

Phase III Randomized Trial of Amifostine as a Radioprotector in Head and Neck Cancer

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Purpose: Radiotherapy for head and neck cancer causes acute and chronic xerostomia and acute mucositis. Amifostine and its active metabolite, WR-1065, accumulate with high concentrations in the salivary glands. This randomized trial evaluated whether amifostine could ameliorate these side effects without compromising the effectiveness of radiotherapy in these patients.

Patients and Methods: Patients with previously untreated head and neck squamous cell carcinoma were eligible. Primary end points included the incidence of grade ≥ 2 acute xerostomia, grade ≥ 3 acute mucositis, and grade ≥ 2 late xerostomia and were based on the worst toxicity reported. Amifostine was administered (200 mg/m² intravenous) daily 15 to 30 minutes before irradiation. Radiotherapy was given once daily (1.8 to 2.0 Gy) to doses of 50 to 70 Gy. Whole saliva production was quantitated preradiotherapy and regularly during follow-up. Patients evaluated their symptoms through a questionnaire during and after treatment.

Local-regional control was the primary antitumor efficacy end point.

Results: Nausea, vomiting, hypotension, and allergic reactions were the most common side effects. Fifty-three percent of the patients receiving amifostine had at least one episode of nausea and/or vomiting, but it only occurred with 233 (5%) of 4,314 doses. Amifostine reduced grade ≥ 2 acute xerostomia from 78% to 51% ($P < .0001$) and chronic xerostomia grade ≥ 2 from 57% to 34% ($P = .002$). Median saliva production was greater with amifostine (0.26 g v 0.10 g, $P = .04$). Amifostine did not reduce mucositis. With and without amifostine, 2-year local-regional control, disease-free survival, and overall survival were 58% versus 63%, 53% versus 57%, and 71% versus 66%, respectively.

Conclusion: Amifostine reduced acute and chronic xerostomia. Antitumor treatment efficacy was preserved.

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THE USE OF IONIZING radiation in cancer therapy may lead to transient and/or permanent injury to normal tissues within the treatment field. The magnitude of damage depends both on the volume of tissue irradiated and the dose of radiation delivered. Radiotherapy plays a significant role in the management of head and neck cancer, either as the primary treatment modality or as a postsurgical adjuvant modality. The most common and clinically significant toxicities arising from head and neck irradiation are acute mucositis and acute and chronic xerostomia, the last of these often being lifelong in duration. Xerostomia disrupts normal activities including eating and speaking and may lead to sequelae including dental caries and tooth loss with the secondary risk of osteonecrosis.

Oral pilocarpine can palliate xerostomia when used in a postradiotherapy setting.^{1,2} Unpleasant cholinergic side effects occur in approximately half of the patients using this drug, and lifelong treatment may be required. The benefits from pilocarpine may arise from the hyperstimulation of small residual volumes of unirradiated parotid gland. The usefulness of pilocarpine when the entirety of both parotids have been irradiated to high doses is unclear. Pilocarpine has no role in the management of mucositis.

Strategies for the prophylaxis of xerostomia and mucositis are needed. The radioprotective potential of thiol-containing compounds has been recognized for decades.³ The

United States Army screened over 4,400 compounds and selected amifostine (WR-2721, Ethylol; Medimmune Oncology, Inc, West Conshohocken, PA) as the most promising of these agents. Amifostine and its active metabolite, WR-1065, accumulate in many epithelial tissues with the highest concentrations found in the salivary glands and kidneys.^{4,5} Amifostine reduces cisplatin-induced nephrotoxicity.⁶ Its putative mechanism of radioprotection is through the scavenging of radiation-induced free radicals. Small clinical trials have suggested that amifostine protects against radia-

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tion-induced xerostomia and mucositis.^{7,8} Although amifostine was generally well tolerated in these early trials, nausea, vomiting, and hypotension were the most commonly reported side effects.

An inherent risk in any toxicity reduction scheme is that the drug could protect the tumor and reduce treatment efficacy. Such an agent would not be clinically useful. The present study was performed to evaluate whether amifostine could protect against xerostomia and mucositis in head and neck cancer patients receiving radiotherapy without compromising the antitumor efficacy of the radiation.

PATIENTS AND METHODS

Patients and Eligibility Criteria

Patients with newly diagnosed, previously untreated squamous cell head and neck cancer were eligible for enrollment in this open-label, phase III, multi-institutional (see Appendix A), randomized trial. Inclusion of $\geq 75\%$ of both parotid glands within the radiation fields to doses ≥ 40 Gy was required. Other inclusion criteria included Karnofsky performance status ≥ 60 , granulocyte count $\geq 2,000/\mu\text{L}$, and platelet count $\geq 100,000/\mu\text{L}$.

