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RADIOPROTECTIVE EFFECT OF AMIFOSTINE ON PAROTID GLAND FUNCTIONING IS REGION DEPENDENT

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Purpose: To investigate the protective ability of amifostine during partial irradiation of the rat parotid gland.

Methods and Materials: Single-dose X-ray irradiation was performed by use of collimators with conformal radiation portals for either the 100% volume (15 Gy) or the 50% cranial/caudal partial parotid gland volumes (30 Gy). Amifostine was administered intraperitoneally at a dose of 250 mg per kg body weight, 25 minutes before irradiation. Saliva flow rates, gland weights, and the tissues of the individual lobes were investigated up to 1 year after treatment.

Results: A clear protective effect of amifostine was found against loss of saliva flow, the altered appearance of gross morphology, loss of gland weight, and histopathologic changes for the 100% volume gland irradiations and for the 50% volume cranial irradiations but not for the 50% volume caudal irradiations.

Conclusions: The protective ability of amifostine is strongly dependent on the irradiated glandular region and observed for later damage only. The major effect of the drug seems to be the prevention of volume effects caused by secondary damage that occurs in shielded parts of the gland. The results of the present study show that understanding of the anatomy and physiology of organs that are to be spared is necessary to ensure optimal preservation of function. © 2006 Elsevier Inc.

INTRODUCTION

Radiotherapy is a successful treatment modality for head-and-neck malignancies. Unfortunately, this treatment often results in damage to major salivary glands because of the inability to exclude these tissues from the radiation field. This problem may lead to radiation injury of salivary gland tissue that results, among other conditions, in xerostomia, impeded oral function, and an increased risk of oral infections and tooth decay (1–4). Methods are urgently needed that avoid these distressing side effects and protect the glands during treatment.

Several approaches have been attempted to prevent or repair radiation damage to salivary glands in the course of a radiation treatment (5): (1) reduction of exposed volume, (2) application of agents that stimulate progenitor cells, (3) gene-transfer techniques, and (4) pharmacological protection. Two important groups of pharmacologically active drugs can be distinguished: (1) agents that protect cells by radical scavenging. Amifostine is an example of the latter. It has received much attention during the past decade as a protector of healthy tissue during the radiotherapy of cancer (6). Amifostine (Ethylol) is a simple phosphorothioate prodrug that was developed as WR-2721 at the Walter Reed Army Hospital in Washington, DC, as the result of an antiradiation drug development program initiated by the U.S. Army in the late 1950s to prevent radiation injury to soldiers and civilians in the event of nuclear war. Amifostine is a prodrug because of its inactivity until dephosphorylated by the enzyme alkaline phosphatase to yield the active free thiol and radical scavenger WR-1065.

Early studies on drug accumulation in the mouse revealed a high and rapid concentration in a selective number of healthy tissues (7) and a poor and slow accumulation in tumors (8). In a recent study with rats, amifostine was shown to reduce radiation-induced lung damage, whereas no tumor protection was observed (9).
The selective accumulation of the drug in nontumor tissue is claimed to be caused by a lower alkaline phosphatase activity in tumor capillaries as compared with the blood vessels of normal tissue (10). Successful protection from oral mucositis in rats has been reported after irradiation of the head-and-neck area (11, 12). Data on the effect of amifostine on salivary gland secretion are scarce, notwithstanding the knowledge that the drug accumulates in these tissues (7). One known animal study reports on the beneficial effect of drug pretreatment on salivary flow, but the effect is restricted to periods shortly after irradiation (13). Substantial radioprotection by amifostine has been demonstrated on parotid structure and gland weight in the rat (14–16).

A clinical trial (17) that indicates the effectiveness of this drug as a radioprotectant to prevent xerostomia in patients treated for head-and-neck cancer has led the FDA to approve this application for regular radiotherapy treatments. However, varying clinical results on the usefulness of this drug have been reported (18–21). In a critical review on the effectiveness of amifostine as a clinical radioprotector, Lindegaard and Grau (22) conclude that most studies that claim success do not have the power to evaluate the influence of the drug on the most important parameter: the therapeutic index.

One of the causes for the variable clinical results may be the fact that the salivary glands are often partly irradiated, which may cause regional-dependent volume effects because of secondary damage in shielded parts (23). This variety in damage might correspond with different protection possibilities by amifostine.

