VOLUME 29 · NUMBER 18 · JUNE 20 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Effect of Amifostine on Survival Among Patients Treated With Radiotherapy: A Meta-Analysis of Individual Patient Data

Jean Bourhis, Pierre Blanchard, Emilie Maillard, David M. Brizel, Benjamin Movsas, Jens Buentzel, Johannes A. Langendijk, Ritsuko Komaki, Swan Swan Leong, Peter Levendag, and Jean Pierre Pignon

Jean Bourhis, Pierre Blanchard, Emilie Maillard, and Jean Pierre Pignon, Institut Gustave Roussy, Villejuif, France; David M. Brizel, Duke University Medical Center, Durham, NC; Benjamin Movsas, Henry Ford Hospital, Detroit, MI; Jens Buentzel, Suedharzkrankenhaus Nodhausen, Nordhausen, Germany; Johannes A. Langendijk, University Medical Center Groningen, University of Groningen, Groningen; Peter Levendag, Erasmus MC–Daniel Den Hoeg, Rotterdam, the Netherlands; Ritsuko Komaki, University of Texas MD Anderson Cancer Center, Houston, TX; and Swan Swan Leong, National Cancer Centre, Singapore.

Submitted October 14, 2010; accepted March 23, 2011; published online ahead of print at www.jco.org on May 16, 2011.

Written on behalf of the Meta-Analysis of Amifostine in Radiotherapy Collaborative Group.

Supported by unrestricted grants from Institut Gustave-Roussy and Ligue Nationale Contre le Cancer, and project grant from Medimmune.

Presented in part at the 48th Annual Meeting of the American Society for Therapeutic Radiation and Oncology, November 5-9, 2006, Philadelphia, PA; and the 33rd Congress of the European Society of Medical Oncology, September 12-16, 2008, Stockholm, Sweden.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Jean-Pierre Pignon, MD, PhD, Meta-analysis Unit, Biostatistics and Epidemiology Department, Institut Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif Cedex, France; e-mail: jppignon@igr.fr.

0732-183X/11/2918-2590/$20.00

DOI: 10.1200/JCO.2010.33.1454

ABSTRACT

Purpose
Controversy exists regarding whether or not amifostine might reduce the efficacy of cancer treatment. The aim of this meta-analysis was to evaluate the impact of amifostine on overall survival (OS) and progression-free survival (PFS) in patients treated with radiotherapy or chemoradiotherapy.

Material and Methods
Updated data from individual patients with non–small-cell lung cancer, head and neck squamous cell carcinoma, and pelvic cancer treated with radiotherapy or chemoradiotherapy and randomly assigned to amifostine or not were included. The primary end point was OS.

Results
Twenty-two randomized trials (2,279 patients) were potentially eligible. Data were available for 16 trials (1,554 patients), but four trials (435 patients) were excluded after data checking. Ultimately 12 trials and 1,119 patients were analyzed. A total of 431 patients were treated with radiotherapy alone (three trials), and 688 patients were treated with chemoradiotherapy (nine trials). Thirty-three percent of patients had lung cancers, 65% had head and neck cancers, and 2% had pelvic carcinomas. Ninety-one percent of patients had locally advanced disease (early stage, 9%). Median follow-up was 5.2 years. The hazard ratio (HR) of death was 0.98 (95% CI, 0.84 to 1.14; $P = .78$). On the basis of 11 trials (1,091 patients), the HR of progression, relapse, or death was 1.05 (95% CI, 0.90 to 1.22; $P = .53$). The tests for heterogeneity were not significant ($P \geq .73$), and there was no significant variation of treatment effect according to sex, age, tumor site, stage, histology, locoregional treatment, or type of administration for either end point.

Conclusion
Amifostine did not reduce OS and PFS in patients treated with radiotherapy or chemoradiotherapy.

J Clin Oncol 29:2590-2597. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Radiotherapy (RT), as other anticancer treatments, has potential short- and long-term adverse effects that must be considered at the moment of prescription. Recently, major progress in radiation oncology have come from different directions: better target volume definition and radiation delivery and use of altered fractionation RT and concurrent systemic therapy (chemotherapy or molecularly targeted therapy). The two latter led to improved survival in many different cancers.[1-3] However, the corresponding survival benefit must be weighed in light of the resulting increase in acute and late toxicity. Supportive care helps patients to manage symptoms related to the disease and treatments, but as these supportive treatments are pharmacologically active, their effects on tumor should always be evaluated. As an example, erythropoiesis-stimulating agents have been shown in a large meta-analysis to worsen OS in most tumor types.[4]

One of the means to decrease RT-related toxicity would be through the use of radioprotective agents. An ideal radioprotectant should protect normal tissues without compromising tumor control. Amifostine is probably the most widely studied and used cytoprotective agent. The adverse effects of ionizing radiation are initiated by the generation of reactive oxygen species (ROS), which induce DNA damages. Amifostine is a synthetic prodrug aminothiol that reduces these ROS through its free sulfhydryl moiety. After the pivotal trial of Brizel et al,[5,6] it was approved by the US Food and Drug Administration and European Medicines Agency for the reduction of xerostomia in patients with head and neck cancer (HNC) undergoing RT.

There have been concerns regarding whether amifostine could protect the tumor as well as normal

tissues. In this case, the use of amifostine would be detrimental in terms of survival by decreasing locoregional control. Neither of the two largest trials of amifostine and radiotherapy showed evidence of tumor protection by amifostine.[5,6] But the median follow-up was relatively short (< 2.5 years), and the power of the studies was too low to provide a definitive answer to this question. Indeed, these trials were designed and powered to evaluate acute and late toxicity and not differences in survival. All other randomized studies of amifostine were smaller and usually included fewer than a hundred patients. Although two meta-analyses of published data have already reported no effect[7] or a beneficial effect[8] of amifostine on response rates during RT, none had access to survival data. A meta-analysis using individual patient data (IPD) was the only solution in this case because it would allow the collection of long-term local control and updated survival data from all the trials. In addition, an IPD meta-analysis would lower the publication bias and allow to some extent to check the quality of the trials' data.[9-11] The Meta-Analysis of Amifostine in Radiotherapy (MAART) project was therefore initiated in 2004 to bring the most rigorous and scientific evidence regarding the potential effects of amifostine on overall survival.