Prophylactic use of pilocarpine during radiotherapy was prohibited. Patients with T1N0 or T2N0 carcinomas of the true vocal cords were ineligible as were those with tumors of the major or minor salivary glands or with a history of malignancy other than in situ cervix carcinoma within the 5 years preceding diagnosis. Patients could not have previously been treated with radiotherapy or chemotherapy. Pregnant women were ineligible. This protocol was approved by the institutional review board of each participating hospital, and written informed consent was obtained from all patients before enrollment.

Tumors were staged according to American Joint Committee on Cancer criteria.⁹ Staging procedures included history and physical examination, fiberoptic endoscopy, computerized tomography of the head and neck, chest x-ray, and examination under anesthesia. Post-therapy follow-up examinations were obtained every 2 months during the first year and every 6 months during the second year. Computerized tomography was repeated 1 year and 2 years after treatment.

Study End Points

The objective of the study was to determine whether daily administration of amifostine could reduce radiotherapy-induced acute and chronic xerostomia and acute mucositis without compromising the antitumor efficacy of the irradiation. Radiation toxicities were graded according to the Radiation Therapy Oncology Group Acute/Late Morbidity Scoring Criteria (see Appendix B). Early radiation toxicities were defined as those occurring within 90 days of the initiation of radiotherapy. Late or chronic toxicities occurred beyond 90 days. Primary end points for the assessment of drug efficacy included the incidence of grade ≥ 2 acute xerostomia, grade ≥ 3 acute mucositis, and grade ≥ 2 late xerostomia (1 year after the initiation of treatment). These parameters were assessed by the treating physician on a weekly basis during treatment and at each follow-up examination.

Whole saliva production was quantitated (5-minute collection period) before the commencement of radiotherapy and at follow-up 1, 5, 11, 17, and 23 months after treatment. Patients also evaluated their symptoms through the administration of an eight-item Patient Benefit Questionnaire (PBQ) given at baseline, weekly during treatment, and at

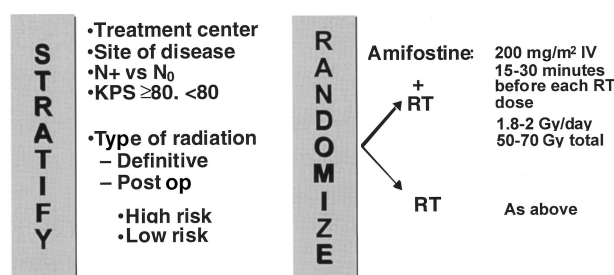


Fig 1. Treatment scheme.

each follow-up visit.¹⁰ Each question was answered on a 10-point scale, where a 10 represented no negative effect from radiotherapy and a 1 signified a severe negative effect. The questions addressed issues including impairment of speaking, taste, and swallowing, need for oral comfort aids, and sensation of mouth dryness. A detailed description of the PBQ will be published elsewhere.

The incidence of \geq grade 2 acute xerostomia, \geq grade 3 acute mucositis, and \geq grade 2 late xerostomia were computed based on the worst toxicity reported and compared using Fisher's exact test. *P* values were adjusted for multiple end points based on the methodology of Westfall and Young.¹¹ The incidence of these toxicities stratified by total radiation dose delivered was compared using the Mantel-Haenszel χ^2 test.

Local-regional control was the primary antitumor efficacy end point. Local-regional failures included disease recurrence or persistence at the primary site or neck nodes. Patients whose first site of failure was distant metastases were still followed and considered to be at risk for local-regional failure. Nonetheless, the occurrence of distant relapses or deaths before local failure could have interfered with reliable estimation of local-regional control.^{12,13} Because of this competing risk problem, disease-free survival and overall survival were used as secondary end points. Each of these parameters was computed from the first day of treatment using the Kaplan-Meier product-limit method¹⁴ and performed using intent-to-treat analysis. Survival curves were compared with the log-rank test.

The estimated sample size for this study was 250 assessable patients (125 per treatment arm), based on an anticipated reduction in grade ≥ 2 acute xerostomia from 80% to 55%, grade ≥ 2 chronic xerostomia from 55% to 35%, and grade ≥ 3 mucositis from 50% to 30%. This yielded an $\alpha = 0.048$, with a statistical power greater than 80% adjusted for multiple comparisons.