The purpose of the present investigation was to compare, in a rat model, the effectiveness of amifostine pretreatment on the flow of saliva after irradiation of different regions of the parotid gland. Conformal radiation portals designed on the outlines of the glands as obtained by high-resolution magnetic resonance imaging (MRI) were used. This approach was necessary to ascertain that an altered excretion function may solely be attributed to gland damage and not (also) to effects of irradiated nongland tissue (24). With this model, we recently demonstrated region-dependent volume effects on parotid gland function after partial X-ray irradiation (25). Pathohistologic studies showed that the observed volume effect was mainly caused by secondary damage in one of the shielded lobes of the gland (23). Because, as of now, experimental studies on gland protection during partial irradiation have never been performed, an investigation is needed to determine whether amifostine may protect against acute and late primary radiation injury and also against the development of secondary radiation damage under these conditions. The study is primarily aimed at prevention of damage to parotid gland function (flow rate). Morphologic and histologic methods were applied to verify and interpret the results.

METHODS AND MATERIALS

Animals

Male albino Wistar rats of the strain Hsd/Cpd: WU (Harlan-CPB, Rijswijk, The Netherlands) were used at 9 to 10 weeks of age. The body weights were 230 to 250 g at time of purchase. The animals were kept 2 weeks to become acclimatized before irradiation and housed in polycarbonate cages (six rats per cage). They had ad libitum access to water and food (RMH-B; Hope Farms, Woerden, The Netherlands). The lights were on from 06:00 to 20:00 hours, the temperature was 22°C ± 2°C, and the relative humidity was 55% ± 5%. All experiments were performed in agreement with the Netherlands Experiments on Animal Act of 1977 and the European Convention for the Protection of Vertebrates Used for Experimental Purposes (Strasbourg, 18.III.1986) and met the standards required by the United Kingdom Coordinating Committee on Cancer Research 1988 Guidelines.

Study design and irradiation conditions

Each experimental group consisted of 10 rats. Applied X-ray doses were 15 Gy for 100% gland volume and 30 Gy for 50% gland volume. The dose of 15 Gy was chosen for the total gland because with this dose, the effect on saliva excretion reaches its nadir. Because the excretion tissue of the parotid gland is assumed to be homogeneous, a comparison of this dose with twice the dose on half of the volume is of interest. Amifostine (Ethyol; Schering-Plough B.V., Maarsenn, The Netherlands) application in the range of 250 to 500 mg/kg was assayed for toxicity and its effect on gland weight. Below 300 mg/kg, no toxic effects were observed. A decision was made to use 250 mg/kg in the irradiation experiments. The drug was administered intraperitoneally (50 mg/mL 0.9% saline) 25 minutes before irradiation. The following seven groups of rats were investigated:

1. Sham irradiation
2. 100% gland volume, 15 Gy
3. 100% gland volume, 15 Gy; 250 mg/kg amifostine
4. 50% cranial volume, 30 Gy
5. 50% cranial volume, 30 Gy; 250 mg/kg amifostine
6. 50% caudal volume, 30 Gy
7. 50% caudal volume, 30 Gy; 250 mg/kg amifostine

The rats were placed in a radiation holder suspended from a positioning rod by their upper incisor teeth. For details, see Cotteleer et al. (26). Before positioning, the rats were anesthetized with an intraperitoneal injection of Rompun (xylazine; Bayer AG, Leverkusen, Germany), 0.48 mg/100 g bodyweight; plus Ketalar (S-ketamine, Pfizer BV; Capelle aan de IJssel, The Netherlands), 3.25 mg/100 g bodyweight; and at least 30 minutes were allowed for anesthesia. For collimation, 3-mm lead collimators were used, which resulted in conformal radiation beams for 100%, 50% cranial, or 50% caudal irradiation volumes. A protocol for absolute dosimetry was designed, and relative-dose measurements were performed. From the three-dimensional (3D) topography data and the 3D dose distributions, dose–volume histograms were determined. The designed setup showed that irradiation of the small parotid volumes could be performed with high accuracy (26). Irradiation was administered by an orthovoltage X-ray machine (Mueller MG 300; Phillips, Eindhoven, The Netherlands) operated at 200-kV high voltage and 15-mA tube current. The beam was filtered by 0.5 mm Cu + 0.5 mm Al. The Al filter was placed at the beam-exit side of the tube housing. This placement results in a first half-value layer of 1.0 mm Cu. To obtain an acceptable field...
homogeneity and percentage dose distribution and to obtain a dose rate that allowed a single irradiation up to 30 Gy within 25 minutes, a focal-spot to skin distance of 213 mm was chosen. During dose measurements and animal irradiation, the tube output was monitored by means of a 0.6 cm$^3$ monitor ionization chamber (PTW Farmer chamber, B30001) connected to an electrometer (PTW Unidos-E 10008), which was placed inside the beam, just outside the portal projections. Detailed information on the 3D topography and the 3D dose distribution that resulted in dose–volume histograms can be found elsewhere (26). Both glands were irradiated.