MATERIALS AND METHODS

Study Design, Search Strategy, and Study Selection

A protocol (available on request) was written before data collection specifying inclusion criteria, end points, and statistical analysis plan. To be included, trials had to be randomized, not be confounded by additional therapeutic differences between the two groups, and had to compare RT (or chemoradiotherapy) with or without amifostine. Patients should have been treated using RT with a curative intent either in a definitive or adjuvant setting. Amifostine had to be administered only during the course of RT and not afterwards. Trials should have started randomization on or after January 1990 and completed accrual before June 2002. Trials should have aimed to include patients with one of the following nonmetastatic cancers: non–small-cell lung cancer, HNC, or pelvic cancer.

To limit publication bias, data from all published and unpublished randomized trials evaluating the above comparison were sought without language restriction using electronic database searching for the period 1966 to 2004 (MEDLINE, Embase, Cancerlit, CINAHL, ACP Journal Club, Cochrane DSR, DARE, CCT meta-register, HealthSTAR/Ovid HealthSTAR), hand searching (review articles, meeting proceedings of the American Society of Clinical Oncology, American Society for Therapeutic Radiology and Oncology, European Cancer Organization, European Society for Therapeutic Radiology and Oncology, and European Society for Medical Oncology from 1994 through 2004), and by contacting experts in the field and members of the meta-analysis steering committee.

Data Collection

The data collected for each patient included age, sex, tumor site, histology, stage, type of administration of amifostine, allocated treatment, and date of randomization. The date of first tumor failure was also recorded, but the type of failure (local, regional, or distant) was not sought for all trials. Survival status and date of last follow-up were updated. Data on patients excluded from the analysis after being randomly assigned were collected whenever possible.

All the data were checked for internal consistency and compared with the trial's protocol and published reports. Standard checks were used to quantify

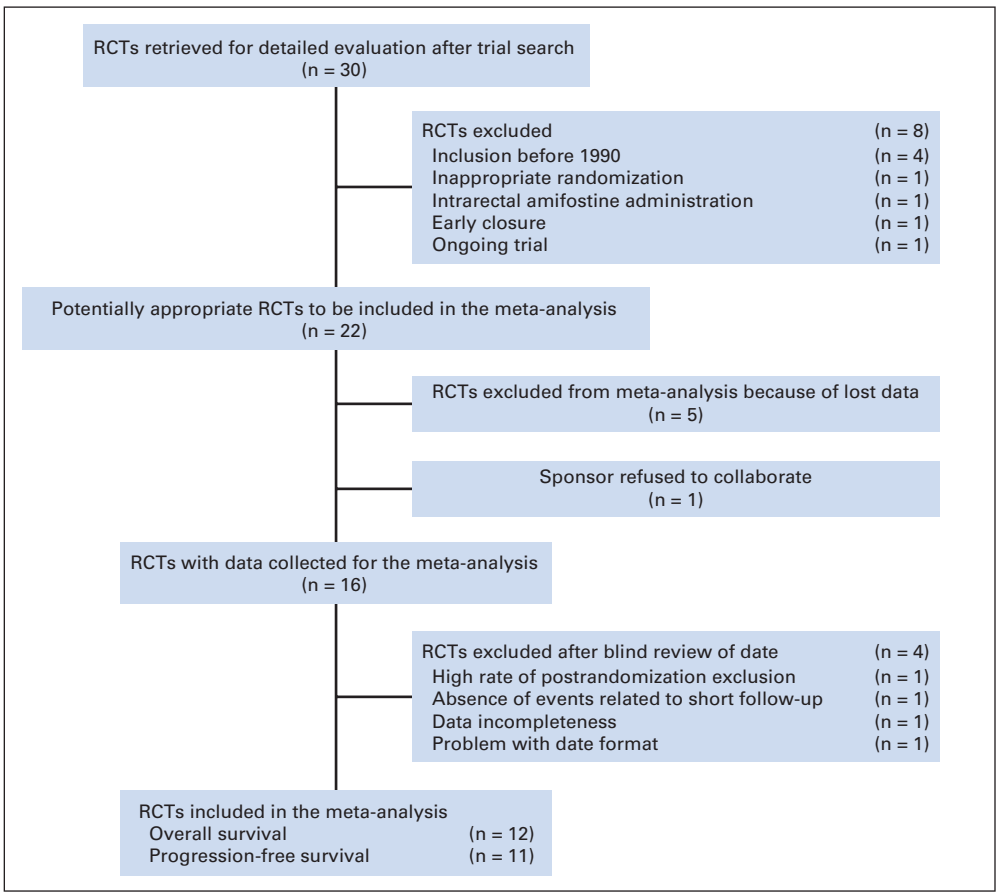

Fig 1. QUOROM flow chart. RCTs, randomized controlled trials.

the amount of missing data, check the order of dates, and assess data validity and consistency. In each trial, randomization integrity was assessed by checking patterns of treatment allocation and balance of baseline characteristics by treatment group. Follow-up of patients was checked to ensure that it was balanced between treatment groups.[12] Each trial was analyzed individually, and these analyses were sent to the trialists for review.

Statistical Analyses

The primary outcome was OS, defined as the time from random assignment until death by any cause. The secondary end point was progression-free survival (PFS), defined as the time from random assignment until first progression or death by any cause. Patients alive without disease were censored on the date of last follow-up.