This study was a multi-institutional, open-label, randomized trial. Treatment assignment was determined by a phone call from the enrolling institution to the protocol sponsor (US Bioscience). Patients were stratified according to the following parameters: treatment center, primary tumor site (nasopharynx, oropharynx, oral cavity, or hypopharynx/larynx), nodal status (N0 v N+), Karnofsky performance status (< 80 v ≥ 80), and type of irradiation (definitive v postoperative). Postoperative patients were further classified as being at low risk or high risk of recurrence based on their pathologic findings.¹⁵ Low-risk patients had negative margins at primary site and no evidence of extracapsular nodal spread if a neck dissection was performed. High-risk patients had positive margins and/or extracapsular spread (Fig 1). Patients were randomized using a dynamic allocation process.¹⁶⁻¹⁸

Radiotherapy and Amifostine

The treatment schema is detailed in Fig 1. Treatment consisted of once daily isocentric external-beam megavoltage irradiation given at

1.8 to 2.0 Gy per fraction. Definitive irradiation was prescribed to a total dose of 66 to 70 Gy. Doses of postoperative irradiation were either 60 to 64 Gy (high-risk patients) or 50 to 54 Gy (low-risk patients). The primary tumor and draining lymphatics were treated with parallel opposed lateral fields. Supraclavicular and low neck nodes were treated with a single anterior field of 40 to 44 Gy with midline blocking to prevent spinal cord overlap. The lateral fields were reduced after 40 to 44 Gy to avoid overdosage of the spinal cord. Posterior cervical lymph nodes were boosted with electron-beam irradiation at the discretion of the treating physician. A second field reduction occurred at 54 to 60 Gy. Patients who received amifostine were irradiated in the same fashion as those who did not.

Diagnostic radiographic studies, dosimetric records, simulator films, and initial treatment portal films for all patients were submitted to a central office for review at the onset of therapy. Reduced-field portal films were submitted during treatment. At the conclusion of the trial, all records and films were reviewed by two of the principal investigators (D.M.B. and T.H.W.) to assess protocol compliance.

Amifostine was delivered 15 to 30 minutes before radiotherapy daily as a 3-minute intravenous (IV) infusion at a dose of 200 mg/m² dissolved in normal saline at a concentration of 1 mg/mL. Prophylactic antiemetic premedication was recommended. Indwelling peripheral venous access lines were used in many patients to minimize the inconvenience of daily venipuncture. Toxicity of amifostine was graded according to National Cancer Institute common toxicity criteria.

RESULTS

Three hundred fifteen patients were enrolled and randomized from October 1995 to October 1997. Twelve patients were randomized but never received any treatment or follow-up. Table 1 lists the demographics, disease characteristics, and treatment classification of the remaining 303 patients. Approximately two thirds of the patients received postoperative irradiation. Nearly half of all primary tumors originated in the oropharynx. Three patients had less than 75% of their parotids in the treatment fields (amifostine plus irradiation, *n* = 1; radiotherapy alone, *n* = 2); 22 patients discontinued amifostine before receiving 40 Gy, but 18 still completed their radiation therapy. They were included in the analysis of the efficacy of the drug. All patients were included in the analyses of local-regional control, progression-free survival, survival, and drug toxicity. All patients who received at least one dose of amifostine were assessable for toxicity.

Amifostine Toxicity

Amifostine was generally well tolerated. Nausea, vomiting, hypotension, and allergic reactions were the most common side effects (Table 2). A total of 4,314 doses of amifostine were delivered. Fifty-three percent of the patients receiving the drug had at least one episode of nausea and/or vomiting, but it only occurred with 233 (5%) of 4,314 doses. It was severe (grade 3) in 7% of all patients and 13 (< 1%) of 4,314 of all doses. Despite the greater incidence of nausea and vomiting associated with amifos-

Table 1. Patient Characteristics and Tumor Classification

Parameter	Amifostine + Radiotherapy Patients (<i>n</i> = 153)		Radiotherapy Alone Patients (<i>n</i> = 150)	
	No.	%	No.	%
Sex				
Male	123		120	
Female	27		33	
Age, years				
Median	55		56	
Range	36-76		28-78	
Performance status				
< 80	41		44	
≥ 80	109		109	
Primary tumor site				
Nasopharynx	5	3	6	4
Oropharynx	77	51	66	43
Oral cavity	28	19	33	22
Hypopharynx	14	9	15	10
Larynx	22	15	24	16
Unknown	4	3	9	6
Tumor stage				
T0	2	1	1	1
T1	25	17	21	14
T2	51	34	53	35
T3	29	19	27	18
T4	38	25	34	22
Tx	5	3	17	11
Node stage				
N0	42	28	46	30
N1	37	25	32	21
N2	68	45	66	43
N3	2	1	8	5
Nx	1	1	1	1
Type of radiation				
Definitive	50	33	52	34
Postoperative high-risk	70	47	65	42
Postoperative low-risk	28	20	36	24

tine, median weight loss at the end of treatment was higher in the group of patients treated with radiotherapy alone than those treated with both radiotherapy and amifostine (5.6% *v* 4.5% of pretreatment weight, respectively; *P* = .026). Hypotension, usually mild and of short duration, was associated with less than 1% of all amifostine dosages.