Collection of saliva
Saliva samples of both left and right parotid gland were collected simultaneously under isoflurane/O$_2$ anesthesia by means of miniaturized Lasley cups (27, 28). The cups were placed upon the orifices of both parotid glands. Saliva was collected for 30 min, after stimulation with 2 mg/kg pilocarpine administered subcutaneously (at $t = 0$ and $t = 15$ min), in preweighed, ice-cooled plastic tubes 4 days before and 10, 30, 60, 120, 180, 240, 300, and 360 days after irradiation. As a parameter of gland function, salivary flow rates were determined. The total volume of saliva secreted was estimated by weight, assuming the specific gravity of saliva to be 1.0 g/cm$^3$. The salivary flow rate ($\mu$L/min) was calculated from the collecting time and volume. Function loss was defined as decrease of flow rate and expressed as a percentage of (sham irradiated) controls ($\pm$SEM).

Tissue preparation and histology
For each experimental condition, five rats were used for histologic examination. At 360 days after irradiation, the rats were anesthetized with an i.p. injection of sodium pentobarbital (60 mg/kg body weight) (Pharmacist University Hospital Groningen), the thorax was opened, and the heart was cut in two. Hereafter, the skin in the neck region was peeled off, and fatty tissue was carefully dissected to expose salivary glands, lymph nodes, and muscle. Digital photographs were taken (Olympus Camedia C-2000 Zoom; Olympus Optical Co., LTD, Tokyo, Japan) at a distance of 50 cm. Both right and left parotid glands were taken out, carefully freed from surrounding tissue, and weighed. The tissue was fixed by immersion in 4% formaldehyde/PBS for 24 hours at room temperature. A standard graded-alcohol procedure was used to dehydrate the glands. The tissues were embedded in Technovit 7100 ( Heraeus Kulzer GmbH, Wehrheim, Germany). Sections of 2 $\mu$m were cut with a Leitz microtome (Wetzlar type 1212). The sections were stained with hematoxylin and eosin (H&E). The dorsal, ventral, and lateral lobes of the glands were individually examined. Each lobe was studied at three different levels, with a distance of 100 $\mu$m. At each level, five fields with an area of 0.034 mm$^2$ (0.185 mm $\times$ 0.185 mm) and at a magnification of 400X were randomly chosen and investigated. In each field, the percentage of acinar cells, duct cells, connective tissue, blood vessels, and fat was scored.

RESULTS

Gland weight and gross morphology
Table 1 shows that 1 year after irradiation of the total gland with a single dose of 15 Gy, the weight of the irradiated gland is about 65% of the sham-irradiated gland. Pretreatment with amifostine could prevent the major part of weight reduction. Irradiation of the 50% caudal volume resulted in less damage, with a negligible protection by amifostine. Irradiation of the cranial 50% volume resulted in 30% loss of gland weight. Amifostine could prevent about half of the damage. The effect of gland irradiation and the protection by amifostine on the (two-dimensional) gross appearance of the glands 1 year after treatment is illustrated in Fig. 1. The caudal 50% volume irradiation has affected the exposed lateral lobe. This damage could partly be prevented by amifostine. Cranial irradiation also affected the (shielded) lateral lobe. This damage could also be prevented by amifostine.