Unless otherwise stated, all analyses were prespecified in the protocol and performed on an intention-to-treat basis. Survival analyses were stratified by trials, and the log-rank observed minus expected number of deaths (O-E) and its variance were used to calculate individual and overall pooled hazard ratios (HRs), with a fixed effect model. The relative weight of each trial in the pooled analysis was proportional to the O-E variance, which is approximately equal to one fourth of the number of deaths.[13] χ^2 tests and I^2 were used to study heterogeneity between trials.[14,15] We calculated the median follow-up for all patients with the reverse Kaplan-Meier method.[16]

To study the interaction between treatment and a covariate, an analysis stratified by trial was performed for each covariate group, and the HRs for each covariate group were compared by a test for interaction or trend as appropriate. Variation of amifostine effect according to tumor site (HNC *v* lung cancer *v* pelvic cancer), type of administration of amifostine (intravenous *v* subcutaneous), type of locoregional treatment (radiotherapy *v* chemoradiotherapy), and patient covariates (age, sex, histology, and stage) was studied. To take into account amifostine delivery, trials were grouped according to whether amifostine was administered before each RT fraction or not (unplanned analysis).

Stratified survival curves taking into account variation of HR over time were computed for control and experimental groups and used to calculate absolute difference at 2 and 5 years.[17] The absolute benefit depends on HR and survival rate. All *P* values are two-sided. All statistical analyses were performed using Statistical Analysis Systems software, version 9.1, for Microsoft Windows (SAS Institute, Cary, NC).

RESULTS

Description of Trials and Patients

The selection of trials is depicted in the QUORUM flow chart (Fig 1). Briefly, 30 trials were identified, of which eight were excluded because they did not fulfill MAART inclusion criteria.[18-24] Twenty-two randomized trials (2,279 patients) were potentially eligible,[5,6,25-44] but data were available for 16 trials (1,554 patients, 68% of patients).[5,6,30-41,43,44] Four trials (435 patients) were eventually excluded after blind review by the steering committee.[38,39,41,44]

In total, data from 12 trials and 1,119 patients were analyzed, among which 23 patients had been excluded from the published trial analyses (of 30 excluded patients from the published analyses). Trial characteristics are summarized in Appendix Table A1 (online only). Whenever possible, patient follow-up was updated because follow-up was quite short in published reports: ≤ 3 years in seven trials and not available in four trials. After this update, median follow-up was 5.2 years, ranging from 1.8 to 10.3 years for the different trials, and did not differ between the two arms. The median follow-up was greater than 60 months (5 years) in seven trials and was between 36 and 60 months (3 to 5 years) in four trials. Only one trial had a follow-up shorter than 2 years.[35] Patients' characteristics are summarized in Table 1. Patients were included in trials of radiotherapy (three trials, 431 patients) or chemoradiotherapy (nine trials, 688 patients) with or without amifostine. Two trials included a total of 27 patients after June 30, 2002.[31,36] There was a good balance between trial arms regarding age, sex, tumor site, stage, histology, and type of administration of amifostine. The distribution of patients according to the tumor site was 33% for lung, 65% for head and neck, and 2% for cervix uteri carcinoma. Overall, 78% of patients had squamous cell carcinomas, and 91% had locally advanced disease.

Table 1. Patient Characteristic for Trials Comparing Radiotherapy (± chemotherapy) With or Without Amifostine

Characteristic	Amifostine (n = 572)		Control (n = 547)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	415	73	400	73
Female	157	27	147	27
Age, years				
≤ 50	133	23	131	24
51-60	220	38	194	35
> 60	219	38	222	41
Tumor site				
NSCLC	181	32	186	34
HNSCC	379	66	351	64
Cervix uteri	12	2	10	2
Histology				
Squamous cell carcinoma	455	80	413	76
Adenocarcinoma	50	9	65	12
Other NSCLC	67	12	69	13
Stage				
Early stage (I-II)	56	10	48	9
Late stage (III-IV)	514	90	497	91
Missing	2		2	
Type of administration				
Intravenous	530	93	504	92
Subcutaneous	42	7	43	8

Abbreviations: HNSCC, head and neck squamous cell carcinoma; NSCLC, non–small-cell lung cancer.

OS

The survival analysis was based on 12 trials, 1,119 patients, and 657 deaths. The HR of death was 0.98 (95% CI, 0.84 to 1.14; $P = .78$). The 2- and 5-year OS changes due to amifostine administration are respectively +1.9% (95% CI, −4.1% to 7.9%) and −0.4% (95% CI, −6.0% to 6.8%). There was no evidence of significant statistical heterogeneity with an I^2 value of 0% (χ^2 test for heterogeneity, $P = .73$). The forest plot and survival curves of OS are shown on Figures 2 and 3.

PFS

The analysis of PFS was based on 11 trials, 1,091 patients, and 705 events. The HR of progression, relapse, or death was 1.05 (95% CI, 0.90 to 1.22; $P = .53$). The 2- and 5-year absolute PFS changes due to amifostine administration are, respectively, −1.1% (95% CI, −6.9% to 5.8%) and −3.0% (95% CI, −9.4% to 3.4%). There was no evidence of significant statistical heterogeneity with an I^2 value of 0% (χ^2 test for heterogeneity, $P = .93$). The forest plot of PFS and the PFS curves are respectively shown in Figure 4 and Appendix Figure A1 (online only). Local control was not analyzed because this item could only be collected for a limited number of trials.

