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The Role of Amifostine as a Radioprotectant in the Management of Patients with Squamous Cell Head and Neck Cancer

Practice Guideline Report # 5-8

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ORIGINAL GUIDELINE: May 13, 2003
NEW EVIDENCE ADDED TO THE GUIDELINE REPORT: November 18 2003
MOST RECENT LITERATURE SEARCH: March 2004

New evidence found by update searches since the completion of the original guideline is consistent with the original recommendation.

SUMMARY

Guideline Question
For patients with squamous cell head and neck cancer, does amifostine safely and effectively ameliorate important side effects of radiotherapy with acceptable toxicity and no tumour protection? Xerostomia, mucositis, and the anti-tumour effects of amifostine were the main outcomes of interest.

Target Population
These recommendations apply to adult patients with any stage of squamous cell head and neck cancer who are receiving radical radiotherapy, encompassing at least 75% of the parotid glands, with or without concurrent chemotherapy.

Recommendations
- On the basis of the available data, amifostine is recommended as an effective treatment option for the reduction of acute and chronic xerostomia associated with radical conventionally fractionated radiotherapy, given to patients in the head and neck region encompassing at least 75% of the parotid glands, with or without standard dose carboplatin.
- The recommended dose and administration of amifostine is an intravenous infusion 15 to 30 minutes prior to radiation, with standard doses of 500mg or doses ranging from 200mg/m^2 to 300 mg/m^2. The Head and Neck Cancer Disease Site Group would be supportive of randomized trials designed to compare amifostine delivered subcutaneously versus intravenously.
- Data on the protective effect of amifostine from mucositis are inconclusive at this time.

Qualifying Statements

- For suitable patients with stage III/IV squamous cell carcinoma, a common practice in Ontario is a conventionally fractionated course of radiotherapy delivered concurrently with low-dose cisplatin or carboplatin. No trials of amifostine added to concurrent low-dose radiochemotherapy were identified in our literature search. While it is reasonable to extrapolate that the radioprotection of acute and chronic xerostomia with amifostine may extend to patients treated with low-dose concurrent chemoradiotherapy, there is the theoretical possibility that amifostine may compromise the anti-tumour effectiveness of low-dose daily cisplatin or carboplatin.
- The data on tumour control and survival outcomes support the conclusion that amifostine does not confer tumour protection; however, long-term data beyond 24 months are not yet available for this population of patients.
- Nausea, vomiting, hypotension, and allergic reactions were reported as the most common side effects of amifostine, but they were rarely severe (≥ grade 3).

Methods

The literature was searched using MEDLINE (1966 through January 2003), CANCERLIT (1983 through October 2002), the Cochrane Library (Issue 4, 2002), the Physician Data Query (PDQ) database, clinical trial and practice guideline Internet sites, and abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1998-2002), the American Society for Therapeutic Radiology and Oncology (1999-2002), and the European Society for Medical Oncology (1998, 2000). Reference lists from relevant articles and reviews were searched for additional trials.

Evidence was selected and reviewed by members of the Practice Guidelines Initiative's Head and Neck Cancer Disease Site Group and methodologists. This practice guideline report has been reviewed and approved by the Head and Neck Cancer Disease Site Group, which comprises surgeons, medical oncologists, and radiation oncologists.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the guideline report was obtained from the Practice Guidelines Coordinating Committee.

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

Update

The original literature search has been updated using MEDLINE (January 2003 through March 2004), EMBASE (1980 through March 2004), the Cochrane Library (Issue 1, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2003), the American Society for Therapeutic Radiology and Oncology (2003), and the European Society for Medical Oncology (2002). Article bibliographies and personal files were also searched to march 2004 for evidence relevant to this practice guideline report. Please note that CANCERLIT is no longer included in update searches: results from an internal PGI project indicated that the overlap with MEDLINE is 100%, making CANCERLIT database searches redundant.

Key Evidence

- Six randomized trials (five published and one presented as an abstract), one quality-of-life paper, and one practice guideline were eligible for inclusion in the systematic review of the evidence.

- The only large randomized trial detected a significant reduction in the severity of acute and chronic xerostomia but not mucositis, with amifostine added to radiotherapy for head and neck cancer.
- From the available data, pooled results across trials indicate that patients had significantly less acute and late xerostomia with amifostine added to radiotherapy or radiochemotherapy with standard-dose carboplatin for head and neck cancer. There were no statistically significant differences in mucositis. Data from one randomized trial have yet to be presented.
- Results indicate that amifostine does not affect the anti-tumour effectiveness of radiotherapy with or without concurrent chemotherapy with carboplatin.
- Nausea, vomiting, hypotension, and allergic reactions were the most commonly reported side effects of amifostine, but they were rarely severe (≥ grade 3).

Update

- One small randomized trial comparing amifostine to control and one randomized trial comparing subcutaneous with intravenous amifostine administration were identified and included in the systematic review of the evidence.
- The second bullet has been revised through the editorial process to provide greater clarity and should now read:

  > Of the seven randomized trials comparing amifostine to control or placebo, only one trial randomized more than 100 patients per treatment arm. That trial detected a significant reduction in the severity of acute and chronic xerostomia, but not mucositis, with amifostine added to radiotherapy for head and neck cancer.
- The last sentence of the third bullet has been revised through the editorial process to provide greater clarity and should now read:

  > Data from one randomized trial published as an abstract have yet to be presented.

Future Research

Randomized trials of amifostine are needed to address issues of efficacy related to concomitant low-dose daily cisplatin or carboplatin, tumour protection, minimally effective doses, optimal routes of delivery, quality of life, and total healthcare costs.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Reports:

- #12-6: *Use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer.*
- #5-5: *Symptomatic treatment of radiation induced xerostomia in head and neck cancer patients.*

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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 (PGCC), 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.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit the CCO Internet site at:
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FULL REPORT

I. QUESTION

For patients with squamous cell head and neck cancer, does amifostine safely and effectively ameliorate important side effects of radiotherapy with acceptable toxicity and no tumour protection? Xerostomia, mucositis, and the anti-tumour effects of amifostine were the main outcomes of interest.

II. CHOICE OF TOPIC AND RATIONALE

Many patients with squamous cell head and neck cancer receive radiotherapy as part of their management. While very effective in the treatment of this patient population, radiotherapy can cause mild to severe xerostomia and/or acute oral mucositis. Radiation-induced xerostomia remains one of the most troubling acute and chronic toxicities. With a change or reduction in saliva flow—or in severe cases, no saliva flow—the patient's quality of life is reduced because of mouth dryness, taste changes, and difficulty eating and swallowing, as well as an increased risk of dental complications including osteoradionecrosis. In some cases, xerostomia can be permanent. Acute oral mucositis, an inflammation of the mucosa of the mouth, can range from mild redness to severe ulceration. The enhanced acute mucositis can cause discomfort or pain and may require intensive nutritional support or the interruption of treatment.

To date, only pilocarpine has been shown in randomized trials to reduce xerostomic symptoms in this group of patients (1). However, this benefit was confined to those patients treated after therapy had been completed and in whom salivary function was still evident. In clinical practice, the most severely affected patients generally experience little or no symptomatic relief from pilocarpine. Recent randomized trials designed to reduce the severity of xerostomia by delivering pilocarpine concurrently with radiation failed to detect any benefit of pilocarpine on xerostomia (2) or were inconclusive based upon preliminary abstract data (3).

The Head and Neck Cancer Disease Site Group (DSG) chose the use of amifostine as a radioprotectant in the treatment of head and neck cancer as an appropriate guideline topic because of the possibility of reducing radiation toxicity in current management approaches.

III. METHODS

Guideline Development

This practice guideline report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (4). Evidence was selected and reviewed by one member of the PGI's Head and Neck Cancer DSG and methodologists. Members of the Head and Neck Cancer DSG disclosed potential conflict of interest information.

The practice guideline report is a convenient and up-to-date source of the best available evidence on the use of amifostine as a radioprotectant in the treatment of head and neck cancer, developed through systematic reviews and evidence synthesis. Because the body of evidence in this report is primarily comprised of mature randomized controlled trial data, the DSG has developed recommendations. The report is intended to promote evidence-based practice. The PGI 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 (PGCC).

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

Literature Search Strategy

The literature was searched using the MEDLINE (1966 through January 2003), CANCERLIT (1983 through October 2002), and Cochrane Library (Issue 4, 2002) databases. In addition, the Physician Data Query clinical trials database, and abstracts published in the conference proceedings from the meetings of the American Society of Clinical Oncology (ASCO) (1998-2002), the American Society for Therapeutic Radiology and Oncology (1999-2002), and the European Society for Medical Oncology (1998, 2000) were searched for reports of new or ongoing trials. The Canadian Medical Association Infobase and the National Guideline Clearinghouse databases were searched for clinical practice guidelines. Reference lists from relevant articles and reviews were searched for additional trials. In the event of incomplete or missing data, authors were contacted for further information.