Assessment of gland function
In Fig. 2a, the effect of irradiation on gland function is depicted after irradiation of the total gland with a single dose of 15 Gy. Within 3 months, the flow rate was reduced to about 40% and remained low up to 1 year after the irradiation until the end of the experiment. Amifostine markedly reduced the radiation-induced loss of parotid gland function and preserved 85% to 90% of the initial salivary flow. The very early loss of function cannot be prevented by amifostine. Irradiation of the 50% cranial volume with a single dose of 30 Gy (Fig. 2b) resulted in a loss of function and preventive potential by amifostine comparable with the situation after irradiation of the whole gland. However, the decline in flow rate starts much later. This phenomenon is thought to be caused by secondary damage after cranial irradiation and is in line with observations from earlier studies (23, 25). Figure 2c shows that only minor damage is present after irradiation of the caudal 50% volume. This outcome may be caused by compensation activity in the shielded ventral and dorsal lobes, as discussed earlier (25). Apparently, the residual early damage is not preventable by amifostine.

Histology
Irradiation of the parotid gland with a single dose of 15 Gy resulted in severe damage 1 year after irradiation, as represented by islands of enlarged acini in areas of connec-

<table>
<thead>
<tr>
<th>Radiation condition</th>
<th>Drug</th>
<th>Gland weight (mg)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (0 Gy)</td>
<td>–</td>
<td>332 $\pm$ 13</td>
<td>100*</td>
</tr>
<tr>
<td>Total gland (15 Gy)</td>
<td>–</td>
<td>215 $\pm$ 8</td>
<td>65</td>
</tr>
<tr>
<td>Total gland (15 Gy)</td>
<td>+</td>
<td>294 $\pm$ 8</td>
<td>89*</td>
</tr>
<tr>
<td>Caudal 50% (30 Gy)</td>
<td>–</td>
<td>263 $\pm$ 8</td>
<td>79</td>
</tr>
<tr>
<td>Caudal 50% (30 Gy)</td>
<td>+</td>
<td>275 $\pm$ 9</td>
<td>83</td>
</tr>
<tr>
<td>Cranial 50% (30 Gy)</td>
<td>–</td>
<td>231 $\pm$ 11</td>
<td>70</td>
</tr>
<tr>
<td>Cranial 50% (30 Gy)</td>
<td>+</td>
<td>284 $\pm$ 10</td>
<td>86*</td>
</tr>
</tbody>
</table>

Note: Data were obtained from 10 rats in each group and expressed $\pm$ SEM.
* Prevention of damage by amifostine is significant in all cases except for the caudal 50% irradiations.
tive tissue (Figs. 3a and 3b). This observation is in accordance with earlier studies (23). After pretreatment with amifostine, the radiation-induced damage is limited. An almost continuous field of acinar cells is observed surrounded by some connective tissue, although the acini are more loosely arranged than in sham-treated glands (Figs. 3a and 3c). When the caudal 50% volume is exposed to the single dose of 30 Gy, the damage to the lateral lobe is devastating (Fig. 4a). Almost no acinar cells can be observed. Pretreatment with amifostine prevents this damage.

Fig. 1. Protective effect of amifostine pretreatment on gross anatomy after total and partial irradiation of the parotid gland 1 year after X-ray irradiation. (a) Sham irradiation (= control). The parotid gland is outlined in the middle of the picture and indicates the three lobes: ventral (V), dorsal (D), and lateral (L). Other visible organs and tissues are submandibular gland (Sub), lacrimal gland (Lac), lymph nodes (Ly), musculus masseter (M), and jugular vein (*). (b) X-ray irradiation of the total gland (100%) with a single dose of 15 Gy. (c) Effect of amifostine pretreatment after X-ray irradiation of the total gland (100%) with a single dose of 15 Gy. (d) X-ray irradiation of the 50% caudal part with a single dose of 30 Gy. (e) Effect of amifostine pretreatment after X-ray irradiation of the 50% caudal part with a single dose of 30 Gy. (f) X-ray irradiation of the 50% cranial part with a single dose of 30 Gy. (g) Effect of amifostine pretreatment after X-ray irradiation of the 50% cranial part with a single dose of 30 Gy. (Bar = 0.5 cm.)

Fig. 2. Effect of amifostine pretreatment on salivary secretion loss up to 1 year after total (a) or partial (b, c) irradiation of the parotid gland. Single doses of X-rays were applied, and gland function was determined for 10 rats in each group, assayed as stimulated saliva flow rate. Data are expressed as percentage ± SEM of the pretreatment value.
to a large extent and yields a picture (Fig. 4b) similar to that of the shielded ventral lobe (Fig. 4c).

