Influence of Amifostine on Late Radiation-toxicity in Head and Neck Cancer – A Follow-up Study

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Abstract. Aim: The late toxicities due to multimodal therapy of advanced head and neck cancers were analysed. The impact of cytoprotection with amifostine is the specific objective of this report. Patients and Methods: A total of 851 patients (717 men, 134 women) with head and neck cancer were included in this prospective study. Of these patients, 519/851 had received amifostine before radio(chemo)therapy, while 332 control patients had not received any kind of cytoprotection before irradiation. Primary radiochemotherapy was performed in 282 patients and adjuvant radiation was administered in 569. The follow-up examination was carried out at our outpatient department 21.4 months (median, range 2.3 to 149 months) after the primary therapy. Results: Late xerostomia was seen in 765/851 patients (89.9%). Altered taste was reported by 284/851 (33.5%). These symptoms were reduced significantly by amifostine. No influence was seen on interstitial lymph edema (48.4%), or stenosis of the cervical esophagus (20.4%). Secondary symptoms such as dysphagia (78.8%) also had a trend for reduction. Conclusion: The administration of amifostine offers an opportunity to reduce selected long-term toxicities for survivors of head and neck cancer.

Between 1995 and 2000, our group investigated the influence of amifostine on different acute toxicities of concurrent chemoradiotherapy in patients with head and neck cancer. Analysing the literature, it was recognised that all reports were focused on acute side-effects and there was insufficient data available regarding sub-acute or late toxicities due to the multimodal treatment approach in anti-cancer strategy. This is the reason for our collecting data during regular follow-up visits in order to gain information about this topic. Two initial aims of this project were defined: (i) to obtain information about the complete spectrum of late side-effects in head and neck cancer patients; (ii) to gain information on the influence of cytoprotection on the late toxicities of our patients.

Patients and Methods

From January 1998, we started to complete individual protocols of each follow-up visit at the outpatient department of the Suhl ENT clinic. These follow-up visits were performed once per week. Together, an ENT oncologist and radio-oncologist investigated each patient and performed the interview regarding subjective symptoms. Late toxicities were recorded according the RTOG (CTC) criteria (1). The evaluation of late toxicities was performed in each patient visiting the outpatient department during the follow-up visits. Performed radiotherapy as a part of baseline therapy was the only inclusion criterion for the data pool of the presented project. Baseline therapy data were transferred from the patient’s hospital file to the individual protocol of each patient. Toxicity data were recorded during the individual consultation. If there was no RTOG or CTC classification, a three-step model was used to estimate the severity of a symptom: 0 – no toxicity, 1 – mild toxicity, and 2 – severe toxicity. Additionally, we noted the type of supportive treatment (amifostine: yes/no). The general appearance of each patient was categorised using the Karnofsky Performance Status Scale and the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale.

Dental status was described (prosthesis, caries etc.), as far as it was possible to give individual remarks for the protocol. All individual protocols were integrated into an MS Excel table. This commercial program was also used to perform statistical analyses (t-test, 2-sided test, analysis of variance, independent groups).

Cross-sectional data. Between 1998 and 2001, 851 patients were included. The median age of 717 men and 134 women was 61.13 years (range 21-85 years). The follow-up interval was a median of 643 days (range 69-4468 days). Baseline diagnoses are summarised in Table I. A primary resection of the tumour was performed in 569 patients. A neck dissection was registered in 459 patients; 768 patients had received simultaneous chemoradiation and 83 radiotherapy without simultaneously administered cytotoxic drugs.

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The TNM status is shown in Table II. Fifty-five patients were registered with recurrent cancer disease. We investigated 276 patients during the first year after baseline therapy, 197 during the second year, 131 during the third year, 71 during the fourth year, 60 during the fifth year, and 116 patients after five years or more.

The distribution of patients regarding the use of amifostine as supportive drug during the baseline therapy is summarised in Table III: 519 patients received amifostine during the primary treatment of their cancer disease, 332 control individuals received the basic treatment without amifostine support.

Longitudinal data. In total, we observed 231 patients (40 women, 191 men): 45 patients were included in the protocol once, 186 patients had repeated visits to our outpatient department. Figure 1 shows the number of investigations per patient.

### Results

The individual symptoms seen in the patients are shown in Table IV. Xerostomia, dysphagia and interstitial lymph edema were the most important late toxicities ≥2 CTC.

The Karnofsky Performance Status and the ECOG status were comparable between both groups. Only in year 2 did the control group show a slightly better Karnofsky index than the patients who received amifostine (p=0.04).