The literature search combined disease-specific terms (head and neck neoplasms/ or carcinoma, squamous cell/ or head and neck cancer.tw.) with treatment-specific terms (amifostine/ or amifostine.tw. or ethyol.tw. or wr-2721.tw.) and (radiotherapy/ or combined modality therapy/) with search-specific terms for the following study designs: practice guidelines, systematic reviews or meta-analyses, reviews, randomized controlled trials, and clinical trials.

Update

The original literature search has been updated using MEDLINE (January 2003 through March 2004), EMBASE (1980 through March 2004), the Cochrane Library (Issue 1, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (2003), the American Society for Therapeutic Radiology and Oncology (2003), and the European Society for Medical Oncology (2002). Article bibliographies and personal files were also searched to March 2004 for evidence relevant to this practice guideline report. Please note that CANCERLIT is no longer included in update searches: results from an internal PGI project indicated that the overlap with MEDLINE is 100%, making CANCERLIT database searches redundant

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they were fully published reports or published abstracts that reported:

- Randomized trials comparing conventionally fractionated radical radiotherapy or concurrent radiochemotherapy, encompassing at least 75% of the parotid glands, with or without amifostine in adult patients with any stage squamous cell head and neck cancer. Conventionally fractionated radiotherapy was defined as single daily fractions ranging from 1.8-2.5 Gy to a total of 5000-7400 cGy.
- Practice guidelines, meta-analyses, or systematic reviews related to the guideline question.
- Outcomes related to radiation-induced side effects, quality of life, or survival differences were reported. Xerostomia, mucositis, and the anti-tumour effects of amifostine, which were the main outcomes of interest. Tumour protection was inferred from differences in rates of response, local recurrence, and/or survival between the intervention group (with amifostine) and the control group (without amifostine).

Update

Through the editorial process the second bullet was revised as a separate paragraph to read:

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

Exclusion Criteria

- Papers published in a language other than English were not considered.

Update

Through the editorial process the document was modified to reflect the removal of the following two exclusion criteria:

- Phase I and II studies were not considered.

- Letters and editorials were not considered.

Synthesizing the Evidence

To estimate the overall radioprotective effect of amifostine on mucositis and xerostomia, the results of the randomized trials were pooled using the meta-analytic software program RevMan 4.1 (Metaview © Update Software). For the event of interest, results are expressed as the odds ratio (OR) with 95% confidence intervals (CI) such that estimates <1.0 favour amifostine and estimates >1.0 favour control. Data were to be analyzed using both fixed-effect (Mantel-Haenszel) and random effect models. If statistical heterogeneity was identified ($p<0.1$), the more conservative estimate of effect, the random effects model would be chosen. Heterogeneity was anticipated given the following trial differences:

- One large and several small randomized trials,
- Amifostine ranging from flat doses of 500 mg or 200mg/m^2 up to 300 mg/m^2,
- Amifostine administered intravenously or subcutaneously,
- Amifostine added to radiotherapy or radiochemotherapy,
- Amifostine administered daily with radiotherapy or only on days of radiochemotherapy.

Despite the anticipated heterogeneity with respect to trial quality, variation in amifostine administration, and use of chemotherapy, the hypothesis upon which amifostine use is based is the same. Therefore, the Head and Neck Cancer DSG considered the examination of the effects of amifostine across these trials appropriate.

In testing for publication bias, the funnel plots of the pooled data seemed to be asymmetric; however, two tests for publication bias, Begg's test and Egger's test, were negative (data not shown).

Update

The first and second bullets were revised through the editorial process to provide greater clarity and should now read:

- Trial size variations: one large randomized trial and several small randomized trials.
- Amifostine ranging from flat doses of 500 mg or doses of 200mg/m^2 up to 300 mg/m^2.

IV. RESULTS

Literature Search Results

Five fully published randomized trials (5, 6,8-10), one randomized trial presented as an abstract (7), one quality of life paper (11), and one practice guideline (12,13) were eligible for inclusion in the systematic review of the evidence (Table 1). Amifostine was delivered intravenously in five trials (5, 7-10) and subcutaneously in one study (6). Amifostine was added to radiotherapy in two trials (5,6) and to radiochemotherapy with carboplatin in four trials (7-10). Amifostine was administered daily with radiotherapy in four trials (5-8) but only on chemotherapy days in two trials (9, 10). Conventionally fractionated radiotherapy ranging from 5000 to 7400 cGy was used in all six trials (5-10). The goal of irradiation was definitive or postoperative in four trials (5,6,7,9), definitive in one trial (8), and not reported in one trial (10).

Patients in one trial were randomized according to birth date (10); in the other trials, the randomization procedure was acceptable (5-7) or not described (8,9). The study arms were balanced for disease site and stage in one trial (8), and in the others, data on patient demographics and disease characteristics were provided without either statistical analysis or comment on the balance of the distribution (5-7,9,10). For those trials with fewer evaluable patients than the total randomised, only Brizel et al (5) explained that these patients were not analyzed because they never received any treatment or follow-up. Sample size calculations were provided for only one trial (5), and this trial involved more evaluable patients than the estimated required sample size.

Update

One small randomized trial (1u) comparing amifostine to control and one randomized trial (2u) comparing subcutaneous versus intravenous amifostine administration were identified and included in the systematic review of the evidence. Please see Table 1u for search results and trial characteristics.

The delivery of amifostine was by infusion in one trial (1u), and one trial compared intravenous with subcutaneous administration (2u). Amifostine was added to radiotherapy in one trial (2u) and to radiochemotherapy with carboplatin in one trial (1u). Amifostine was administered daily with radiotherapy in both trials (1u,2u). Conventionally fractionated radiotherapy ranging from 5000 to 7400 cGy was used in one trial (1u), while one trial required that patients received at least 40 Gy (2u). In that one trial, patients received total radiotherapy doses ranging from 5000 to 7000 cGy (2u). The goal of irradiation was definitive or postoperative in one trial (2u) and postoperative-only in one trial (1u). The randomization procedure was not described in either trial (1u,2u). For both trials, data patient demographics and disease characteristics were provided without statistical analysis or comment, on the balance of the distribution (1u,2u). Sample size calculations were provided for in one trial (2u), but not in the other (1u).

Table 1. Search results of amifostine for patients with squamous cell head and neck cancer.

Author, Year (Reference)	No. of Pts	Treatment Groups	Radiation Dose, Fractions	Radiation Type, % of Total Population	Amifostine/Chemotherapy (Dose, Route and Timing)
Trials of Radiotherapy with or without Amifostine					
Brizel 2000 (5)	153 150	RT + A RT	5000-7000 cGy 1.8-2.0Gy/day 5 fractions/week	Definitive 34% Postop HR 45% Postop LR 21%	Amifostine: 200 mg/m^2 iv (daily with RT)
Koukourakis 2000 (6)	20 20	RT + A RT	6400-7000 cGy 2.0Gy/day 5 fractions/week	Definitive 68% Postop HR 33%	Amifostine: 500 mg sc flat dose* (daily with RT)
Trials of Radiochemotherapy with or without Amifostine					
Buntzel 2001 (7) abstract data	137 total	RT + CT + A RT + CT + placebo (double-blind)	6000-7000 cGy 2.0Gy/day 5 fractions/week	Definitive 31% Postop HR 25% Postop LR 44%	Amifostine: 300 mg/m^2 iv (days 1-5, 21-25 with RT), 200 mg/m^2 iv (days 6-20, 26-30/35 + carboplatin 70 mg/m^2 iv + RT)
Antonadou 1998 (8)	24 26	RT + CT + A RT + CT	6000-7400 cGy 2.0Gy/day 5 fractions/week	Definitive 100%	Amifostine: 300 mg/m^2 iv (daily with RT + carboplatin 90 mg/m^2 iv once per week)
Buntzel 1998 (9)	14 14	RT + CT + A RT + CT	6000 cGy 2.0Gy/day 5 fractions/week	Definitive 25% Postop 75%	Amifostine: 500 mg iv (days 1-5, 21-26 with carboplatin 70 mg/m^2 iv + RT)
Peters 1999 (10)	14 14	RT + CT + A RT + CT	6300 cGy 1.8Gy/day 5 fractions/week	Definitive NR Postop NR	Amifostine: 500 mg iv (days 1-5, 29-33 with carboplatin 70 mg/m^2 iv + RT)
Quality of Life					
Wasserman 2000 (11)	Effect of amifostine on patient assessed clinical benefit in irradiated head and neck cancer.				
Clinical Practice Guideline					
ASCO 2002 (12,13)	2002 Update of Recommendations for the use of Chemotherapy and Radiotherapy Protectants: Clinical Practice Guidelines of the American Society of Clinical Oncology				

Note: A, amifostine; ASCO, American Society of Clinical Oncology; CT, chemotherapy with carboplatin; No., number; NR, not reported; postop, postoperative; Postop HR, postoperative high-risk patients; Postop LR, postoperative low-risk patients; RT, radiotherapy; sc, subcutaneously;

* A flat dose of 500 mg of amifostine is an approximate equivalent of 250 mg/m^2 to 340 mg/m^2.