Figure 5 shows the situation in the exposed ventral lobe and the shielded lateral lobe 1 year after irradiation of the cranial 50% volume. Heavily damaged tissue is seen in the exposed lobe (Fig. 5a) as well as in the shielded lobe (Fig. 5c). From earlier results (23), we know that the damage in the shielded lobe has developed later and is of a secondary nature. As can be seen in Figs. 5b and 5d, both types of damage can be prevented by pretreatment with amifostine. For reasons of objectivity, comparison of the two conditions of partial-gland irradiations (caudal vs. cranial 50% volumes) was made by a quantitative assessment of the histopathological changes as is illustrated in Fig. 6. About 80% of the gland volume in sham-treated glands consists of acinar cells; the remaining volume consists mostly of connective tissue (5–10%) (Figs. 6a and 6d). The degree of primary damage in the exposed ventral lobe (Fig. 6b) is comparable to the degree of secondary damage in the shielded lateral lobe (Fig. 6e) after irradiation of the cranial 50%, except for the amount of fat present in the exposed ventral lobe. In accordance with Fig. 4a, the data show that the exposed lateral lobe, after irradiation of the cranial 50% volume, is more severely damaged as compared with the exposed ventral lobe after irradiation of the cranial 50% volume. Almost no acinar cells are left, and the amount of connective tissue is about 70% of the volume. Figures 6c, 6f, and 6h show that this radiation damage can effectively be prevented by pretreatment with amifostine, including the secondary damage in the shielded lateral lobe (Fig. 6h).

**DISCUSSION**

**Effects on saliva flow rate**

The current study is the first to demonstrate long-term protection by amifostine against loss of salivary secretion. The 60% reduction in flow rate 1 year after irradiation of the whole parotid gland with a single dose of 15 Gy is almost completely prevented by amifostine treatment (Fig. 2a). The preservation of gland function correlates very well with gland weight (Table 1), gross appearance (Fig. 1), and histopathological changes (Fig. 3).

The early loss of salivary secretion cannot be prevented by amifostine. This diminished gland function is not caused by indirect effects from damaged surrounding tissue that contain low amounts of the drug, because, in contrast to some other studies (11, 12, 16) in which the whole head-and-neck region is irradiated, our rat model (26) includes conformal radiation portals based on the outlines of the glands, which minimizes indirect radiation effects. From early studies, we already knew that the acute loss of gland function is probably caused by membrane damage (29) that results in disturbed signaling pathways essential for the water secretion part of the saliva (30). The role of radiation-induced membrane damage in cell injury (31, 32) and specifically the issue of radiation damage to membrane-bound signaling pathways in the major salivary glands is well documented (5, 33).

With this knowledge in mind, we can speculate that the radical scavenger WR-1065 cannot penetrate effectively into the plasma membrane of the acinar cells and, therefore,
does not reach the target molecules (e.g., SH groups) to prevent damage to signaling pathways. If this hypothesis is true, then the residual damage may possibly be prevented by a category of drugs that protect cells via a different mechanism of action, such as the modulation of receptor-coupled signaling pathways (5).

