, MA. Results are expressed as the odds ratio (OR) with 95% confidence intervals (CI) such that estimates >1.0 favour control and estimates <1.0 favour neoadjuvant chemotherapy. Data were analyzed using both fixed-effect (Mantel-Haenszel) and random effect (2) models. The results were similar and those of the random effects model are shown. Finally, a subgroup analysis was performed to determine whether the addition of adjuvant chemotherapy to neoadjuvant therapy was beneficial, and to determine whether neoadjuvant trials employing the combination of cisplatin and infusional 5-fluorouracil (CP-FU) were beneficial.

The original report (December, 1994) combined the results of trials in the meta-analysis by selecting a common follow-up period across studies. For the current version, a constant odds ratio over time has been assumed to allow for a longer follow-up period in each trial. The follow-up time was restricted to a point at which at least 50% of patients had been followed (median follow-up). The assumption of constant odds ratio is sufficiently robust for the purposes of this analysis. The analytic method overestimates the precision of the confidence limits because the denominators used in the analyses were based on patients randomized, which is higher than the number of patients at risk for the period of follow-up. This should not affect the point estimates themselves, and in light of the overall results, this overestimation of precision does not alter the conclusions.

Update

With the recent publication of a pooled analysis using individual patient data (2u), new studies were not added to the original meta-analysis.

IV. RESULTS

Literature Search Results

The previous report (December, 1994) included 12 trials (3-14). Seven further trials of neoadjuvant chemotherapy (4,15-20) (Figure 1) and an additional four trials for the subgroup analysis of neoadjuvant plus adjuvant therapy (21-24) have been added. Some trials were published before 1994 but were missed in the literature search for the previous version of this guideline. Of the seven new trials, four are abstracts (15-17,19). The combination of CP-FU was used in six trials (3,14-17,19), and in a seventh trial with the addition of vindesine (4) (Figure 2).

Update

The updated literature search identified three published meta-analyses (2u-4u) and twelve new or updated randomized trials (5u-16u) that met the inclusion criteria. In addition, a follow-up study (17u) of quality-of-life data from a randomized trial cited in the earlier report (27) was located.

Outcomes

The summary results of all analyses are shown in Table 1. Figures 1 and 2 display graphically the meta-analyses for the results of the analysis of 19 trials of neoadjuvant chemotherapy and for the seven trials of CP-FU neoadjuvant chemotherapy respectively. Except CP-FU, all of the odds ratios show a survival trend in favour of control treatment, and none of the analyses show a benefit for neoadjuvant treatment, including the use of CP-FU (OR, 1.02; 95% CI, 0.71 to 1.47). These results are consistent with those of three previously published meta-analyses (1,25,26).

In addition, a trial of the Department of Veterans' Affairs (27), involving 332 patients with stage III or IV resectable larynx cancer, randomized patients to either conventional treatment (surgery followed by radiation) or an organ preservation strategy (neoadjuvant chemotherapy with radiation added for chemotherapy responders; chemotherapy nonresponders were offered surgery). At two years, survival was nearly equivalent, with just more than 60% of patients randomized to chemotherapy and radiation avoiding laryngectomy. The equivalent survival of these groups seems to be holding up in longer term follow-up [meeting presentations]. However, lack of a radiotherapy alone control group does not allow a definitive statement on the need for chemotherapy for organ preservation.

Table 1. Summary results of meta-analyses of neoadjuvant chemotherapy in squamous cell head and neck cancer.

Treatments	Number of Trials	Number of Patients	Odds Ratio	95% Confidence Intervals	
				lower	upper
All trials	23	3205	1.08	0.92	1.28
Neoadjuvant only	19	2915	1.07	0.89	1.29
Neoadjuvant + adjuvant	4	290	1.23	0.75	2.04
CP-FU neoadjuvant	7	953	1.02	1.02	1.47

Note: CP-FU, cisplatin plus infusional 5-fluorouracil.

Figure 1. Meta-analysis of 19 trials reported in original guideline report.