Update

Table 1u. Search results of amifostine for patients with squamous cell head and neck cancer.

Author, Year (Reference)	No. of Pts.	Treatment Groups	Radiation Dose, Fractions	Radiation Type, % of Total Population	Amifostine/Chemotherapy (Dose, Route and Timing)
Trials of Radiochemotherapy with or without Amifostine					
Vacha 2003 (1u)	25 25	RT + CT + A RT + CT	6000-7000 cGy 2.0Gy/day 5 fractions/week	Postop 100%	Amifostine: 250 mg/m^2 iv (daily with RT + carboplatin 70 mg/m^2 iv days 1-5, 21-26)
Trials of Amifostine Administration					
Bardet 2003 (2u)	54 total	RT + A (iv) RT + A (sc)	NR NR	Definitive NR Postop NR†	Amifostine: 200 mg/m^2 iv (daily with RT) Amifostine: 500 mg sc flat dose* (daily with RT)

Note: A, amifostine; ASCO, CT, chemotherapy with carboplatin; No. of Pts., number of patients; NR, not reported; Postop, postoperative; Postop HR, postoperative high-risk patients; Postop LR, postoperative low-risk patients; RT, radiotherapy; sc, subcutaneously; iv, intravenously.

* A flat dose of 500 mg of amifostine is an approximate equivalent of 250 mg/m^2 to 340 mg/m^2.

† This trial reported a majority of patients treated with postoperative radiotherapy, however specific data are not reported.

Acute Xerostomia

Results from the six randomized trials on ≥ grade 2 acute xerostomia are reported in Table 2. The large trial by Brizel et al (5) detected a significant reduction in ≥ grade 2 acute xerostomia with amifostine. Although the trial of subcutaneous amifostine added to radiotherapy (6) detected a difference in severe mouth dryness, and persistent use of water as a substitute for saliva, favouring amifostine, this difference was not statistically significant. Of the four radiochemotherapy trials, the trial reported as an abstract by Buntzel et al (7) did not report separate results per treatment arm, two small trials (8, 9) detected a significant reduction in ≥ grade 2 acute xerostomia with amifostine, and one small trial with 28 patients randomized (10) did not detect any differences in the pre/post-scintigram of salivary glands.

Update

Results from the randomized trials on ≥ grade 2 acute xerostomia are reported in Table 2u. One trial did not report overall results (1u), and one trial reported similar results for acute xerostomia in patients who received intravenous versus subcutaneous amifostine (2u).

Table 2. Randomized trials of amifostine in head and neck cancer – acute xerostomia.

Author, Year (Reference)	Treatment Groups	Scale*	Number of Patients	Patients with ≥ Grade 2 Xerostomia	p-value
Trials of Radiotherapy with or without Amifostine					
Brizel 2000 (5)	RT + A RT	RTOG ≥ grade 2	143 153	73 (51%) 120 (78%)	p<0.0001
Koukourakis 2000 (6)	RT + A RT	Mouth dryness and water use	19 20	11 (58%) 15 (75%)	P=0.32
Trials of Radiochemotherapy with or without Amifostine					
Buntzel 2001 (7) abstract data	RT + CT + A RT + CT + placebo	RTOG ≥ grade 2	137 in total	48 (35%) entire population	NR
Antonadou 1998 (8)	RT + CT + A RT + CT	RTOG ≥ grade 2	22 23	6 (27%) 19 (83%)	p=0.0001
Buntzel 1998 (9)	RT + CT + A RT + CT	WHO ≥ grade 2	14 14	3 (21%) 14 (100%)	P<0.001
Peters 1999 (10)	RT + CT + A RT + CT	Salivary gland scintigram	14 14	NR NR	P=NS

Note: A, Amifostine; NR, not reported; NS, no significant difference; RT, radiotherapy; RT + CT, radiotherapy with concurrent chemotherapy;; RTOG, Radiation Therapy Oncology Group; WHO, World Health Organization.

* See Appendix I for ROTG and WHO grading information.

Update

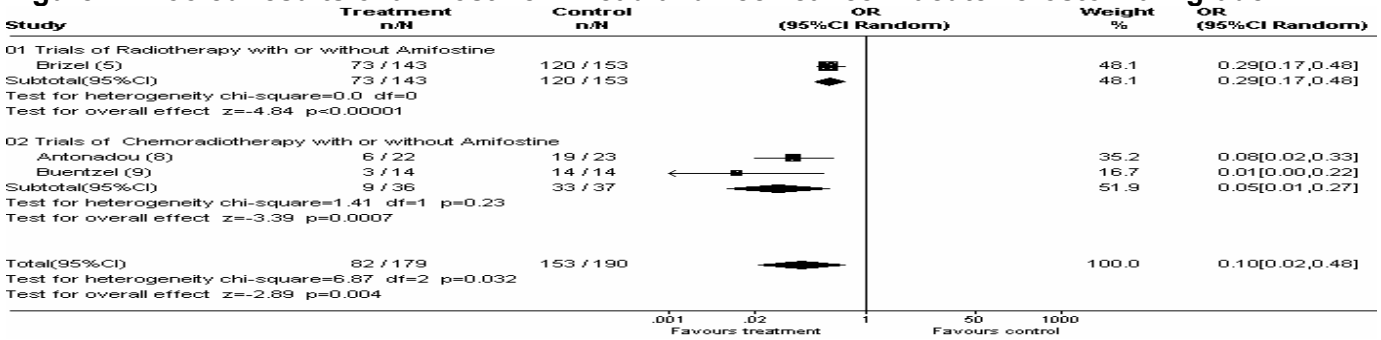
Table 2u. Randomized trials of amifostine in head and neck cancer– acute xerostomia.

Author, Year (Reference)	Treatment Groups	Scale*	Number of Patients	Patients with ≥ Grade 2 Xerostomia	p-value
Trials of Radiochemotherapy with or without Amifostine					
Vacha 2003 (1u)	RT + CT + A RT + CT	RTOG	19 21	NR NR	p=NR
Trials of Amifostine Administration					
Bardet 2003 (2u)	RT + A (iv) RT + A (sc)	RTOG ≥ grade 2	54 total	NR (23%) NR (19%)	p=NR

Note: A, Amifostine; NR, not reported; RT, radiotherapy; RT + CT, radiotherapy with concurrent chemotherapy, sc, subcutaneously; iv, intravenously.
* See Appendix I for ROTG and WHO grading information.

Pooled results from three randomized trials (5,8,9) using data from recognized symptomatic scoring scales (Radiation Therapy Oncology Group [RTOG] and World Health Organization [WHO] scoring criteria) were pooled to assess the effect of amifostine on acute xerostomia in patients with head and neck cancer (Figure 1). Data from the remaining three trials (6,7,10) were either not reported or were from non-standardized physiological measures that were not directly comparable. The overall effect was a statistically significant benefit with amifostine (OR, 0.10; 95% CI, 0.02 to 0.48, p=0.004); however, significant heterogeneity was present (Please see the discussion below on heterogeneity). Significant differences were detected, by treatment type, in favour of amifostine added to the one trial of radiotherapy (OR, 0.29; 95% CI, 0.17 to 0.48, p=0.004) and to the two trials of radiochemotherapy (OR, 0.05; 95% CI, 0.01 to 0.48, p=0.027).

Figure 1. Pooled results of amifostine in head and neck cancer - acute xerostomia ≥ grade 2.



Late Xerostomia

Results from the six randomized trials on ≥ grade 2 late xerostomia are reported in Table 3. Of the two radiotherapy trials with or without amifostine, the trial by Brizel et al (5) detected a significant reduction in ≥ grade 2 late xerostomia with amifostine, while the trial reported by Koukourakis et al (6) did not report data on late xerostomia. Of the four radiochemotherapy trials, two trials did not report data on late xerostomia (7,10), and the remaining two small trials (8,9) detected a significant reduction in ≥ grade 2 chronic xerostomia with amifostine.

Update

Results from the randomized trials on ≥ grade 2 late xerostomia are reported in Table 3u. Neither trial reported results for patients with late xerostomia (1u,2u).