Complications caused by venous catheters (ie, catheter infection, catheter malfunction, catheter site drainage, catheter site edema, and IV perfusion infiltrates) and daily IV punctures (injection site pain and injection site red) occurred in seven patients (5%) in the amifostine arm, with no grade 3 or 4 toxicity. Infections (ie, general, fungal, and bacterial) were seen in 21 patients (14%) in both treatment arms, with only three patients (2%) in the amifostine arm reporting grade 3 toxicity. Clotting/vascular disorders (ie, phlebitis, thrombosis, and disseminated intravascular coag-

Table 2. Patients Experiencing One or More Episodes of Amifostine Toxicity

Event	Amifostine + Radiotherapy Patients		Radiotherapy Alone Patients		P
	No.	%	No.	%	
Nausea					
Grade 3	4	3	1	<1	.2
Any grade	66	44	25	16	<.0001
Vomiting					
Grade 3	8	5	0		.003
Any grade	55	37	11	7	<.0001
Hypotension					
Grade 3	4	3	0		.06
Any grade	22	15	2	<2	<.0001
Allergic reaction					
Grade 3	4	3	0		.06
Any grade	8	5	0		.003

ulation) occurred in five patients (3%) in the amifostine arm, with one patient (< 1%) reporting a grade 4 toxicity.

A total of 35 patients (21%) discontinued amifostine before the completion of the scheduled treatment. Twenty-two patients discontinued amifostine before receiving 40 Gy, and 31 patients discontinued amifostine before receiving 60 Gy. Of the 22 patients who discontinued amifostine before receiving 40 Gy, 16 discontinued amifostine because of adverse events and six patients for other reasons (ie, patient request). Nausea/vomiting (nine patients) and hypotension (two patients) were the most common adverse events that resulted in discontinuation of amifostine. Other adverse events included weakness/anxiety, drowsiness, cachexia, allergic reaction, and erythema/fever.

A total of 119 patients were treated with antiemetics prophylactically in this study. The most frequently used antiemetics were oral 5-hydroxytryptamine-3 antagonists. Seventy-four patients (62%) received 5-hydroxytryptamine-3 antagonists, and 45 patients (38%) received phenothiazine and/or metoclopramide. A total of 31 patients received no antiemetics. Side effects definitely or probably reported caused by antiemetics were not reported. However, it cannot be ruled out that antiemetics contributed to some side effects.

Efficacy of Amifostine

Amifostine significantly reduced the overall incidence of grade ≥ 2 acute xerostomia from 78% to 51% ($P < .0001$) (Table 3). Moreover, the dose required to cause this side effect in 50% of all patients was markedly higher in those patients receiving amifostine compared with those who did not (60 Gy v 42 Gy, respectively; $P = .0001$). Likewise, 1 year after the completion of treatment, chronic xerostomia

Table 3. Xerostomia and Mucositis

	Amifostine + Radiotherapy Patients		Radiotherapy Alone Patients		P
	No.	%	No.	%	
Grade ≥ 2 acute xerostomia					
Total incidence		51		78	<.0001*
50-59 Gy†	6/12	50	8/9	89	.16‡
60-65 Gy†	26/66	40	43/58	74	.001‡
> 65 Gy†	41/65	63	69/86	80	.03‡
Median dose to onset, Gy		60		42	.0001§
Grade ≥ 2 late xerostomia¶		34		57	.002*
Saliva production¶					
Median quantity, g		0.26		0.10	.04
> 0.1 g unstimulated		72		49	.003*
Mucositis					
Grade 0	8	5	1	1	
Grade 1	24	16	22	14	
Grade 2	64	43	70	46	
Grade 3	47	32	57	37	
Grade 4	5	3	3	2	

*Fisher's exact test.

†No. of patients experiencing toxicity/total no. of patients at radiotherapy level.

‡Mantel-Haenszel χ^2 test.

§Kaplan-Meier procedure/log-rank test.

||Wilcoxon rank sum test.

¶One year after treatment.

grade ≥ 2 was significantly less frequent in patients who received amifostine compared with those who did not (34% v 57%, respectively; $P = .002$). Patients who received amifostine also produced significantly more saliva than patients treated with radiotherapy alone. One year after the completion of radiotherapy, 72% of the patients who received amifostine could produce more than 0.1 mL of saliva, a clinically relevant volume,^{19,20} compared with only 49% of the patients who did not receive amifostine ($P = .003$; Table 3).

Patients' assessment of their symptoms coincided with the clinical evidence of diminished xerostomia secondary to amifostine. The overall mean score on the PBQ 1 year after treatment was 7.36 versus 6.66 in favor of amifostine (Fig 2; $P = .008$). Late xerostomia grade ≥ 2 was significantly correlated with both saliva production ($r = 0.313$, $P = .0001$) and the PBQ mean score ($r = 0.455$, $P = .0001$). The PBQ score was also significantly correlated with saliva production ($r = 0.304$, $P = .0001$).