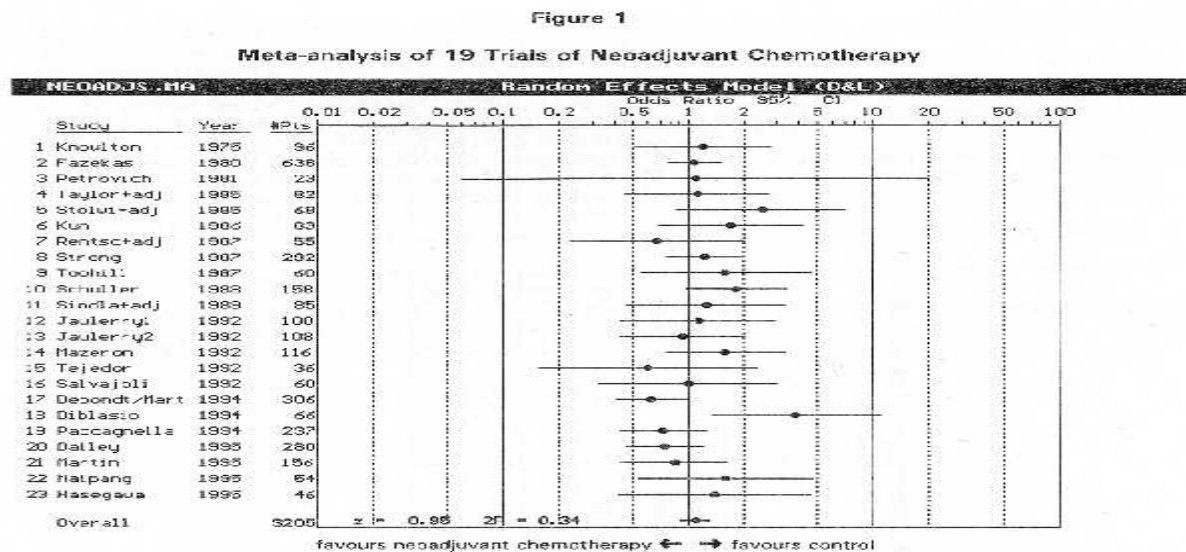
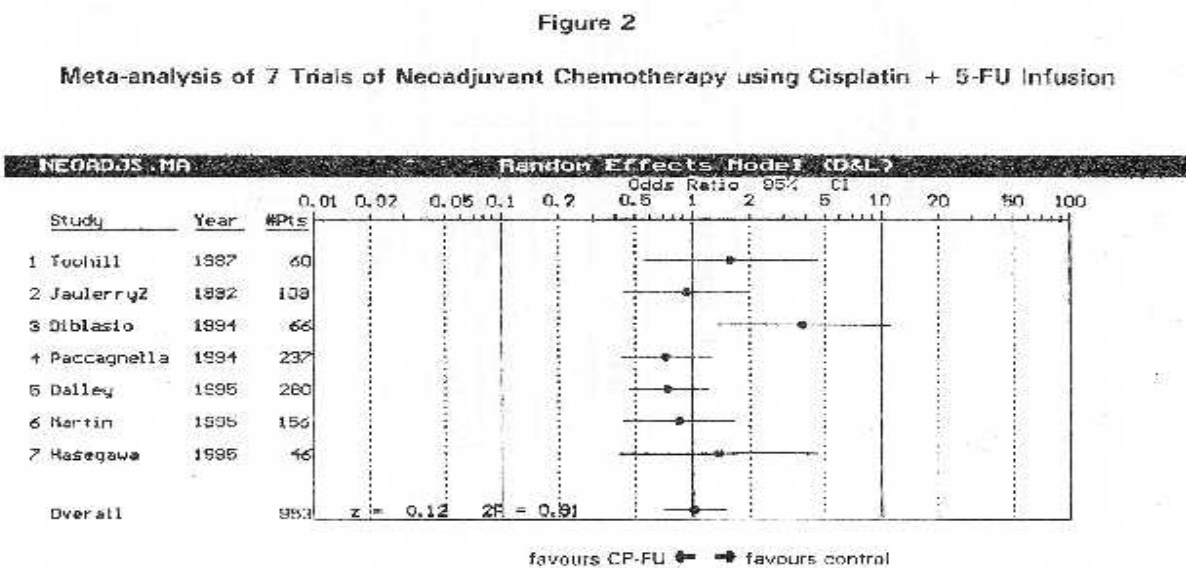


Figure 2. Meta-analysis of 7 trials reported in original guideline report.



Update

Of the three meta-analyses published since the release of the original guideline report (2u-4u), the most rigorous and credible study is an individual patient data meta-analysis of 31 randomized trials (5269 patients) of locoregional treatment with or without neoadjuvant chemotherapy by Pignon et al (2u). The results demonstrated no significant survival benefit for neoadjuvant chemotherapy (hazard ratio, 0.95; 95% CI, 0.88 to 1.01; p=0.10). There was no significant heterogeneity among the pooled results. A subgroup analysis of 15 trials (2487 patients) detected significantly improved survival with neoadjuvant chemotherapy using fluorouracil plus either cisplatin or carboplatin compared with locoregional treatment alone (hazard ratio, 0.88; 95% CI, 0.79 to 0.97; p<0.05). Individual patient data from three trials of larynx-preservation versus surgery were pooled in a separate analysis (2u). The hazard ratio for death was not-significant in favour of surgery over larynx preservation (HR = 1.19, 95% CI, 0.97 to 1.46; p=0.10). There was significant heterogeneity. Results were similar when adjusted for nodal status and tumour sub-site.