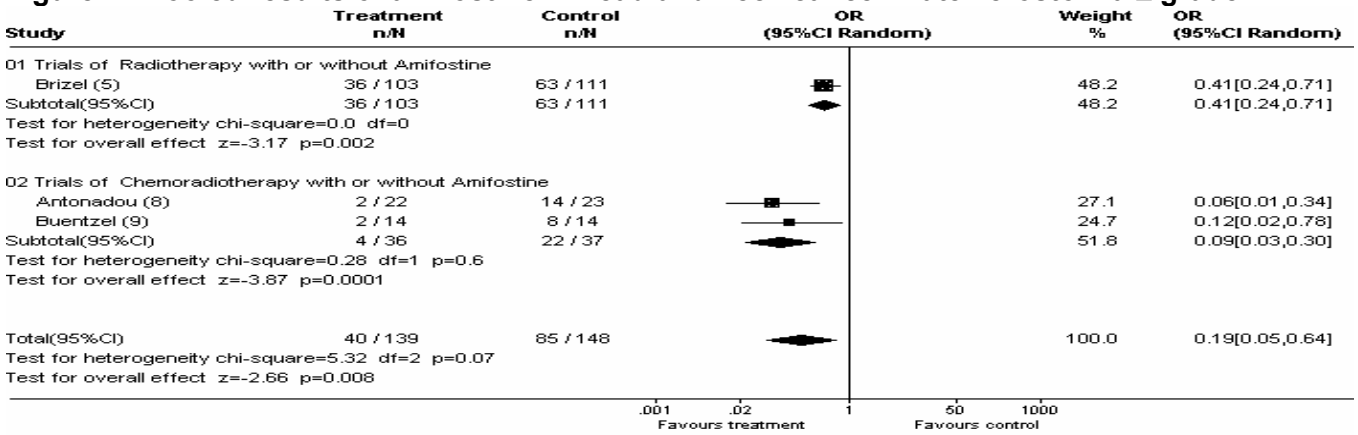
Table 3. Randomized trials of amifostine in head and neck cancer – late xerostomia.

Author, Year Reference	Treatment Groups	Scale *	Number of Patients	Patients with ≥ Grade 2 Xerostomia	p-value
Trials of Radiotherapy with or without Amifostine					
Brizel 2000 (5)	RT + A RT	RTOG ≥ grade 2 (12 months)	103 111	36 (35%) 63 (57%)	P=0.002
Koukourakis 2000 (6)	RT + A RT	Mouth dryness and water use	NR NR	NR NR	NR
Trials of Radiochemotherapy with or without Amifostine					
Buntzel 2001 (7) abstract data	RT + CT + A RT + CT + placebo	RTOG ≥ grade 2 (12 months)	NR NR	NR NR	NR
Antonadou 1998 (8)	RT + CT + A RT + CT	RTOG ≥ grade 2 (12 months)	22 23	2 (9%) 14 (61%)	0.0004
Buntzel 1998 (9)	RT + CT + A RT + CT	WHO ≥ grade 2	14 14	2 (17%)† 8 (55%)†	0.05
Peters 1999 (10)	RT + CT + A RT + CT	Salivary gland scintigram	NR NR	NR NR	NR

Note: A, Amifostine; NR, not reported; NS, no significant difference; RT, radiotherapy; RT + CT, radiotherapy with concurrent chemotherapy
* See appendix I for ROTG and WHO grading information.
† Approximate results calculated from table data.

Data from three randomized trials (5,8,9) using recognized symptomatic scoring scales (RTOG and WHO scoring criteria) were pooled to assess the effect of amifostine on late xerostomia in patients with head and neck cancer (Figure 2). Data on late xerostomia were not available in the remaining three trials (6,7,10). The overall effect was a statistically significant benefit with amifostine (OR, 0.19; 95% CI, 0.05 to 0.64, p=0.008). By treatment type, significant differences in favour of amifostine were detected for the one trial of radiotherapy alone (OR, 0.41; 95% CI, 0.24 to 0.71, p=0.002) and for the two trials of radiochemotherapy (OR, 0.0001; 95% CI, 0.09 to 0.30, p=0.027). Heterogeneity was present in the estimation of overall effect (Please see the discussion on heterogeneity).

Figure 2. Pooled results of amifostine in head and neck cancer - late xerostomia ≥ grade 2



Mucositis

Results from the six randomized trials on ≥ grade 3 mucositis are reported in Table 4. Of the two radiotherapy trials, the large randomized trial of amifostine added to radiotherapy (5) did not detect any significant reduction in severe mucositis with amifostine, while the small subcutaneous trial (6) detected a significant difference in favour of amifostine. Of the four radiochemotherapy trials, one trial reported as an abstract (7) did not report separate results per treatment arm, two small trials (8,9)

detected a significant reduction in severe mucositis with amifostine, and one small trial (10) did not detect any cases of severe mucositis for either treatment arm.

Update

Results from the randomized trials on ≥ grade 3 mucositis are reported in Table 4u. One trial reported identical rates of severe mucositis in the amifostine and control arms (1u), and one trial (2u) reported results for mucositis ≥ grade 2 for with amifostine administered intravenously versus subcutaneously (69% versus 68%, p=not reported), however results were not reported for mucositis ≥ grade 3.

Table 4. Randomized trials of amifostine in head and neck cancer – mucositis.

Author, Year (Reference)	Treatment Groups	Scale*	Number of Patients	Patients with Mucositis ≥ Grade 3	p-value
Trials of Radiotherapy with or without Amifostine					
Brizel 2000 (5)	RT + A RT	RTOG ≥ grade 3	148 153	52 (35%) 60 (39%)	p=0.48
Koukourakis 2000 (6)	RT + A RT	WHO ≥ grade 3	19 20	0 (0%) 6 (30%)	p=0.02
Trials of Radiochemotherapy with or without Amifostine					
Buntzel 2001 (7) abstract data	RT + CT + A RT + CT + placebo	RTOG ≥ grade 3	137 in total	44 (32%) for entire population	NR
Antonadou 1998 (8)	RT + CT + A RT + CT	RTOG ≥ grade 3	22 23	14 (64%)† 22 (96%)†	P=0.0098
Buntzel 1998 (9)	RT + CT + A RT + CT	WHO ≥ grade 3	14 14	0 (0%) 12 (86%)	p<0.001
Peters 1999 (10)	RT + CT + A RT + CT	WHO ≥ grade 3	14 14	0 (0%) 0 (0%)	p=NS

Note: A, Amifostine; NR, not reported; NS, no significant difference; RT, radiotherapy; RT + CT, radiotherapy with concurrent chemotherapy
* See appendix I for ROTG and WHO grading information.
† Results are reported for the highest weekly incidence of mucositis occurring in a seven-week period.

Update

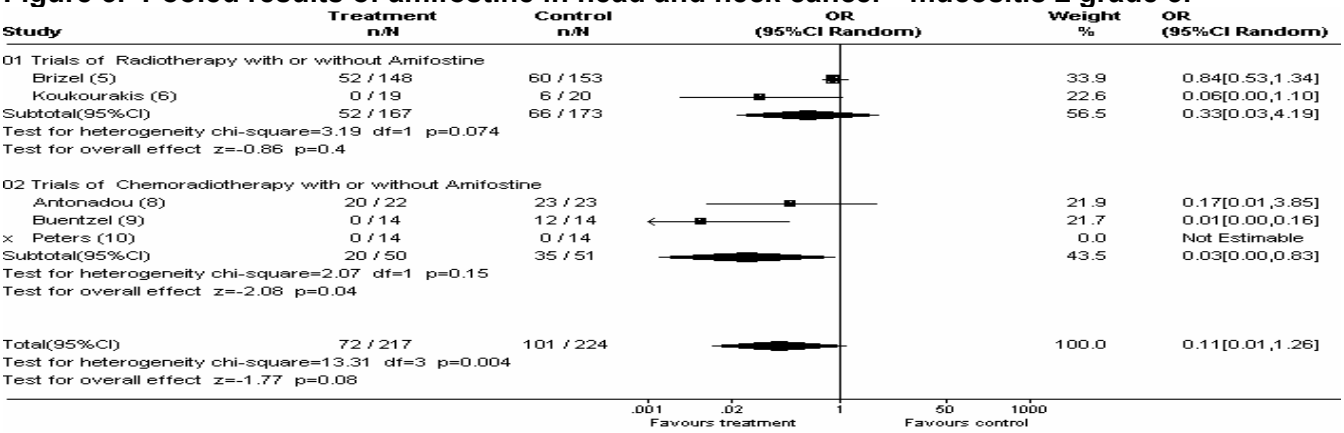
Table 4u. Randomized trials of amifostine in head and neck cancer – mucositis.