Amifostine did not reduce the incidence of mucositis. Mucositis grade ≥ 3 occurred in 35% of the amifostine group and in 39% of the radiotherapy alone patients ($P = .48$). The median duration of mucositis was also similar in the two groups of patients (41 days v 38 days, respectively; $P = .685$).

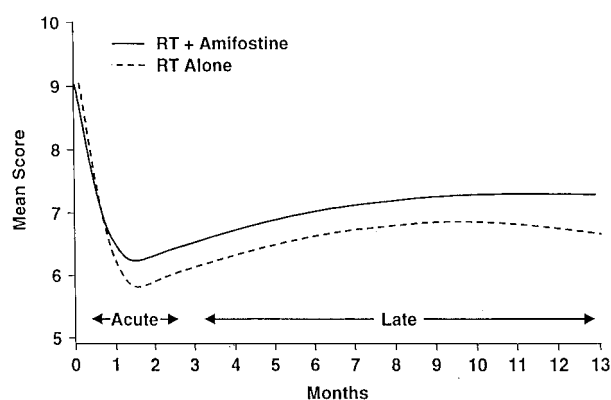


Fig 2. Comparison of mean scores on PBQ during treatment and during the posttreatment follow-up period; patients receiving amifostine plus radiotherapy had a significantly higher mean score ($P = .008$).

Review of the treatment portals and field sizes demonstrated that smaller quantities of mucosa received the total prescribed dose of irradiation for patients treated in the United States and France than for those treated in Canada, Britain, and Germany. Analysis of this subset revealed that grade ≥ 2 mucositis occurred in 69% of amifostine plus radiotherapy patients ($n = 51$) and 93% of the radiation alone patients ($n = 57$) ($P = .004$). There was no detectable dose-response relationship for the development of mucositis.

Antitumor Efficacy

The mean dose (\pm SD) of irradiation delivered was 64 ± 8 Gy in the amifostine plus radiation patients and 65 ± 5 Gy in the radiotherapy alone patients. Minimum follow-up for surviving patients is 18 months, and median follow-up is 26 months. Amifostine did not compromise the antitumor efficacy of radiotherapy. Eighteen-month actuarial local-regional control (Fig 3) was 65% versus 68% with and without amifostine, respectively. Overall survival (Fig 4) was better in patients receiving amifostine than in those who did not, although this difference was not statistically significant (81% v 73%, respectively). The hazard ratios and lower limits of the 95% confidence intervals are sufficiently high to assure noninferiority of amifostine plus radiotherapy.

DISCUSSION

This trial is the first large-scale randomized study to report the successful clinical use of a radioprotective agent. Patients who were pretreated daily with amifostine had a significantly lower incidence of acute grade ≥ 2 xerostomia than those who received radiotherapy alone. Furthermore, those patients pretreated with amifostine who did develop

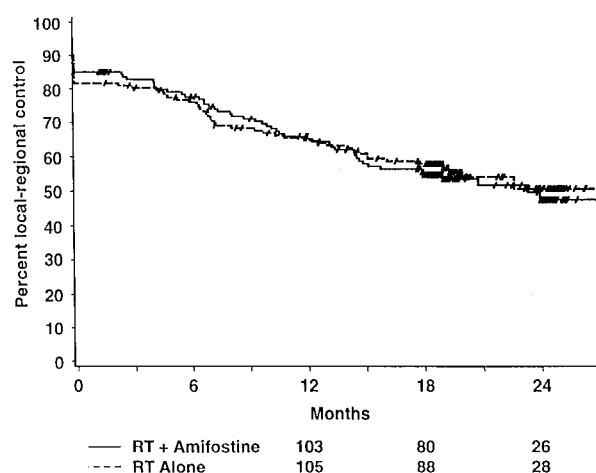


Fig 3. Local-regional control: the hazard ratio is 0.954 (95% confidence interval, 0.809 to 1.126). The number of patients at risk is indicated below each time point.

xerostomia did not do so until higher cumulative doses of irradiation had been delivered. Moderate to severe chronic xerostomia was significantly less prevalent with the use of amifostine. The volume of saliva produced was significantly greater in patients receiving amifostine. Longitudinal post-treatment patient self-assessment showed fewer symptoms in the patients who received amifostine.