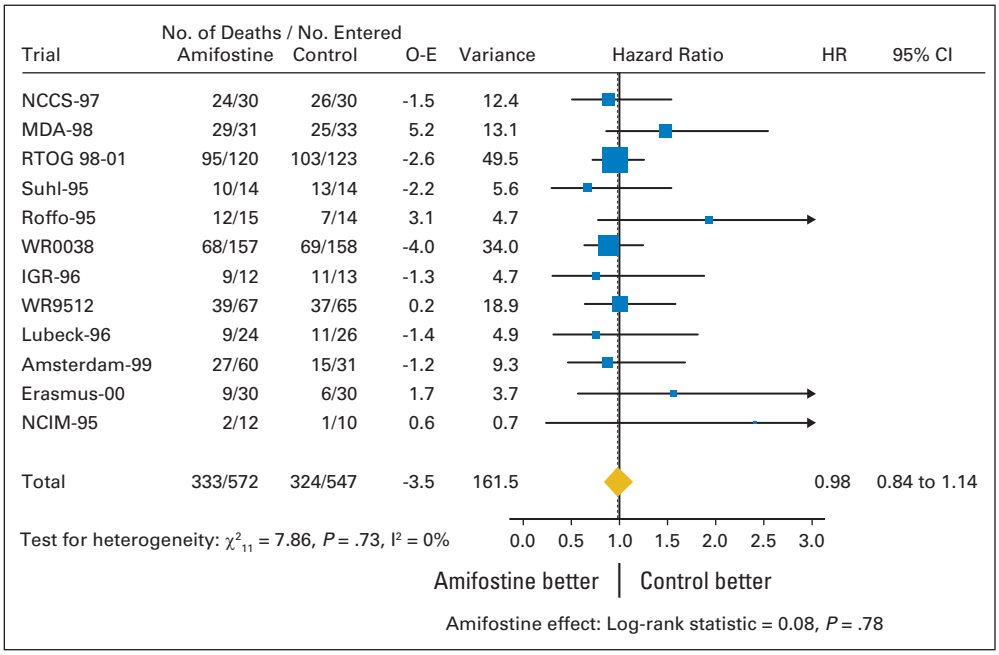

Fig 2. Hazard ratio (HR) of death with locoregional treatment plus amifostine versus locoregional treatment alone. O-E, observed minus expected number of deaths.

Interaction With Patient and Trial Characteristics

There was no significant difference of amifostine effect in either OS (Fig 5) or PFS (Appendix Fig A2, online only) according to the following patient characteristics: sex, age, tumor site, histology, and stage. There was no significant difference of amifostine effect in either OS (Fig 6) or PFS (Appendix Fig A3, online only) according to the following trial characteristics: type of amifostine administration, locoregional treatment, trial size, follow-up time, and whether amifostine was given before each RT fraction or not.

DISCUSSION

This individual patient data meta-analysis of definitive RT with or without amifostine demonstrates that the use of amifostine concurrently with RT has no significant effect on OS or PFS with a follow-up greater than 5 years. No heterogeneity of amifostine effect was recorded between trials. There was no statistically significant interaction between trials and patients characteristics and amifostine effect. This meta-analysis therefore provides the most rigorous evidence regarding the effects of amifostine on survival both for definitive RT or for chemoradiotherapy.

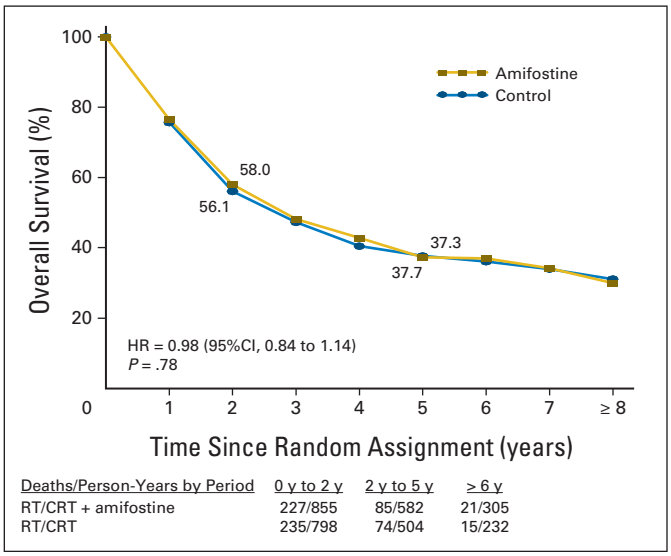

Fig 3. Hazard ratio (HR) of recurrence or death with locoregional treatment plus amifostine versus locoregional treatment alone. O-E, observed minus expected number of deaths.

Data from 10 trials have not been included in the analysis, either because they were not "available" (six trials) or because they were deemed of poor quality after blind review by the steering committee (four trials). Therefore, the number of trials included has decreased with two major consequences: a decrease of the power of the meta-analysis and a larger influence of the three main trials on the meta-analysis results, which represent two thirds of the events.[5,6,32] However, none of the six unavailable trials provided published results on OS. The data included in the present analysis are all of good quality, but in a smaller amount than foreseen at the time when the meta-analysis protocol was written. Nevertheless, using individual patient data allowed for an increase in follow-up and therefore power and for an inclusion of only high-quality data. All of this strengthens the conclusions of the present meta-analysis.

Considering the number of patients included and events observed, the meta-analysis showed that the risk of death associated with amifostine was reduced by 2% (HR, 0.98), with a 95% CI between −16% and +14%. It is important not to emphasize the absolute benefits estimated for OS or PFS. Indeed, the effect seen for PFS at 5 years, although it seems detrimental, with an increase of events by 3% (95% CI, −9.4% to 3.4%), must be viewed in light of its CI and of the HR estimated for the entire curve. In addition, it is known that to rely on only one point estimate can lead to biased estimation of treatment effect.[45] For example, in Figure 3, the amifostine OS curve is over the control curve for all time points except for the 5-year survival, suggesting that patients receiving amifostine in general do better than control patients, although not significantly. This is why we believe that the