Author, Year (Reference)	Treatment Groups	Scale**	Number of Patients	Patients with Mucositis ≥ Grade 3	p-value
Trials of Radiochemotherapy with or without Amifostine					
Vacha 2003 (8)	RT + CT + A RT + CT	Common Toxicity Criteria (specific scale not reported)	19 21	2 (8%) 2 (8%)	p=NS
Trials of Amifostine Administration					
Bardet 2003 (12)	RT + A (iv) RT + A (sc)	NR	54 total	NR NR	p=NR

Note: A, Amifostine; NR, not reported; NS, no significant difference; RT, radiotherapy; RT + CT, radiotherapy with concurrent chemotherapy, sc, subcutaneously; iv, intravenously.
** See appendix I for ROTG and WHO grading information.

Data from four randomized trials (5,6,8,9) were pooled to assess the effect of amifostine on mucositis in patients with head and neck cancer (Figure 3). The remaining two trials did not report sufficient data for analysis (7,10). The overall effect was a difference with amifostine that was not statistically significant (OR, 0.11; 95% CI, 0.01 to 1.26, p=0.08). No statistically significant differences in mucositis were detected, by treatment type, for the two trials of amifostine added to radiotherapy alone (OR, 0.33; 95% CI, 0.03 to 4.19, p=0.4). The two trials of radiochemotherapy detected a significant effect (OR, 0.03; 95% CI, 0.00 to 0.83, p=0.04) in favour of amifostine. Heterogeneity was present in the estimate of overall effect and in the trials of amifostine added to radiotherapy alone.

Figure 3. Pooled results of amifostine in head and neck cancer - mucositis ≥ grade 3.



Heterogeneity Identified Between Trials

Differences in trial quality, amifostine administration, and type of standard therapy were previously identified as possible sources of heterogeneity. The trial reported by Brizel et al (5) is the only large randomized trial available for analysis, and results of this trial are more conservative for all of the outcomes measured than any of the smaller trials included in the analysis. The results from the smaller trials may possibly overestimate the effect of amifostine. However, given that the amifostine dose administered in the large trial (200 mg/m^2 IV daily) was different from the dose administered in the other trials, it is feasible that the 200 mg/m^2 dose is less protective. Heterogeneity could also be present through other trial differences; of the two trials of daily amifostine added to radiotherapy alone, amifostine was delivered intravenously in one (5) and subcutaneously in the other (6). Of the four trials of radiochemotherapy, two trials delivered amifostine daily with radiotherapy (7,8) and two trials administered amifostine only on chemotherapy days (9,10).

In spite of the identified statistical heterogeneity and the noted differences between trials, the results are consistent in the direction of an effect favouring amifostine. The Head and Neck Cancer DSG felt that in the presence of heterogeneity, the emphasis must remain on the results from the large trial of amifostine with or without radiotherapy by Brizel et al (5).). Once fully published, the results from the double-blind placebo-controlled trial of amifostine added to chemoradiation from Buntzel et al (7) should clarify the source of the heterogeneity and provide a greater estimate of impact of amifostine upon radiation-induced xerostomia and mucositis.

Tumor Protection

Results from five of the six randomized trials indicate that amifostine does not affect the anti-tumour efficacy of radiotherapy with or without concurrent carboplatin. No significant differences were detected in any of the tumour control or survival outcomes reported (Table 5); however, the longest reported survival data was 24 months. Buntzel et al (7) did not report any response or survival results.

Update

Neither trial (1u,2u) reported response or survival outcomes (Table 5u) .

Table 5. Randomized trials of amifostine in head and neck cancer – tumour protection.

Author Year (Reference)	Treatment Groups	Number of Patients	Response	Control	Survival		
			CR	Loco-regional	Disease- free	Median	Overall
Trials of Radiotherapy with or without Amifostine							
Brizel 2000 (5)	RT + A RT	153 150	NR	89 (58%) 95 (63%) (24 month)	81 (53%) 86 (57%) (24 month)	NR NR	109 (71%) 99 (66%) (24 month)
Koukourakis 2000 (6)	RT + A RT	12 13	7 (54%) 7 (58%)	NR NR	NR NR	NR NR	NR NR
Trials of Radiochemotherapy with or without Amifostine							
Buntzel 2001 (7) abstract data	RT + CT + A RT + CT + placebo	137 in total	NR NR	NR NR	NR NR	NR NR	NR NR
Antonadou 1998 (8)	RT + CT + A RT + CT	22 23	20 (91%) 18 (78%)	21 (96%) 20 (87%) (6 month)	18 (82%) 17 (74%) (18 month)	NR NR	NR NR
Buntzel 1998 (9)	RT + CT + A RT + CT	14 14	NR 6(43%)	NR NR	11 (79%) 9 (64%) (12 month)	NR NR	NR NR
Peters 1999 (10)	RT + CT + A RT + CT	14 14	NR NR	NR NR	NR NR	19 months 10 months	~9 (63%) ~5 (39%) (12 month)

Note: No significant differences were found between treatment groups for any of the treatment outcomes listed above; A, Amifostine; CR, complete response; NR, not reported; RT, radiotherapy; RT+ CT, radiotherapy with concurrent chemotherapy
~ Reviewer's calculation from table data.

Update

Table 5u. Randomized trials of amifostine in head and neck cancer- tumour protection.

Author Year (Reference)	Treatment Groups	Number of Patients	Response	Control	Survival		
			CR	Loco-regional	Disease- free	Median	Overall
Trials of Radiochemotherapy with or without Amifostine							
Vacha 2003 (8)	RT + CT + A RT + CT	19 21	NR NR	NR NR	NR NR	NR NR	NR NR
Trials of Amifostine Administration							
Bardet 2003 (12)	RT + A (iv) RT + A (sc)	54 total	NR NR	NR NR	NR NR	NR NR	NR NR

Note: No significant differences were found between treatment groups for any of the treatment outcomes listed above; A, Amifostine; CR, complete response; NR, not reported; RT, radiotherapy; RT+ CT, radiotherapy with concurrent chemotherapy, sc, subcutaneously; iv, intravenously.

Adverse Effects of Amifostine

In the trial reported by Brizel et al (5), nausea, vomiting, hypotension, and allergic reactions were the most common side effects of amifostine. Although 53% of the patients who received amifostine experienced at least one episode of nausea and/or vomiting, it occurred in only 5% of the total of 4314 doses and was severe (grade 3) in less than 1% of all doses. Hypotension occurred with less than 1% of all doses of amifostine. Venous catheters and daily intravenous punctures caused complications in 5% of patients receiving amifostine, but there was no grade 3 or 4 toxicity. Three patients (2%) receiving amifostine experienced grade 3 infections. A total of 35 patients (23%) discontinued amifostine before the end of the course of radiotherapy. Of these patients, 22 (14%) discontinued amifostine injections prior to receiving 40 Gy, and 13 (8%) discontinued prior to 60 Gy. Reasons given for discontinuation included adverse events (19%) and other reasons (4%).

Koukourakis et al (6) reported on adverse effects associated with subcutaneous amifostine during conventional radiotherapy. No results were reported separately for the patients with head and neck cancer; the data presented were for the group of 70 patients with thoracic, head and neck, or pelvic tumours who received amifostine. Grade 2 vomiting occurred in two patients (3%), grade 2/3 asthenia in 11 patients (16%), transient grade 1 hypotension in two patients (3%), grade 3 fever in six patients (9%), and grade 2 generalized rash in four patients (6%). Overall, 10 patients (14%), one with head and neck cancer, required an interruption of amifostine treatment due to fever/rash syndrome or severe asthenia.

Buntzel et al (7) did not provide any amifostine toxicity data in the 2001 abstract of 137 patients randomized to radiochemotherapy with amifostine or placebo.

Antonadou et al (8) reported few side effects with amifostine administration. Only one patient (4.5%) in the amifostine arm experienced nausea/vomiting, and three (13.6%) developed transient hypotension. To prevent possible side effects, antiemetics, hydration, and dexamethasone were used for patients enrolled in the amifostine arm of the trial.

Buntzel et al (9) noted that antiemetic medications were used effectively to control nausea and vomiting, and these side effects were not observed in either treatment group. Forty percent of patients randomized to amifostine experienced a transient decrease in blood pressure, but this effect did not interrupt the infusion of amifostine, and in no cases was treatment discontinued due to hypotension.

Peters et al (10) did not provide any amifostine toxicity data on the 28 patients randomized to radiochemotherapy with or without amifostine.

Update

Vacha et al (1u) reported that the common side effects of nausea, vomiting, and clinically relevant hypotension were not observed in patients given amifostine, nor were there any significant differences in side effects between the two treatment groups.

In the comparison of intravenous versus subcutaneous administration of amifostine, Bardet et al (2u) reported the proportion of patients who experienced nausea and vomiting (12% versus 13%, p=not reported), skin rash (15% versus 16%, p=not reported), hypotension (6% versus 0%, p=not reported), and asthenia (4% versus 0%, p=not reported). No significant differences between treatment groups were reported for any of the adverse events presented.