Most clinical attempts to improve the therapeutic ratio in head and neck cancer have focused on increasing tumor control probabilities. Successful strategies have included hyperfractionated and accelerated fractionation schemes and the integration of radiotherapy and concurrent chemotherapy.²¹⁻²⁴ The increased intensity of these programs can

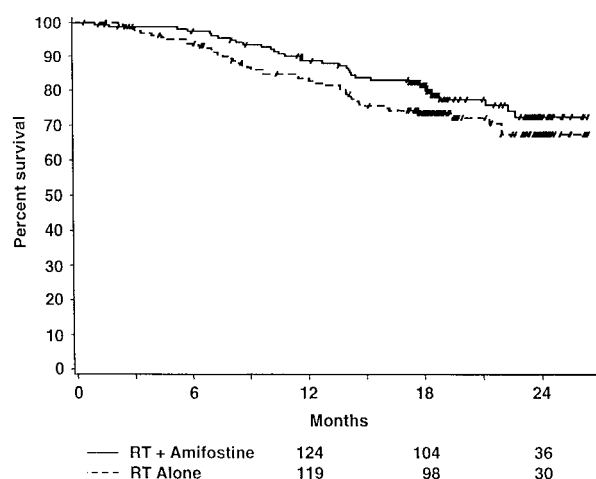


Fig 4. Survival: the hazard ratio is 1.12 (95% confidence interval, 0.983 to 1.270). The number of patients at risk is indicated below each time point.

increase both acute and chronic treatment-related toxicity, which may partially offset improvements in treatment efficacy.

Xerostomia and mucositis are the most common and severe side effects of radiotherapy for head and neck cancer. The former is often permanent when doses ≥ 50 Gy, which are the lowest doses used in the treatment of squamous cell carcinoma of the head and neck. Despite the clear need to prevent or ameliorate these toxicities, previous attempts to achieve this goal have been unsatisfactory.

Xerostomia was assessed (1) by the physician using Radiation Therapy Oncology Group criteria, (2) by the quantitation of saliva flow, and (3) by the administration of a validated PBQ. One could argue that in an open-label trial, such as this one, assessment by the treating physician could lead to a bias in favor of the patients receiving amifostine. A placebo-controlled trial would have been ideal, but the potential risks and inconvenience of daily intravenous placebo injections were felt to be unjustified. Likewise, having separate treating and assessing physicians²⁵ would have been desirable but was logistically impractical. Subjective patient assessment of benefit was consistent with the physician assessment, which speaks against the likelihood of any significant bias.

Amifostine did not diminish the severity of acute mucositis. The subgroup analysis, however, suggested a mucoprotective benefit in those patients treated with smaller fields. Other studies examining the impact of amifostine on mucositis imply that daily doses more than 300 mg/m² are desirable.⁷ The dose of 200 mg/m²/d in this study may have been inadequate to provide full mucosal protection especially when large areas of mucosa were irradiated. Given its impact against xerostomia, further evaluation of the effectiveness of higher daily doses of amifostine against mucositis is warranted.

Tumor protection is the greatest potential risk associated with the use of any toxicity modifier. An agent that ameliorated treatment toxicity but that also reduced antitumor efficacy would be unsuitable for clinical use. Local-regional relapses (primary site or nodes) constitute the vast

majority of initial recurrences after the treatment of head and neck cancer. Therefore, an increased incidence of local-regional failure would provide strong evidence of tumor protection with the use of a localized treatment modality such as radiotherapy. Actuarial estimates of local-regional control and disease-free survival and overall survival were equivalent among patients who did or did not receive amifostine and argue against any such protection. Moreover, the prognosis of both groups of patients was similar to that of more than 2,000 head and neck cancer patients in the Radiation Therapy Oncology Group database²⁶ (T. Pajak, personal communication, June, 1999).

Analysis of the time course of the cumulative frequency of all recurrences reinforces the concept that amifostine did not impair the efficacy of radiotherapy. It is well established that those patients who will recur after treatment of head and neck cancer will do so quickly. Approximately 50% of all recurrences transpire within 6 months of initial treatment, 70% within 1 year, and 80% to 90% within 2 years.²⁷ This same pattern was observed in both cohorts of patients in the current study (data not shown).

This trial has demonstrated that daily administration amifostine can successfully reduce the incidence and severity of acute and chronic xerostomia that develops during the radiotherapy of head and neck cancer without compromising the efficacy of the radiation. It has established the proof of principle that lays the foundation for the investigation of normal tissue radioprotection strategies for other types of cancer.

Several problems still need to be addressed regarding the use of radioprotectors in general and in head and neck cancer in particular and form the basis of ongoing studies. These include whether or not an administration route more convenient than daily IV injection is possible and associated with less toxicity, understanding the role of this drug in treatment schemes that use modified fractionation schedules and/or concurrent chemotherapy, and more clearly delineating the mucoprotective effects, if any, of amifostine. The answers will help to define the role of this drug in clinical practice.