Xerostomia. Patients suffered from dry mouth at a rate of nearly 90%. The development of the symptom is shown in Figure 2. There were no statistical differences between the mean values of the groups. During the first 12 months this symptom was statistically significantly milder in the amifostine group (1.236 versus 1.364, p=0.05).

Loss of taste. The loss of taste was significantly lower in the amifostine group (0.381 versus 0.464, p=0.04). This symptom occurs mainly during the first year after anti-cancer treatment.

Stricture of the cervical esophagus. The rare development of strictures in the upper part of the cervical esophagus was observed in both groups. During the first two years, the statistical analysis demonstrated an advantage of the control group (year 1: 0.215 versus 0.114, p=0.03; year 2: 0.242 versus 0.159, p=0.002). This phenomenon is a result of a higher number of patients with definitive chemoradiation in the amifostine group. Severe strictures were seen after three years or more.

Dysphagia. Dysphagia is the compound result of all symptoms which disturb the eating and drinking of our patients. Hence it was difficult to explain the development of this syndrome during the follow-up period (Figure 3). No real differences between groups were found.

Interstitial lymph edema. Patients of both groups developed submental or supraglottal edema during the follow-up period. This symptom disturbed patients particularly during the first two years after radiochemotherapy. Amifostine was not able to protect the patients against this interstitial lymph edema. Differences between the groups were seen during the second year (mean values 0.684 versus 0.640, p=0.03) and the fourth...
year (0.444 versus 0.125, \( p = 0.05 \)). These differences are a result of the described imbalances regarding those patients with definitive radiochemotherapy and higher radiation doses. The development of interstitial lymph edema in the whole patient population (n=851) is shown in Figure 4.

**Dental status.** Of 519 patients of the amifostine group, 293 had a total prosthesis (56.5%) compared to 213/332 patients of the control group (64.1%). The remaining patients of the amifostine group had to contact the dentist much more often than the patients of the control group. The reason for this was a higher incidence of caries in the amifostine group (\( p = 0.008 \)).

**Discussion**

The present study seems to be the largest investigation regarding the late toxicities due to multimodal treatment of head and neck cancer of those published until the end of 2005.
The project was performed as a prospective investigation and is influenced by the general developments in the therapy of advanced head and neck cancer. Local specialities (adjunctive radiochemotherapy) also had an impact on the observed late toxicities as well as trends in supportive care.

The follow-up analysis was performed as an investigation regarding the influence of amifostine on various toxicity profiles of head and neck cancer patients. Controlled phase-III studies have shown different results regarding chronic xerostomia. Brizel et al. (2) found 63% ≥2 xerostomia in unprotected subjects (control patients). Antonadou’s trial (3), as well as our pilot trial (4), found similar values. The placebo-controlled study has shown a completely different result (5). Only 24% of all placebo patients developed ≥2 xerostomia due to radiochemotherapy of head and neck cancer. The reduction of ≥2 xerostomia in all cited studies is summarised in Table V. Our results support the hypothesis that amifostine usage has limited influence on the development of late xerostomia. It would seem its usage only provides protection in the first year after radiotherapy. These changes are important for the majority of HNC patients.

Similar results were found regarding the development of the loss of taste. During the first 12 months we found a significant reduction of the typical changes in the taste perception of HNC patients. After recovery, no statistical differences were seen because of the low incidence of irreversible tissue damage. The dental status of our patients was also improved. We found a reduced number of patients with total or partial prosthesis in the amifostine group. An increasing number of patients registered visiting dentists without loss of all teeth.

One of the main results of this study is to show that some categories of toxicities were not influenced by scavenging free radicals, i.e. amifostine use. The development of interstitial lymph edema was registered in both groups, as well as the fibrotic strictures of the upper esophagus. Although scavengers of free radicals are able to treat interstitial lymph edema in nearly 70% of all head and neck cancer patients (6, 7), selective cytoprotection with amifostine was not able to prevent this toxicity. The non-randomised character and the specific treatment modalities of our monocentric trial limit the conclusions of this report. We have investigated people receiving amifostine during their basic therapy and have seen some benefits regarding xerostomia, loss of taste and the dental status. It is possible that another dose schedule of amifostine alone and/or with other interventions, such as targeting transforming growth factor-β, or the use of other antioxidants, might have prevented some of the late effects seen in our follow-up study.

**References**


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**Table V. Radiation-induced late xerostomia ≥2 RTOG in HNC trials with amifostine.**

![Figure 4. Development of interstitial lymph edema after chemonadation.](image-url)