Quality of Life

Wasserman et al (11) reported quality-of-life data in a separate paper based on 299 patients who participated in the randomized trial reported by Brizel et al (5). Using a validated 8-item Patient Benefit Questionnaire, patients receiving radiotherapy with or without amifostine provided data at baseline and at different time points up to a year after treatment. The symptoms assessed included difficulty with eating, speaking, and sleep, mouth and tongue dryness, use of oral comfort aids or fluids, and tongue soreness. Data were available from 299 patients at baseline and 180 patients at eleven months after treatment. Reasons for drop-out or non-compliance were not reported; however, attrition rates were roughly similar between patients in the amifostine and control arm (44% and 35%). No significant differences in baseline scores were detected between patients with or without amifostine. Differences in mean symptom scores at one, seven, and 11 months after treatment were significant in favour of patients who received amifostine.

Guideline from the American Society of Clinical Oncology

An evidence-based guideline on the use of chemotherapy and radiotherapy protectants was developed by ASCO in 1999 (12) and was updated in 2002 (13). The relevant literature was identified primarily through a search of MEDLINE and CANCERLIT (1966 through 2001) and reviewed by an expert panel. Recommendations were developed through a process of consensus. The expert panel developed the following recommendations for the use of amifostine in radiotherapy-associated complications:

- Amifostine may be considered to decrease the incidence of acute and late xerostomia in patients who undergo fractionated radiation therapy in the head and neck region.
- Present data are insufficient to recommend amifostine to prevent mucositis associated with radiation therapy.
- When given with radiation therapy, the recommended amifostine dose is 200 mg/m^2/d given as a slow intravenous push over three minutes, 15 to 30 minutes before each fraction of radiation therapy. Administration of amifostine requires close patient monitoring, but side effects are fewer at this dose. Many patients require antiemetics. Blood pressure should be measured just before and immediately after the three-minute amifostine infusion. The hypotension associated with amifostine at this dose is less frequent but still requires close monitoring.

The ASCO guideline on amifostine as a radioprotectant was based primarily upon the results of the randomized trial reported by Brizel et al (5). Supporting evidence included the small randomized trial reported by Buntzel et al (9), trials involving different cancer sites (6,14), trials not using conventional fractionation (15,16,17), and papers that reported quality of life based on randomized (11) or retrospective data (18). The ASCO guideline did not investigate the role of amifostine in radiotherapy with concurrent chemotherapy.

V. INTERPRETIVE SUMMARY

Acute and Chronic Xerostomia

Two trials of amifostine added to radical radiotherapy were identified. The large randomized study reported by Brizel et al (5) detected differences in acute and late xerostomia that were clinically and statistically significant. In this trial, patients who received 200 mg/m^2 of amifostine prior to each radiation fraction had significantly less ≥ grade 2 acute xerostomia (51% versus 78%, $p<0.0001$) and significantly less ≥ grade 2 chronic xerostomia (35% versus 57%, $p=0.002$) than did those who did not receive amifostine. The second radiotherapy trial reported by Koukourakis et al (6) was a small trial that randomized 40 patients with head and neck cancer to radiotherapy alone or to subcutaneous amifostine added to radiotherapy. This trial detected no significant difference in severe mouth dryness and persistent use of water as a substitute for saliva ($p=0.32$), but it was noted that xerostomia was not assessed using a specific test.

Four trials of amifostine added to radiochemotherapy were identified. One trial (7) has yet to report individual results per treatment arm, two small trials (8, 9) detected a significant reduction in ≥ grade 2 acute and chronic xerostomia with amifostine, and the fourth trial (10) reported no significant differences in salivary gland scintigram between treatment arms. This trial administered 500mg of amifostine on days 1-5 and 29-33 only at the time of the concurrent carboplatin. It is unlikely that the scintigram appearances of the salivary glands were related to relevant symptoms in the patients.

Pooled data from three trials detected a significant benefit with amifostine in both acute and chronic xerostomia. The three remaining trials did not report results or use accepted symptomatic scoring criteria.

The ASCO guideline provided recommendations on the use of amifostine largely based on the randomized trial by Brizel et al (5). The expert panel concluded that amifostine was effective in the reduction of acute and chronic xerostomia induced by radiotherapy to the head and neck.

Update

The small trial by Vacha et al (1u) did not report overall results and was not included in the interpretation of the evidence.

Mucositis

The data on mucositis is less consistent. Of the two radiotherapy trials, Brizel's trial (5) of amifostine added to radiotherapy did not detect any significant differences in severe mucositis, while the small trial of subcutaneous amifostine added to radiotherapy (6) detected a significant reduction in severe mucositis favouring amifostine. Of the four radiochemotherapy trials with or without amifostine, Buntzel et al (7) did not report separate results per treatment arm, two small trials (8, 9) detected a significant

reduction in severe mucositis with amifostine, and the fourth trial (10) did not detect any cases of severe mucositis for either treatment arm.

The Head and Neck DSG noted the wide variation of reported rates of mucositis across trials; Brizel et al (5) reported severe mucositis in the control and treatment arms as 39% and 35% respectively, Buntzel et al (7) reported severe mucositis in 32% of their study population, two trials (6,9) did not report any cases of severe mucositis in patients who received amifostine, one trial (10) did not detect any severe mucositis for either treatment arm, and in another trial (8), almost all of the patient population experienced ≥ grade 3 mucositis.

Pooled data from four trials detected no significant difference in mucositis with amifostine added to radiotherapy/radiochemotherapy. However, it is interesting to note that the OR is very positive in the direction of effect favouring amifostine (OR, 0.11). Further research, especially mature results from the Buntzel trial (7), will be needed to determine a more accurate effect of amifostine in the reduction of radiation-induced mucositis.

The ASCO guideline reported insufficient data to provide recommendations on the role of amifostine on mucositis by radiotherapy to the head and neck.

Update

Vacha et al (1u) reported no differences in mucositis between the two treatment groups, and the one trial (2u) of intravenous versus subcutaneous amifostine administration reported similar rates of mucositis ≥grade 2.

Tumour Control

The evidence supports the conclusion that amifostine does not influence tumour control. The large radiotherapy trial reported by Brizel et al (5) did not detect any differences between amifostine and control in actuarial loco-regional control, disease-free survival, or overall survival. In the remaining trials with radiotherapy or radiochemotherapy with standard dose carboplatin, no significant differences were detected in any of the response or survival outcomes. This data is encouraging.

No trials of amifostine added to concurrent low-dose radiochemotherapy were identified in our literature search. While it is reasonable to extrapolate that the radioprotection of acute and chronic xerostomia with amifostine may extend to patients treated with low-dose concurrent chemoradiotherapy, there is the theoretical possibility that amifostine may compromise the anti-tumour effectiveness of low-dose daily cisplatin or carboplatin.

Update

The last sentence of the first paragraph has been revised through the editorial process to provide greater clarity. It now should read: These data are encouraging; however, long-term data beyond 24 months are not yet available for this population of patients.

Side Effects

While the side effects of amifostine were generally manageable, in the Brizel trial (5), 19% of patients discontinued amifostine treatment due to adverse events. Nausea, vomiting, hypotension, and allergic reactions were the most common side effects of amifostine, but they were rarely severe (≥ grade 3).

Quality of Life

Quality-of-life data from randomized trials of amifostine in the management of patients with head and neck cancer are sparse. One trial reported quality of life using mean scores derived through a patient-benefit questionnaire. After treatment, differences in mean scores were significant in favour of patients who received amifostine, but there was also a large attrition rate. It is unclear to what extent the results described are clinically meaningful.

Strength of the Evidence

The Head and Neck DSG weighed several important considerations when interpreting the identified body of evidence on amifostine. As the overall body of evidence is relatively weak with only six

randomized trials identified, the issue of power was considered. Of the six trials, four enrolled less than 26 patients per arm. These smaller trials were likely underpowered to detect significant differences between treatment groups, and any differences that were detected are more likely to occur by chance alone, leading to false positive results. The remaining two trials were likely sufficiently powered; however, one trial did not report separate results per treatment arm (7).

Study design was also a special consideration in the interpretation of this evidence. With an outcome like xerostomia, which is very subjective and is subject to potential treatment effect, placebo control and blinding become important methodological issues. Of the six trials, only one, reported as an abstract, was a double-blind placebo-controlled trial (7). This trial, however, did not report separate results per treatment arm. None of the other trials employed a study design that included blinding or placebo control. As a result, patients in these remaining randomized trials were more likely to be subject to a potential false treatment effect.