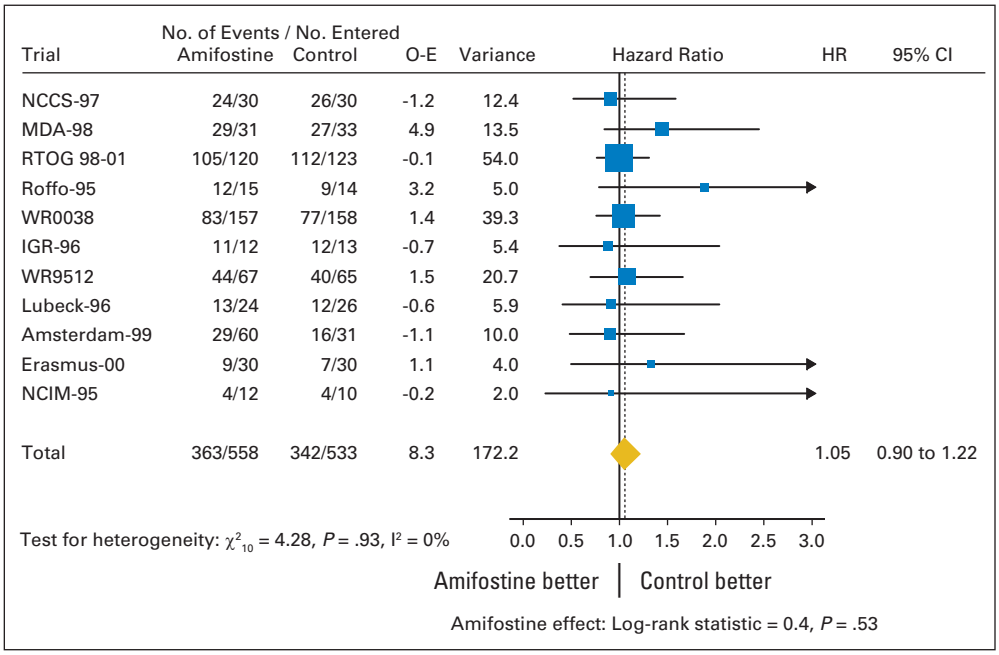

Fig 4. Hazard ratio (HR) of recurrence or death with locoregional treatment plus amifostine versus locoregional treatment alone. O-E, observed minus expected number of deaths.

conclusion of this meta-analysis should be based on the HRs and not on the absolute benefits at one time point.

The ability of amifostine to reduce short- and long-term toxicity has been evaluated in all the randomized trials included in this meta-analysis. The two largest trials included patients with HNC[5] and lung cancer.[6] Brizel et al[5] conducted a phase III trial in 315 patients with HNC randomly assigned to intravenous amifostine plus RT (standard fractionation) versus RT alone. Amifostine reduced the incidence of both acute (78% *v* 51%, $P < .0001$) and late (57% *v* 35%, $P = .001$) grade ≥ 2 xerostomia. In this trial, amifostine did not reduce the rate of acute mucositis. The second largest trial randomly assigned 243 patients with stage II to IIIA/B non–small-cell lung cancer to induction chemotherapy followed by concurrent chemoradiotherapy with or without intravenous amifostine. This trial failed to show a significant reduction of grade 3 esophagitis with the use of amifostine,[6] although there was significant improvement in some patient-reported outcomes, such as pain, with amifostine.[46] Common dose-limiting toxicities of amifostine are nausea, emesis,[47] rare but severe allergic

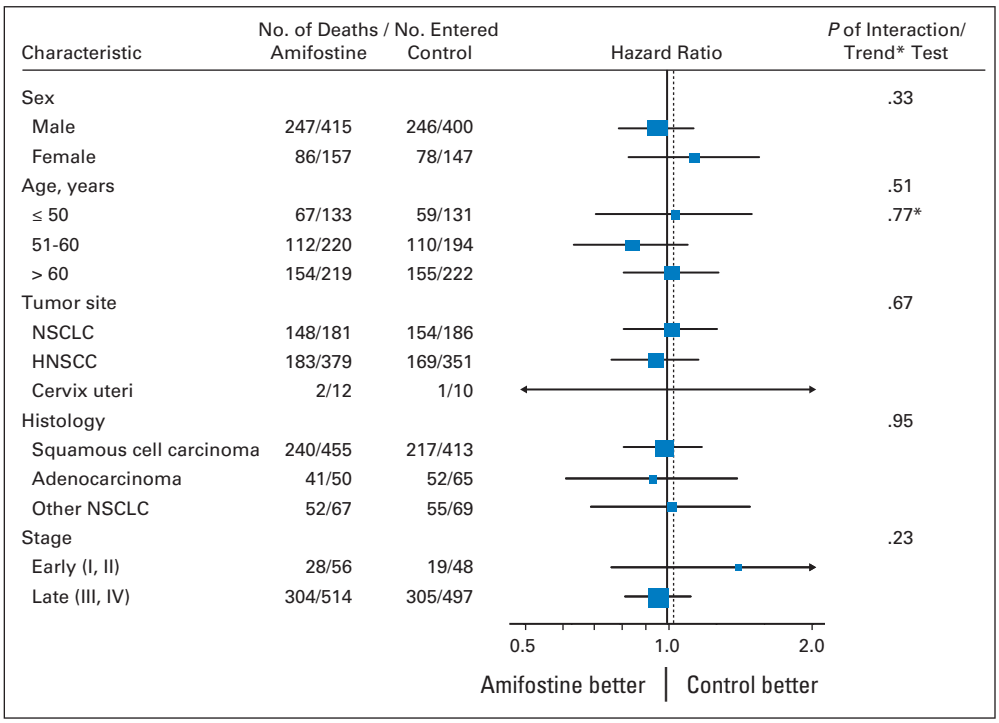

Fig 5. Hazard ratio of death with locoregional treatment plus amifostine versus locoregional treatment alone by patient characteristics. HNSCC, head and neck squamous cell carcinoma; NSCLC, non–small-cell lung cancer.