Volume effects and secondary damage

As shown, protection by amifostine is particularly effective after irradiation of the cranial 50% volume. The loss of salivary secretion could be limited by amifostine to about 10% (Fig. 2b). Irradiation of the caudal 50% volume results in only minor damage to the gland, probably because of compensating mechanisms in the shielded parts (25). As can be seen in Figs. 4a and 6g, the lateral lobe is severely damaged after caudal irradiation, and compensational activity has, therefore, to be provided by the shielded dorsal and ventral lobe (Fig. 4c). Thus, less compensation activity is thought to be needed after pretreatment with amifostine because of the degree of intactness of the irradiated lateral lobe (Figs. 4b and 6h). The residual, not-preventable component of damage may, as discussed above, be caused by nonaccessibility of the radical scavenger to the interior of the plasma membrane. The difference between gland damage after irradiation of the cranial vs. the caudal 50% is mainly caused by secondary damage in the shielded lateral lobe. The phenomenon of secondary damage in the partly irradiated parotid gland is extensively discussed in a recently published article (23). In a time study, the acinar cells in the exposed lateral lobe were shown to disappear at a rapid rate 60 days after irradiation and that at Day 120, the percentage cells had declined to around 30%. Replacement by new acinar cells failed because of a radiation-induced shortage of proliferating (stem) cells. The time scale of damage development in the shielded lateral lobe appeared to be very different from that of the exposed lateral lobe. Even at Day 240 after irradiation, no major histopathological aberrations in the shielded lateral lobe were seen, and acinar cells still occupied about 60% of the area. The damage in the shielded lateral lobe appeared to be of a very late and secondary nature that occurred between Day 240 and Day 360 after irradiation. The explanation for this late development of secondary damage is probably related to the anatomy of the rat parotid gland. The hilus region of this gland is located between the ventral and dorsal lobe. At this position, the main excretory duct leaves the organ. It also is the region of the entry of large blood vessels and nerves. Primary injury to this facility area during radiation exposure of the ventral and dorsal lobes is the most obvious explanation for the induction of the observed secondary damage in the shielded lateral lobe. Proper functioning of the latter lobe seems to depend on the intactness of drainage and supply routes in the hilus region. The shielded part of the gland (lateral lobe) stays histomorphologically intact until the damage in the ventral and dorsal lobe (hilus region) has developed. Hereafter, the shrinkage of the shielded lobe
starts, as does the formation of fibrotic patches and the loss of acini, all of which resemble the histopathological changes seen after ligation of main excretory ducts (34). Recent studies with MR sialography in humans showed that the ductal architecture of the human parotid gland was clearly visible before, but not after, radiotherapy and that the changes in visibility correlated well with changes in gland function (35).

From the results in Fig. 2b (salivary secretion), Figs. 5c and 5d (histology), and Figs. 6e and 6f (quantification of induced mucositis), we see that the secondary damage in the shielded part can be prevented by amifostine, which indicates that it originates from primary free radical–driven reactions in exposed parts. The results of this study show that understanding of the anatomy and physiology of organs that have to be spared is necessary to ensure optimal preservation of function and define the conditions of suitable amifostine applicability.

Unexpected volume effects caused by secondary damage in shielded parts of organs with an apparently homogeneous distribution of radiosensitive elements may especially show up after IMRT. Minor differences in IMRT fields may result in major differences in late (secondary) injury: injury that is preventable by amifostine.

Drug dose effectiveness and tolerability

The drug dose of 250 mg/kg intraperitoneally, as applied in the current investigation to prevent saliva-flow dysfunction, is effective and well tolerated by rats; it is also well below the 400 mg/kg intraperitoneally used in an earlier study (13). Experiments with rats (16) have also shown that a daily dose of 250 mg/kg intravenously can be endured in 30 fractions during 6 weeks. Thus, in a fractionated radiation protocol, a dose lower than 250 mg/kg might be effective in saliva-flow protection because, in a recent rat study (12), a daily dose of 50 mg/kg merely prevented radiation-induced mucositis.

In humans, decreased complaints of xerostomia have been reported (18–21) after use of this drug, but serious adverse effects (36) led to discontinuation of treatment and sometimes to delay of radiotherapy. The type of animal investigations presented in the current report may provide insight into conditions where a tolerable dose of amifostine can successfully be applied. The next step in animal research should be the application of different doses of amifostine in a clinical equivalent-fractionation scheme, with partial irradiation of the glands.

Although we still have a long way to go, appropriate clinical research aimed at the estimation of the type and degree of expected damage, proper adjustment of dose distributions, and an assessment of the possible influence of chemotherapy on drug toxicity might ultimately lead to a nondebatable successful use of amifostine in the clinic.

CONCLUSIONS

The main finding in this study is the dependence of the protective ability of amifostine on the region of the parotid gland that has been irradiated. The efficiency of the drug is mainly dependent on the extent of secondary damage that might develop. In the rat model, irradiation of the cranial part causes a high degree of secondary damage. This damage could successfully be prevented by amifostine. When the caudal part of the gland is irradiated, however, no secondary damage develops and only minor residual damage is present, probably because of compensation reactions in the shielded part of the glands. Amifostine cannot prevent the residual damage that develops early after the start of the irradiation, possibly because the drug cannot penetrate into the target area. Supplementation with drugs that have a different mechanism of action (e.g., receptor agonists) and provide protection against the very early component of function loss might, in a number of occasions, be indicated. Furthermore, this study emphasizes the need for a selective and individual patient approach to the radiotherapeutic treatment of head-and-neck cancer.

REFERENCES