The final consideration in the interpretation of this evidence was the use of data from unpublished sources. To be explicit, the Head and Neck DSG is generally unwilling to use data from unpublished sources, especially in the case of positive findings; however, because negative results are often not published, the solicitation of unpublished trial information is sometimes warranted. Given the available evidence and subsequent methodological considerations, the Head and Neck DSG felt that further information was needed to fully inform the decision-making process leading to the guideline recommendations. The Head and Neck DSG decided to contact the authors of the only double-blind randomized trial (7) to obtain separate results per treatment arm. At the time of writing, the trial authors have provided the Head and Neck DSG with preliminary unpublished data that appears to be consistent in direction of effect when compared with the other randomized trial results but that are, however, negative for acute xerostomia. Results for acute mucositis were negative as well. The DSG will wait for fully published results from this trial, but these initial results had to at least be considered, albeit informally, in the development of the guideline recommendations.

Update

The introduction of two small randomized trials (1u,2u) did little to strengthen the body of evidence surrounding amifostine.

VI. ONGOING TRIALS

EORTC 24981: Phase II randomized study of paclitaxel and carboplatin followed by cisplatin and radiotherapy with or without amifostine in patients with locally advanced undifferentiated nasopharyngeal cancer (19). A total of 41-93 patients will be accrued for this study. Date summary last modified: 2002-12-27. Status: closed. The Head and Neck Cancer DSG will monitor the literature for results from this trial.

VII. DOSING AND SCHEDULING

Amifostine has been given in different radiation fractionation courses with and without concomitant chemotherapy. However, five of the six trials used intravenous infusion usually 15 to 30 minutes prior to the radiation fraction (5,7-10). The reported dose levels range from a standard dose of 500mg to doses of 200mg/m^2 up to 300 mg/m^2. The large trial reported by Brizel et al (5) used 200 mg/m^2 iv daily 15 to 30 minutes prior to radiation. These doses are well below the dose levels reported for the normal tissue protection from chemotherapy by amifostine (12,13,20). The intravenous route can be difficult for patients and can cause logistical challenges in the current management approaches incorporating concomitant chemotherapy and multiple daily fractionated radiotherapy or both. Alternative approaches to delivering amifostine appear to have promise and should be supported by further research. A small non-randomized trial reported by Wagner et al (21) explored the efficacy of amifostine delivered as a bolus injection. Forty-two patients receiving radiotherapy for head and neck, rectal, or bronchial cancer were divided into four groups. Amifostine (200 mg/m^2) was administered as a 15-minute infusion in 14 patients, a five-minute infusion in nine patients, and as a bolus injection with or without pretreatment in nine and 10 patients respectively. This trial detected that overall acute side

effects associated with amifostine were significantly less for patients who received bolus infusions as compared with those who received short infusions (p=0.012). Rates of mucositis were similar between the four treatment groups.

The data reported by Koukourakis (6) is especially interesting. It was shown in a randomized setting that 500mg of subcutaneous amifostine prior to radiation appeared to be effective and well-tolerated. This data is supported in part by non-randomized data from another subcutaneous study reported by Anne et al (22). In this study, results from 54 patients who received two 250mg subcutaneous doses of amifostine 60 minutes before radiotherapy were compared with results from Brizel's randomized trial (5). Similar rates of acute xerostomia were observed between amifostine treatment groups, and there were no reports of grade 3/4 hypotension or nausea/vomiting with the subcutaneous administration. This administration route appears promising and merits further investigation.

Update

In a randomized setting, Koukourakis et al (6) reported that 500mg of subcutaneous amifostine prior to radiation appeared to be effective and well-tolerated. This data is supported in part by preliminary data from the randomized trial by Bardet et al (2u). This trial compared intravenous versus subcutaneous administration of amifostine. With subcutaneous administration, similar rates of acute xerostomia were observed when compared with intravenous administration (2u). In addition, with the subcutaneous route, there were no cases of grade 3 or 4 hypotension or asthenia (2u). This administration route appears promising and merits further investigation.

VIII. IMPLICATIONS FOR POLICY

Amifostine is an expensive drug, retailing in Canada at CA$0.50/mg or CA$250 for each 500 mg vial (19). For an average individual of 1.7 m^2 in height and with the recommended dose of 200 mg/m^2, a course of amifostine given prior to each of a 33-fraction radical radiation course would cost CA$5610. At 500mg prior to each fraction, the cost becomes CA$8250. Unfortunately, the Head and Neck Cancer DSG is not aware of any evidence based on Canadian data that indicates whether the economic cost of amifostine is outweighed by the economic cost of toxic side effects when amifostine is not delivered.

An economic analysis by Bennett et al (23) reported data from the randomized trial of 28 patients by Buntzel et al (9). Bennett reports that, including the cost of amifostine, the mean per patient supportive care costs (in German Deutsche Marks [DM]) are significantly lower in patients who receive amifostine than those who do not receive the drug (DM4,401 versus DM5,873, p=0.02). Abstract information on cost of xerostomia and mucositis were reported by Bonomi et al (23). In 1997 US dollars, the estimated cost of severe xerostomia was $2144 per episode, while the average cost for severe mucositis was estimated to be $4543 per episode.

With the existing evidence, it is clear that both the cost of amifostine and supportive care costs for xerostomia and/or mucositis are substantial. There is some evidence from one small trial to suggest that amifostine may be more cost-effective than providing increased supportive care without amifostine, but more data based on patients within the Canadian health care system are needed.

IX. DISEASE SITE GROUP CONSENSUS PROCESS

The Head and Neck Cancer DSG convened to discuss the evidence surrounding amifostine as a radioprotectant in the treatment of head and neck cancer. The best evidence comes from the large trial reported by Brizel et al (5) investigating radiotherapy alone with or without amifostine. The members of the DSG agreed that the presentation of results from the small trials should be framed in this context. The DSG felt that the smaller studies were largely consistent with the trial reported by Brizel (5), which detected a significant reduction in acute and chronic xerostomia with amifostine. In terms of mucositis, the evidence was less conclusive. The large trial did not detect a significant difference in mucositis, while three of the small trials demonstrated a significant difference in mucositis

favouring amifostine. Pooled results from the four trials detected a non-significant difference in mucositis favouring amifostine.

Given the evidence presented, the DSG felt that amifostine may be considered effective in reducing acute and chronic xerostomia associated with radical conventionally fractionated radiotherapy, with or without standard-dose carboplatin, given to patients in the head and neck region. The data on mucositis are inconclusive.

The DSG identified several concerns with the use of amifostine in the context of clinical practice in Ontario. First, a common practice for suitable patients with stage III/IV squamous cell carcinoma in Ontario is a conventionally fractionated course of radiotherapy delivered concurrently with low-dose cisplatin or carboplatin. No trials of amifostine added to concurrent low-dose radiochemotherapy were identified in the literature search. While it is reasonable to extrapolate that the radioprotection of acute and chronic xerostomia with amifostine may extend to patients treated with low-dose concurrent chemoradiotherapy, there is the theoretical possibility that amifostine may compromise the anti-tumour effectiveness of low-dose daily cisplatin or carboplatin.

Second, the data on tumour control and survival outcomes support the opinion that amifostine does not confer tumour protection; however, long-term data beyond 24 months are not yet available.

Finally, the optimum dose and delivery of amifostine has yet to be determined. In the large trial reported by Brizel et al (5), a daily intravenous dose of 200 mg/m^2 15-30 minutes before radiotherapy was effective in reducing xerostomia; however, the smaller randomized trials support the opinion that different doses may confer a greater magnitude of benefit against both xerostomia and mucositis. The role of amifostine delivered subcutaneously warrants further investigation as it is a very attractive alternative but there is little evidence to advocate its use at this point. Timing and minimum dose of amifostine are also of interest. Of the two small trials that administered amifostine only on chemotherapy days, one trial detected a benefit of amifostine for patients in both xerostomia and mucositis, while the other did not.

In the context of current practice in Ontario, the efficacy of amifostine in cisplatin-based concomitant radiochemotherapy has yet to be fully established, and the practical logistics of delivering amifostine, cisplatin, and radiotherapy within a short time period in the cancer centres are substantial. Conversely, the demonstrated benefit of amifostine--the reduction in radiation-induced acute and chronic xerostomia--makes it a possible treatment option for suitable cancer patients in Ontario.

X. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Recommendations

Based on the evidence above, the Head and Neck DSG drafted the following recommendations:

Target Population

These recommendations apply to adult patients with squamous cell head and neck cancer who are receiving radical radiotherapy with or without concurrent chemotherapy.