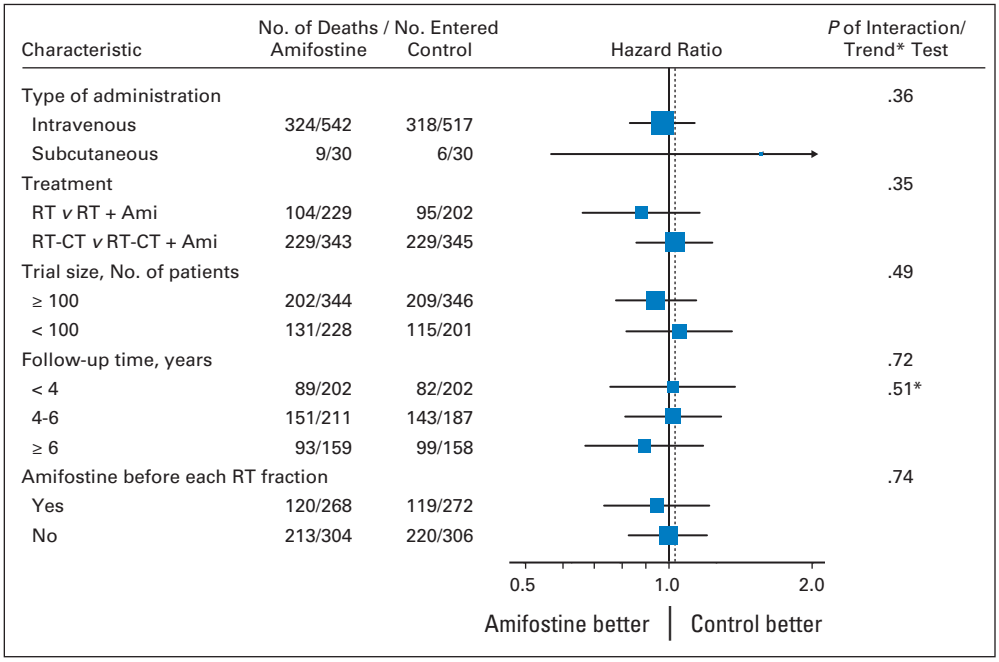

Fig 6. Hazard ratio of death with locoregional treatment plus amifostine (Ami) versus locoregional treatment alone by trial characteristics. RT, radiotherapy; RT-CT, radiotherapy and chemotherapy.

reactions,[48] and hypotension, which can lead to the discontinuation of amifostine in as many as 25% of patients.[49]

The largest meta-analysis of published data evaluated the reduction in acute and late radiation toxicity achieved by amifostine. It included 14 randomized trials and 1,451 patients. It concluded that amifostine significantly reduced the risk of mucositis, xerostomia, dysphagia, pneumonitis, and cystitis in patients undergoing RT, without a difference in overall response.[8] However, this analysis suffers from several biases. First, because negative trials are less likely to be published than positive ones, publication bias cannot be ruled out. Our trial search found all the trials included by Deeke Sasse et al and identified another six eligible trials, which represent 645 patients,[32,34,36,40,43,44] of which five are included in the present analysis (one trial was excluded after data checking). Second, the quality of the included trials is of concern. Indeed seven of the 14 trials included by Deeke Sasse et al have been either considered not eligible (too old),[18] not included (data lost),[25-29] or excluded after data checking[38,39] in our meta-analysis. Third, classification bias could explain part of the heterogeneity reported in this meta-analysis. Indeed, most of the trials included are open-label studies and use patient-reported outcomes, which are known to be sensitive to the absence of blinding. Furthermore, different scales are used to score the toxicities across the studies, therefore creating heterogeneity. It is known that toxicity scoring can vary if different toxicity scales are used.[50]

The subjectivity of the outcome measurement could be overcome by the use of blinding procedures, but only two of the trials included in the present IPD meta-analysis are placebo-controlled.[32,40] However, maintaining an effective blinding procedure would be difficult because of the high rate of amifostine-related adverse effects. Alternative options could be to use objective outcomes (eg, stimulated/unstimulated saliva production[51]) or a blind assessment of subjective outcomes. Because it is completely objective, the measure of OS is not sensitive to treatment blinding, so this criticism is not relevant for the purpose of the analysis presented here.

Nowadays the relevant question is whether amifostine can reduce toxicity in the setting of modern multimodality therapy. In HNC, concurrent chemotherapy and altered fractionation RT improve disease control and survival and have become standard of care, despite an increase in toxicity.[2,3] Intensity-modulated RT (IMRT) has been developed to allow better target coverage along with a better sparing of organs at risk. This technique has become widely implemented in HNC because it is an effective means to prevent xerostomia. Atlases for salivary gland delineation have been published.[52] A retrospective analysis of 100 patients has shown that both amifostine and IMRT reduced long-term salivary dysfunction after RT,[53] and recently a randomized phase III trial showed that IMRT is able to reduce long-term xerostomia in patients with HNC.[54] However, the criticisms made to amifostine apply to IMRT, as the reduction of the irradiation fields could lead to marginal recurrences and lower survival. No survival data based on randomized trials with adequate follow-up are available for IMRT. The benefit of amifostine when used in conjunction with IMRT is unknown and is the subject of current investigation.[55,56] Whether amifostine and IMRT are complementary or synergistic must be answered by properly designed clinical trials. However, it is reasonable to consider that the absence of an amifostine-mediated reduction in survival could be translated from conventional RT to the IMRT setting. Furthermore, the association of amifostine with other radioprotectants has shown promising preclinical results on the reduction of mucositis.[57]