REFERENCES

1. Johnson JT, Ferretti GA, Nethery WJ, et al: Oral pilocarpine for post-irradiation xerostomia in patients with head and neck cancer. *N Engl J Med* 329:390-395, 1993
2. LeVeque FG, Montgomery M, Potter D, et al: A multicenter, randomized, double-blind, placebo-controlled, dose-titration study of oral pilocarpine for treatment of radiation-induced xerostomia in head and neck cancer patients. *J Clin Oncol* 11:1124-1131, 1993
3. Yuhas JM, Spellman JM, Culo F: The role of WR-2721 in radiotherapy and/or chemotherapy. *Cancer Clin Trials* 3:211-216, 1980
4. Utley JF, Marlowe C, Waddell WJ: Distribution of ³⁵S-labeled WR-2721 in normal and malignant tissues of the mouse. *Radiat Res* 68:284-291, 1976
5. Rasey JS, Grunbaum Z, Krohn KA, et al: Biodistribution of the radioprotective drug S-labeled 3-amino-2-hydroxy-propyl phosphorothioate (WR77913). *Radiat Res* 102:130-137, 1985
6. Kemp G, Rose P, Lurain J, et al: Amifostine pretreatment for protection against cyclophosphamide-induced and cisplatin-induced toxicities: Results of a randomized control trial in patients with advanced ovarian cancer. *J Clin Oncol* 14:2101-2112, 1996

7. Buntzel J, Kuttner K, Frohlich D, et al: Selective cytoprotection with amifostine in concurrent radiochemotherapy for head and neck cancer. *Ann Oncol* 9:505-509, 1998
8. McDonald S, Meyerowitz C, Smudzin T, et al: Preliminary results of a pilot study using WR-2721 before fractionated irradiation of the head and neck to reduce salivary gland dysfunction. *Int J Radiat Oncol Biol Phys* 29:747-754, 1994
9. American Joint Committee on Cancer: Manual for Staging of Cancer (ed 3). Philadelphia, PA, JB Lippincott Co, 1988
10. Mackowiak JI, Scott-Lennox J, Lennox R, et al: Patient benefit questionnaire (PBQ) for xerostomia: Development and validation report. *Value Health* 2:197, 1999 (abstr)
11. Westfall PH, Young SS: P value adjustments for multiple tests in multivariate binomial models. *J Am Stat Assoc* 84:780-786, 1989
12. Gelman R, Gelber R, Henderson IC, et al: Improved methodology for analyzing local and distant recurrence. *J Clin Oncol* 8:548-555, 1990
13. Kaplan RJ, Pajak TF, Cox JD: Analysis of the probability and risk of cause-specific failure. *Int J Radiat Oncol Biol Phys* 29:1183-1186, 1994
14. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 53:457-481, 1958
15. Peters LJ, Goepfert H, Ang KK, et al: Evaluation of the dose for postoperative radiation therapy of head and neck cancer: First report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys* 26:3-11, 1993
16. Pocock SJ, Simon R: sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 31:103-115, 1975
17. Zelen M: The randomization and stratification of patients to clinical trials. *J Chron Dis* 27:365-375, 1975
18. Taves DR: Minimization: A new method of assigning patients to treatment and control groups. *Clin Pharmacol Ther* 15:443-453, 1974
19. Wolf A, Fox PC, Ship JA, et al: Oral mucosal status and major salivary gland function. *Oral Surg Oral Med Oral Pathol* 70:49-54, 1990
20. Valdez IH, Atkinson JC, Ship JA, et al: Major salivary gland function in patients with radiation-induced xerostomia: Flow rates and sialochemistry. *Int J Radiat Oncol Biol Phys* 25:41-47, 1992
21. Horiot JC, LeFur R, N'Guyen T, et al: Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: Final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiother Oncol* 25:231-241, 1992
22. Horiot JC, Bontemps P, van den Bogaert W, et al: Accelerated fractionation (AF) compared to conventional fractionation (CF) improves local regional control in the radiotherapy of advanced head and neck cancers: Results of EORTC 22851 randomized trial. *Radiother Oncol* 44:111-121, 1997
23. Brizel DM, Albers MA, Fisher SR, et al: Hyperfractionated irradiation with and without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 338:1798-1804, 1998
24. Merlano J, Benasso M, Corvo R, et al: Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. *J Natl Cancer Inst* 88:583-589, 1996
25. Johnson KP, Brooks BR, Cohen JA, et al: Extended use of glatiramer acetate (Copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability: Copolymer 1 Multiple Sclerosis Study Group. *Neurol* 50:701-708, 1998
26. Cooper JS, Farnan NC, Asbell SO, et al: Recursive partitioning analysis of 2105 patients treated in Radiation Therapy Oncology Group Studies of head and neck cancer. *Cancer* 77:1905-1911, 1996
27. Fu KK, Clery M, Ang KK, et al: Randomized phase I/II trial of two variants of accelerated fractionated radiotherapy regimens for advanced head and neck cancer: Results of RTOG 88-09. *Int J Radiat Oncol Biol Phys* 32:589-597, 1995

ERRATA

Two appendices were omitted from the October 1, 2000, article by Brizel et al, entitled "Phase III Randomized Trial of Amifostine as a Radioprotector in Head and Neck Cancer" (J Clin Oncol 18:3339-3345, 2000). The appendices are reprinted below in their entirety.