Draft Recommendations

- Amifostine is effective in the reduction of acute and chronic xerostomia associated with radical conventionally fractionated radiotherapy given to patients in the head and neck region. The data on mucositis are inconclusive.
- Emerging evidence suggests that protection from xerostomia extends to concomitant chemo-radiation therapy with carboplatin. The data on mucositis are inconclusive.
- Amifostine should preferably be given in the context of a clinical trial because: a) the protective effect of amifostine has not been fully demonstrated within current practice patterns in Ontario for patients with stage III and IV squamous carcinoma; i.e. amifostine has not been established for patients who receive concurrent cisplatin with radiotherapy, b) while no tumour protection has been detected with amifostine, long-term data are not yet available, c) the optimum dose and delivery of amifostine has yet to be determined.

Practitioner Feedback
Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
Practitioner feedback was obtained through a mailed survey of 52 practitioners in Ontario (12 medical oncologists, 24 radiation oncologists, and 16 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 results of the survey have been reviewed by the Head and Neck DSG.

Results
Key results of the practitioner feedback survey are summarized in Table 6. Thirty-two (62%) surveys were returned. Fifteen (47%) respondents indicated that the practice guideline report was relevant to their clinical practice, and they completed the survey.

Table 6. Practitioner responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	13 (87)	2 (13)	0
There is a need for a clinical practice guideline on this topic.	12 (80)	2 (13)	1 (7)
The literature search is relevant and complete.	14 (93)	1 (7)	0
The results of the trials described in the report are interpreted according to my understanding of the data.	14 (93)	1 (7)	0
The draft recommendations in this report are clear.	12 (80)	1 (7)	2 (13)
I agree with the draft recommendations as stated.	13 (87)	0	2 (13)
This report should be approved as a practice guideline.	9 (60)	3 (20)	3 (20)
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Very likely or likely**	**Unsure**	**Not at all likely or unlikely**
	6 (40)	5 (33)	4 (27)

NOTE: Some percentages do not add to 100 because of missing data.

Summary of Main Findings
Four (27%) respondents provided written comments. The main points were:

1. Four practitioners responded that more definitive recommendations regarding the use of amifostine outside the context of a clinical trial were needed.
2. One practitioner commented that greater critical appraisal around the Brizel trial was needed to determine a possible anti-tumour effect with amifostine. The practitioner suggested that confidence intervals around the local control rates between the two treatment arms should be calculated.
3. In addition, the same practitioner noted that with the high percentage of postoperative patients treated in the Brizel trial, an extrapolation of response and survival results to other patient populations (patients treated with definitive radiation) should not be assumed.

Modifications/Actions
Based upon practitioner feedback, the following modifications/actions were made:
1. The recommendations were revised to clarify that amifostine is recommended to reduce the incidence of acute and chronic xerostomia in patients receiving radiotherapy or radiochemotherapy with carboplatin. In addition, a recommendation on the dose and administration of amifostine was provided, and two qualifying statements were added.
2. As reported in the text of the document, there were no significant differences in local-regional control, disease-free survival, or in overall survival for any of the studies included in this report. In the trial by Brizel et al (5), the hazard ratio for local-regional control was 0.954 (95% CI, 0.809 to 1.126). No modifications to the report were made.
3. While the trial by Brizel et al (5) is the largest contributing study in the interpretation of the overall evidence, the supporting randomized trials are consistent with the findings of this one trial. Two trials (6,10) had greater than two-thirds of patients receiving definitive radiotherapy, and no control or survival differences were detected. A column showing the proportion of patients receiving definitive versus postoperative radiotherapy was added to Table 1.

Practice Guidelines Coordinating Committee Approval Process
The practice guideline report was circulated to 16 members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Twelve of the 16 members convened to review and discuss the practice guideline. All 12 PGCC members approved the practice guideline report as written, with only minor modifications required.

Modifications/Actions
1. The outcomes reported in the qualifying statements were revised from "response" to "tumour control" to better reflect the evidence and the discussion in the text.
2. A comment pointing out the adverse effects of amifostine was added in the qualifying statements.
3. As amifostine is not currently administered as standard practice in Ontario, the PGCC suggested that the practice guideline report be forwarded to the Policy Advisory Committee for consideration.

XI. RECOMMENDATIONS
Update
This section was revised to reflect the current guideline template. The section should now read:
XI. PRACTICE GUIDELINE
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 DSG and the Practice Guidelines Coordinating Committee.

Target Population
These recommendations apply to adult patients with any stage of squamous cell head and neck cancer who are receiving radical radiotherapy, encompassing at least 75% of the parotid glands, with or without concurrent chemotherapy.

Recommendations
- On the basis of the available data, amifostine is recommended as an effective treatment option for the reduction of acute and chronic xerostomia associated with radical conventionally fractionated radiotherapy, given to patients in the head and neck region encompassing at least 75% of the parotid glands, with or without standard dose carboplatin.
- The recommended dose and administration of amifostine is an intravenous infusion 15 to 30 minutes prior to radiation, with standard doses of 500mg or doses ranging from 200mg/m^2 to 300 mg/m^2. The Head and Neck Cancer DSG would be supportive of randomized trials designed to compare amifostine delivered subcutaneously versus intravenously.

- Data on the protective effect of amifostine from mucositis are inconclusive at this time.

Qualifying Statements

- For suitable patients with stage III/IV squamous cell carcinoma, a common practice in Ontario is a conventionally fractionated course of radiotherapy delivered concurrently with low-dose cisplatin or carboplatin. No trials of amifostine added to concurrent low-dose radiochemotherapy were identified in our literature search. While it is reasonable to extrapolate that the radioprotection of acute and chronic xerostomia with amifostine may extend to patients treated with low-dose concurrent chemo-radiotherapy, there is the theoretical possibility that amifostine may compromise the anti-tumour effectiveness of low-dose daily cisplatin or carboplatin.
- The data on tumour control and survival outcomes support the conclusion that amifostine does not confer tumour protection; however, long-term data beyond 24 months are not yet available for this population of patients.
- Nausea, vomiting, hypotension, and allergic reactions were reported as the most common side effects of amifostine, but they were rarely severe (≥ grade 3).

Future Research

Randomized trials of amifostine are needed to address issues of efficacy related to concomitant low-dose daily cisplatin or carboplatin, tumour protection, minimally effective doses, optimal routes of delivery, quality of life, and total healthcare costs.

Related Guidelines

Practice Guidelines Initiative's Practice Guideline Reports:

- #12-6: *Use of amifostine to ameliorate the toxic effects of chemotherapy in the treatment of cancer.*
- #5-5: *Symptomatic treatment of radiation induced xerostomia in head and neck cancer patients.*

XII. JOURNAL REFERENCE

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XIII. ACKNOWLEDGEMENTS

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For a full list of members of the Head and Neck Cancer Disease Site Group and the Practice Guidelines Coordinating Committee, please visit the Cancer Care Ontario Web site at http://www.cancercare.on.ca/access_PEBC.htm.

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Update

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Appendix 1: Radiation Therapy Oncology Group (RTOG) - acute and late scoring criteria.

Acute Radiation Morbidity Scoring Criteria

	[0]	[1]	[2]	[3]	[4]
MUCOUS MEMBRANE	No change over baseline	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinous discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
SALIVARY GLAND	No change over baseline	Mild mouth dryness/ slightly thickened saliva/ may have slightly altered taste such as metallic taste/ these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste	-------	Acute salivary gland necrosis

Late Radiation Morbidity Scoring Criteria

	0	Grade 1	Grade 2	Grade 3	Grade 4	5
MUCOUS MEMBRANE	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucous	Marked atrophy with complete dryness Severe telangiectasia	Ulceration	Death Directly Related To Radiation Late Effects
SALIVARY GLANDS	None	Slight dryness of mouth Good response on stimulation	Moderate dryness of mouth Poor response on stimulation	Complete dryness of mouth No response on stimulation	Fibrosis	

World Health Organization (WHO) - Acute and Late Scoring Criteria

Mucositis due to Radiation

Grade 1:	erythema of the mucosa
Grade 2:	patchy pseudomembranous reaction (patches generally ≤1.5 cm in diameter and non-contiguous)
Grade 3:	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)
Grade 4:	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Grade 5:	death related to toxicity

Salivary Gland Changes

Grade 1:	slightly thickened saliva; may have slightly altered taste (e.g., metallic); additional fluids may be required
Grade 2:	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required
Grade 3:	
Grade 4:	acute salivary gland necrosis
Grade 5:	death related to toxicity

Late RT Morbidity Scoring

Grade 1:	slight dryness of mouth; good response on stimulation
Grade 2:	moderate dryness of mouth; poor response on stimulation
Grade 3:	complete dryness of mouth; no response on stimulation
Grade 4:	fibrosis
Grade 5:	death related to adverse event

RTOG scoring criteria taken from http://www.rtog.org/
WHO scoring criteria taken from http://ctep.cancer.gov/reporting/ctc.html