In conclusion, this meta-analysis shows that the use of amifostine concurrently with RT has no detectable impact on OS or PFS. The reduction of radiation toxicity associated with amifostine must be weighed against the costs and adverse effects of amifostine in the context of evolving technologies and better sparing of organs at risk. Therefore, well-designed placebo-controlled randomized trials associated with cost–benefit analyses are needed, particularly in the IMRT setting, to further explore the potential benefits of amifostine.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Jean Bourhis, Jean Pierre Pignon
Administrative support: Jean Pierre Pignon
Provision of study materials or patients: Jean Bourhis, David M. Brizel, Benjamin Movsas, Jens Buentzel, Johannes A. Langendijk, Ritsuko Komaki, Swan Swan Leong, Peter Levendag
Collection and assembly of data: Jean Bourhis, Emilie Maillard, David M. Brizel, Benjamin Movsas, Jens Buentzel, Johannes A. Langendijk, Ritsuko Komaki, Swan Swan Leong, Peter Levendag, Jean Pierre Pignon
Data analysis and interpretation: Jean Bourhis, Pierre Blanchard, Emilie Maillard, Jean Pierre Pignon
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Aupérin A, Le Pechoux C, Rolland E, et al: Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non–small-cell lung cancer. J Clin Oncol 28:2181-2190, 2010
2. Bourhis J, Overgaard J, Audry H, et al: Hyperfractionated or accelerated radiotherapy in head and neck cancer: A meta-analysis. Lancet 368:843-854, 2006
3. Pignon JP, le Maitre A, Maillard E, et al: Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): An update on 93 randomised trials and 17,346 patients. Radiother Oncol 92:4-14, 2009
4. Bohlius J, Schmidlin K, Brillant C, et al: Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: A meta-analysis of randomised trials. Lancet 373:1532-1542, 2009
5. Brizel DM, Wasserman TH, Henke M, et al: Phase III randomized trial of amifostine as a radioprotector in head and neck cancer. J Clin Oncol 18:3339-3345, 2000
6. Movsas B, Scott C, Langer C, et al: Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: Radiation therapy oncology group trial 98-01. J Clin Oncol 23:2145-2154, 2005
7. Mell LK, Malik R, Komaki R, et al: Effect of amifostine on response rates in locally advanced non-small-cell lung cancer patients treated on randomized controlled trials: A meta-analysis. Int J Radiat Oncol Biol Phys 68:111-118, 2007
8. Sasse AD, Clark LG, Sasse EC, et al: Amifostine reduces side effects and improves complete response rate during radiotherapy: Results of a meta-analysis. Int J Radiat Oncol Biol Phys 64:784-791, 2006
9. Pignon JP, Hill C: Meta-analyses of randomised clinical trials in oncology. Lancet Oncol 2:475-482, 2001
10. Piedbois P, Buyse M: Meta-analyses based on abstracted data: A step in the right direction, but only a first step. J Clin Oncol 22:3839-3841, 2004
11. Stewart LA, Parmar MK: Meta-analysis of the literature or of individual patient data: Is there a difference? Lancet 341:418-422, 1993
12. Stewart LA, Clarke MJ: Practical methodology of meta-analyses (overviews) using updated individual patient data: Cochrane Working Group. Stat Med 14:2057-2079, 1995
13. Yusuf S, Peto R, Lewis J, et al: Beta blockade during and after myocardial infarction: An overview of the randomized trials. Prog Cardiovasc Dis 27: 335-371, 1985
14. Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials—Non-small Cell Lung Cancer Collaborative Group. BMJ 311:899-909, 1995
15. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 21:1539-1558, 2002
16. Schemper M, Smith TL: A note on quantifying follow-up in studies of failure time. Control Clin Trials 17:343-346, 1996
17. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women—Early Breast Cancer Trialists' Collaborative Group. Lancet 339:71-85, 1992
18. Kligerman MM, Liu T, Liu Y, et al: Interim analysis of a randomized trial of radiation therapy of rectal cancer with/without WR-2721. Int J Radiat Oncol Biol Phys 22:799-802, 1992
19. Niibe H, Takahashi I, Mitsuhashi N, et al: [An evaluation of the clinical usefulness of amifostine (YM-08310), radioprotective agent: A double-blind placebo-controlled study. 1. Head and neck tumors]. Nippon Gan Chiryo Gakkai Shi 20:984-993, 1985
20. Niibe H, Takahashi I, Miyaishi K, et al: [An evaluation of the clinical usefulness of amifostine (YM-08310), radioprotective agent: A double-blind placebo-controlled study. 2. Abdominal and pelvic tumors]. Nippon Gan Chiryo Gakkai Shi 20:994-1001, 1985
21. Takahashi M, Abe M, Kawamura T, et al: [Radioprotective effect of YM-08310 in radiotherapy of cervical cancer]. Nippon Igaku Hoshasen Gakkai Zasshi 42:435-442, 1982
22. Peters K, Mucke R, Hamann D, et al: Supportive use of amifostine in patients with head and neck tumors undergoing radio-chemotherapy: Is it possible to limit the duration of the application of amifostine? Strahlenther Onkol 175:23-26, 1999 (suppl 4)
23. Kouloulias VE, Kouvaris JR, Pissakas G, et al: A phase II randomized study of topical intrarectal administration of amifostine for the prevention of acute radiation-induced rectal toxicity. Strahlenther Onkol 180:557-562, 2004
24. Leung SF, Teo P, Zee B, et al: Subcutaneous amifostine for reduction of radiation xerostomia in nasopharynx cancer: A prospective randomised study. J Clin Oncol 23:463s, 2005 (suppl; abstr 8043)
25. Antonadou D, Athanassiou H, Sarris G, et al: Randomized phase III trial of chemoradiation treatment +/-amifostine in patients with colorectal cancer. Proc Am Soc Clin Oncol 22:S325, 2003 (abstr 1176)
26. Antonadou D, Coliarakis N, Synodinou M, et al: Randomized phase III trial of radiation treatment +/- amifostine in patients with advanced-stage lung cancer. Int J Radiat Oncol Biol Phys 51:915-922, 2001
27. Antonadou D, Pepelassi M, Synodinou M, et al: Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer. Int J Radiat Oncol Biol Phys 52:739-747, 2002
28. Antonadou D, Throuvalas N, Petridis A, et al: Effect of amifostine on toxicities associated with radiochemotherapy in patients with locally advanced non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 57:402-408, 2003
29. Athanassiou H, Antonadou D, Coliarakis N, et al: Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: Results of a randomized trial. Int J Radiat Oncol Biol Phys 56:1154-1160, 2003
30. Bourhis J, De Crevoisier R, Abdulkarim B, et al: A randomized study of very accelerated radiotherapy with and without amifostine in head and neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys 46:1105-1108, 2000
31. Braaksma M, van Agthoven M, Nijdam W, et al: Costs of treatment intensification for head and neck cancer: Concomitant chemoradiation randomised for radioprotection with amifostine. Eur J Cancer 41:2102-2111, 2005
32. Buentzel J, Micke O, Adamietz IA, et al: Intravenous amifostine during chemoradiotherapy for head-and-neck cancer: A randomized placebo-controlled phase III study. Int J Radiat Oncol Biol Phys 64:684-691, 2006
33. Büntzel J, Glatzel M, Kuttner K, et al: Amifostine in simultaneous radiochemotherapy of advanced head and neck cancer. Semin Radiat Oncol 12:4-13, 2002
34. Gallardo D, Mohar A, Calderillo G, et al: Cisplatin, radiation, and amifostine in carcinoma of the uterine cervix. Int J Gynecol Cancer 9:225-230, 1999
35. Giglio R, Mickiewicz E, Pradier E, et al: Alternating chemotherapy (CT) + radiotherapy (RT) with amifostine (A) protection for head and neck cancer (HN). Early stop of a randomized trial. Proc Am Soc Clin Oncol 15:106, 1997 (abstr 1639)
36. Jellema AP, Slotman BJ, Muller MJ, et al: Radiotherapy alone, versus radiotherapy with amifostine 3 times weekly, versus radiotherapy with amifostine 5 times weekly: A prospective randomized study in squamous cell head and neck cancer. Cancer 107:544-553, 2006
37. Komaki R, Lee JS, Kaplan B, et al: Randomized phase III study of chemoradiation with or without amifostine for patients with favorable performance status inoperable stage II-III non-small cell lung cancer: Preliminary results. Semin Radiat Oncol 12:46-49, 2002
38. Koukourakis MI, Kyrias G, Kakolyris S, et al: Subcutaneous administration of amifostine during fractionated radiotherapy: A randomized phase II study. J Clin Oncol 18:2226-2233, 2000
39. Kouvaris J, Kouloulias V, Malas E, et al: Amifostine as radioprotective agent for the rectal mucosa during irradiation of pelvic tumors: A phase II randomized study using various toxicity scales and rectosigmoidoscopy. Strahlenther Onkol 179:167-174, 2003