Twelve new or updated randomized trials comparing neoadjuvant chemotherapy plus local treatment (surgery and/or radiotherapy) with local treatment alone in patients with locally advanced squamous cell carcinoma of the head and neck were identified (5u-16u). Of the 12 trials, results from nine studies (5u-13u) were included in the individual patient data meta-analysis by Pignon et al (2u). These nine trials contribute to the overall body of evidence and need not be further considered on an individual basis. Results from two new trials (14u, 15u) failed to show any significant survival benefit with the addition of neoadjuvant chemotherapy.

One randomized controlled trial (16u), published as an abstract, compared 547 patients randomized to neoadjuvant chemotherapy, radiotherapy alone, or concomitant chemotherapy and radiotherapy in a large larynx preservation trial. For patients randomized to neoadjuvant therapy or to radiotherapy alone, there were no significant differences in 5-year overall survival (~75% vs. ~75%; p=not reported), loco-regional control (61% versus 56%; p=not reported), or number of laryngectomies (43 versus 49; p=not reported). Patients randomized to the concomitant treatment arm had similar overall survival, but significantly greater loco-regional control and laryngectomy preservation than patients randomized to the other two treatment arms.

The updated literature search also identified a follow-up study (17u) of the long-term quality of life of patients who had participated in the Veterans Affairs Laryngeal Cancer Study No. 268 (27). Of 76 survivors, 65 (86%) patients could be contacted and 46 (71%) completed health status assessment instruments, including a validated head and neck cancer-specific quality of life questionnaire (HNQOL). Of the 46 respondents, 21 had been randomized to neoadjuvant chemotherapy plus radiotherapy and 25 to surgery plus radiotherapy. Scores on the mental health and pain domains were significantly better for patients randomized to neoadjuvant chemotherapy and radiation compared with patients randomized to surgery and radiation ($p<0.05$). Patients who had successful organ preservation (neoadjuvant chemotherapy and radiation) had significantly better scores on the mental health, pain and emotion domains as well as a better assessment of their response to treatment compared with patients who underwent laryngectomy (surgery and radiation or salvage laryngectomy after neoadjuvant chemotherapy and radiation) ($p<0.05$). Scores on the speech domain of the HNQOL were similar for patients randomized to neoadjuvant chemotherapy plus radiation versus surgery plus radiation as well as patients with an intact larynx versus those who underwent laryngectomy.

V. INTERPRETIVE SUMMARY

Update

For patients with locally advanced squamous cell head and neck cancer, either surgery or radiotherapy are the definitive curative modalities. Evidence is mounting that conventional radiotherapy alone is less effective than concomitant chemotherapy plus radiotherapy or some sort of altered fractionation schedule (refer to Cancer Care Ontario Practice Guidelines Initiative's guideline, *Concomitant Chemotherapy and Radiotherapy in Squamous Cell Head and Neck Cancer [Excluding Nasopharynx]*, #5-6a). When the aim of treatment is to improve survival in either resectable or unresectable cases, the evidence is now clear that there is no benefit for routine use of neoadjuvant chemotherapy. However, randomized controlled trials should continue to be supported.

For patients with resectable disease in whom it may be technically feasible to preserve organ function in order to maintain quality of life, neoadjuvant chemotherapy followed by radiotherapy is becoming more commonly used. The randomized trials demonstrate that when neoadjuvant chemotherapy is combined with radiotherapy, organ function can be preserved in a substantial proportion of otherwise resectable patients with improved quality of life. However, there is a trend for reduced survival which is not significant (mortality OR, 1.19; 95% CI, 0.97 to 1.46; $p=0.10$). Preliminary evidence from one large trial, reported as an abstract, shows that no significant differences between neoadjuvant chemotherapy and radiotherapy alone were detected in any of the outcomes measured. Patients randomized to a third arm of the trial, concomitant chemotherapy and radiotherapy, had similar overall survival, but significantly greater loco-regional control and organ preservation than patients randomized to the other treatment arms.