APPENDIX A Participating Institutions and Principal Investigators

Institute Name	Principal Investigator
Markischer Kreis Strahlenklinik	Ahlemann, Lute
Harper Hospital	Ahmad, Syamala
St Mary's Medical Center	Ahmad, Khurshid
Hno Klinik Graz	Anderhuber, Wolfgang
Abteilung Strahlentherapie	Bamberg, Michael
Centre Antoine-Lacassagne	Bedsadoun, Rene-Jean
Klinikum Der Johann Wolfgang	Bottcher, Heinz D.
Mercy Hospital-Scranton	Brereton, Harmar D.
Clinique Sainte Catherine	Brewer, Yvelise
Duke University Medical Center	Brizel, David M.
Humboldt University	Budach, Volker
University Klinik Fur Strahlentherapie	Dobrowsky, Werner
Martin-Luther Universitat	Dunst, Jurgen
Philipps University	Engenhart-Cabillic, Rita
Institute Gustave-Roussy	Eschwege, Francois
M.D. Anderson Cancer Center, Orlando, FL	Forbes, Alan R.
Hotel Dieu De Quebec	Fortin, Andre
Hospital Notre-Dame	Gelinals, Michel
St Vincentius Krankenhaus	Haase, Wulf
University of Wisconsin	Harari, Paul
Freiburg University	Henke, Michael
Klinikum Der Universitat	Herbst, Manfred
Cross Cancer Institute	Jha, Naresh
Radiation Oncology Center	Jones, Christopher U.
Pacific Coast Hem/Onc Medical	Karon, Donald
East Orange VA Medical Center	Kasimis, Basil
Klinikum Ernst Von Bergmann	Koch, Karin
Mary Babb Randolph Cancer	Korb, Leroy J.
VA Medical Center, Washington, DC	Krasnow, Steven H.
Centre Alexis Vautrin	Lapeyre, Michel
University of Pennsylvania	Machtay, Mitchell
Centre Hospitalier Bouilloche	Monnier, Alain
Nottingham City Hospital	Morgan, David
M.D. Anderson Cancer Center, Houston, TX	Morrison, William H.
Universitat Koln	Muller, Rolf-Peter
Clinic of Radiation Oncology,	Sauer, Rolf
Medical College of Wisconsin	Schultz, Christopher
B.C. Cancer Agency	Sheehan, Finbarr G.
Zentralklinikum Kzva	Voss, Arndt
Sektion Strahlentherapie Der Drg	Wannenmacher, Michael

APPENDIX B
Radiation Therapy Oncology Group Toxicity Scales

Acute xerostomia

Grade 1

Mild mouth dryness/slightly thickened saliva

May have slightly altered taste

Changes not reflected in alteration in baseline feeding behavior such as increased use of liquids with meals

Grade 2

Moderate to complete dryness

Thick, stick saliva

Markedly altered taste

Grade 3

None

Grade 4

Acute salivary gland necrosis

Chronic xerostomia

Grade 1

Slight dryness of mouth

Good response to stimulation

Grade 2

Moderate dryness of mouth

No response to stimulation

Grade 3

Complete dryness of mouth

No response to stimulation

Grade 4

Fibrosis

The November 1, 2000, Supplement article by Shepherd, entitled "Chemotherapy for Advanced Non-Small-Cell Lung Cancer: Modest Progress, Many Choices" (J Clin Oncol 18:35s-38s, 2000 [suppl]), contained errors in the doses and results of Table 2. The correct dosage is 75 mg/m² of docetaxel, not 100 mg/m². The correct response rate is 17.3% for the docetaxel arm, not 7.3%. Table 2 is reprinted below in its entirety.

Table 2. Efficacy Summary of ECOG 1594

	A Paclitaxel 135 mg/m ² over 24 hours Cisplatin 75 mg/m ²	B Gemcitabine 1 g/m ² days 1, 8, 15 Cisplatin 100 mg/m ²	C Docetaxel 75 mg/m ² Cisplatin 75 mg/m ²	D Paclitaxel 135 mg/m ² over 3 hours Carboplatin AUC 6
Response rate,* %	21.3	21.0	17.3	15.3
Time to progression, months	3.5	4.5†	3.3	3.3
Survival				
Median, months	7.8	8.1	7.4	8.3
1-year, %	31	36	31	34

Abbreviation: AUC, area under the curve.

*A v B *P* > .05, A v C *P* > .05, A v D *P* = .08.†A v B *P* = .002.