40. Leong SS, Tan EH, Fong KW, et al: Randomized double-blind trial of combined modality treatment with or without amifostine in unresectable stage III non-small-cell lung cancer. J Clin Oncol 21:1767-1774, 2003

41. Patni N, Patni S, Bapna A, et al: The role of amifostine in prophylaxis of radiotherapy induced mucositis and xerostomia in head and neck cancer. J Clin Oncol 22:505s, 2004 (suppl; abstr 5568)

42. Senzer N: A phase III randomized evaluation of amifostine in stage IIIA/IIIB non-small cell lung cancer patients receiving concurrent carboplatin, paclitaxel, and radiation therapy followed by gemcitabine and cisplatin intensification: Preliminary findings. Semin Oncol 29:38-41, 2002

43. Vacha P, Fehlauer F, Mahlmann B, et al: Randomized phase III trial of postoperative radiochemotherapy +/- amifostine in head and neck cancer: Is there evidence for radioprotection? Strahlenther Onkol 179:385-389, 2003

44. Veerasarn V, Phromratanapongse P, Suntornpong N, et al: Effect of Amifostine to prevent radiotherapy-induced acute and late toxicity in head and neck cancer patients who had normal or mild impaired salivary gland function. J Med Assoc Thai 89:2056-2067, 2006

45. Michiels S, Piedbois P, Burdett S, et al: Meta-analysis when only the median survival times are known: A comparison with individual patient data results. Int J Technol Assess Health Care 21:119-125, 2005

46. Sarna L, Swann S, Langer C, et al: Clinically meaningful differences in patient-reported outcomes with amifostine in combination with chemoradiation for locally advanced non-small-cell lung cancer: An analysis of RTOG 9801. Int J Radiat Oncol Biol Phys 72:1378-1384, 2008

47. Monroe AT, Reddy SC, Gibbs GL, et al: Factors associated with radiation-induced nausea and vomiting in head and neck cancer patients treated with intensity modulated radiation therapy. Radiother Oncol 87:188-194, 2008

48. Valeyrie-Allanore L, Poulalhon N, Fagot JP, et al: Stevens-Johnson syndrome and toxic epidermal necrolysis induced by amifostine during head and neck radiotherapy. Radiother Oncol 87:300-303, 2008

49. Rades D, Fehlauer F, Bajrovic A, et al: Serious adverse effects of amifostine during radiotherapy in head and neck cancer patients. Radiother Oncol 70:261-264, 2004

50. van der Laan HP, van den Bergh A, Schilstra C, et al: Grading-system-dependent volume effects for late radiation-induced rectal toxicity after curative radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 70:1138-1145, 2008

51. Wasserman TH, Brizel DM, Henke M, et al: Influence of intravenous amifostine on xerostomia, tumor control, and survival after radiotherapy for head-and- neck cancer: 2-year follow-up of a prospective, randomized, phase III trial. Int J Radiat Oncol Biol Phys 63:985-990, 2005

52. van de Water TA, Bijl HP, Westerlaan HE, et al: Delineation guidelines for organs at risk involved in radiation-induced salivary dysfunction and xerostomia. Radiother Oncol 93:545-552, 2009

53. Rudat V, Munter M, Rades D, et al: The effect of amifostine or IMRT to preserve the parotid function after radiotherapy of the head and neck region measured by quantitative salivary gland scintigraphy. Radiother Oncol 89:71-80, 2008

54. Nutting CM, Morden JP, Harrington KJ, et al: Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomised controlled trial. Lancet Oncol 12:127-136, 2011

55. Thorstad WL, Chao KS, Haughey B: Toxicity and compliance of subcutaneous amifostine in patients undergoing postoperative intensity-modulated radiation therapy for head and neck cancer. Semin Oncol 31:8-12, 2004

56. Rosenthal DI, Chambers MS, Weber RS, et al: A phase II study to assess the efficacy of amifostine for submandibular/sublingual salivary sparing during the treatment of head and neck cancer with intensity modulated radiation therapy for parotid salivary sparing. Semin Oncol 31:25-28, 2004

57. Mangoni M, Yue X, Morin C, et al: Differential effect triggered by a heparan mimetic of the RGTA family preventing oral mucositis without tumor protection. Int J Radiat Oncol Biol Phys 74:1242-1250, 2009