VI. ONGOING TRIALS

CNR-012309: Phase III randomized study of neoadjuvant cisplatin and fluorouracil followed by surgery with or without radiotherapy versus surgery alone with or without radiotherapy alone in patients with stage II-IV squamous cell carcinoma of the oral cavity. A total of 240 patients will be accrued. Summary Last Modified October 2000.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

There was a general consensus among DSG members about the main thrust of this recommendation. Areas of discussion in the previous report included: 1) the potential uses of cause-specific survival as opposed to overall survival as the appropriate outcome; and 2) whether patients with advanced resectable larynx cancer should be advised of the results of the VA trial for the purpose of shared decision making. The DSG members felt that: 1) for treatment purposes, overall survival is the most appropriate outcome on which to base decisions at this time; 2) the lack of a radiation alone control arm in the VA study is sufficiently serious to preclude a recommendation for offering patients with resectable larynx cancer the option of an organ preservation strategy that includes chemotherapy; however, the DSG members remained split on this issue, with some advocating full information being given to patients for shared decision making.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

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 described in the original report above, the Head and Neck Cancer DSG drafted the following recommendations:

- Neoadjuvant chemotherapy should not be used in the routine management of patients with locally advanced SCHNC if the objective is improved survival.

Practitioner Feedback

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

Methods

Practitioner feedback was obtained through a mailed survey of 63 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 Head and Neck Cancer Disease Site Group.

Results

Forty-seven (75%) surveys were returned. Thirty-three (70%) respondents indicated that the practice-guideline-in-progress report was relevant to their clinical practice and they completed the survey. Ten (30%) respondents provided written comments.

Summary of Main Findings

Ninety-two percent of respondents agreed with the quality of the data synthesis, 94% endorsed the draft recommendation and 78% agreed that the report should be approved as a practice guideline. Practitioner feedback did not express a need to modify the draft recommendation.

Modifications/Actions

The draft recommendation was not modified based on practitioner feedback. However, the guideline report was updated to reflect the current evidence.

Approved Practice Guideline Recommendations

These practice guideline recommendations reflect the integration of the draft recommendations with feedback obtained from the External Review process. They have been approved by the Head and Neck Cancer DSG and the Practice Guideline Coordinating Committee.

- Neoadjuvant chemotherapy should not be used in the routine management of patients with locally advanced SCHNC if the objective is improved survival.
- It is premature to recommend neoadjuvant chemotherapy in a combined modality approach with radiation versus radiation alone to preserve organ function to achieve enhanced quality of life in patients with otherwise resectable disease.

Update

The second bullet of the recommendations was modified as a qualifying statement. The new information from review and updating activities was not subject to external review because the new evidence is consistent with the data used to inform the original guideline.

IX. PRACTICE GUIDELINE

This practice guideline reflects the most current information reviewed by the Head and Neck Cancer DSG.

Target Population

These recommendations apply to adult patients with locally advanced squamous cell carcinoma of the head and neck (SCHNC) (excluding nasopharynx).

Recommendations

Key Recommendations

- Neoadjuvant chemotherapy should not be used in the routine management of patients with locally advanced squamous cell carcinoma of the head and neck if the main objective is improved survival.

Qualifying Statement

- Since the initial release of this guideline, it has become common practice to use neoadjuvant chemotherapy in a combined modality approach with radiation to preserve organ function to achieve enhanced quality of life in patients with otherwise resectable disease. The randomized trials demonstrate that when neoadjuvant chemotherapy is combined with radiotherapy, organ function can be preserved in a substantial proportion of otherwise resectable patients with improved quality of life. However, there is a trend for reduced survival which is not significant. Preliminary results from a large organ preservation trial indicate that with no differences in overall survival, neoadjuvant chemotherapy with radiotherapy produces similar outcomes as radiotherapy alone. Neither treatment was as effective as concomitant chemotherapy and radiation in terms of laryngectomy preservation rate and loco-regional control.

X. JOURNAL REFERENCE

This practice guideline report was not submitted to a peer reviewed journal, but was published to the Internet in 1996 and has been kept current since that time (<http://www.cancercare.on.ca/ccopgi/>).

XI. ACKNOWLEDGMENTS

The Head and Neck Cancer Disease Site Group would like to thank Dr. G. Browman for taking the lead in drafting and revising this practice guideline report.

The Head and Neck Cancer Disease Site Group would like to thank Dr. G. Browman, Ms. Manya Charette, and Mr. Tom Oliver for taking the lead in updating this practice guideline report.

For a full list of members of the Cancer Care Ontario Head and Neck Disease Site Group, please visit the Website of the Program in Evidence-based Care at <http://www.cancercare.on.ca/ccopgi/>

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Update

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