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CLINICAL INVESTIGATION **Head and Neck**

EFFECT OF CISPLATIN ON PAROTID GLAND FUNCTION IN CONCOMITANT RADIOCHEMOTHERAPY

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Purpose: To determine the influence of concomitant radiochemotherapy with cisplatin on parotid gland tissue complication probability.

Methods and Materials: Patients treated with either radiotherapy (n = 61) or concomitant radiochemotherapy with cisplatin (n = 36) for head-and-neck cancer were prospectively evaluated. The dose and volume distributions of the parotid glands were noted in dose–volume histograms. Stimulated salivary flow rates were measured before, during the 2nd and 6th weeks and at 4 weeks and 6 months after the treatment. The data were fit using the normal tissue complication probability model of Lyman. Complication was defined as a reduction of the salivary flow rate to less than 25% of the pretreatment flow rate.

Results: The normal tissue complication probability model parameter TD_{50} (the dose leading to a complication probability of 50%) was found to be 32.2 Gy at 4 weeks and 32.1 Gy at 6 months for concomitant radiochemotherapy and 41.1 Gy at 4 weeks and 39.6 Gy at 6 months for radiotherapy. The tolerated dose for concomitant radiochemotherapy was at least 7 to 8 Gy lower than for radiotherapy alone at TD_{50}.

Conclusions: In this study, the concomitant radiochemotherapy tended to cause a higher probability of parotid gland tissue damage. Advanced radiotherapy planning approaches such as intensity-modulated radiotherapy may be partiticularly important for parotid sparing in radiochemotherapy because of cisplatin-related increased radiosensitivity of glands. **© 2009 Elsevier Inc.**

Chemotherapy, Head and neck cancer, Radiation, Saliva, Normal tissue complication probability.

INTRODUCTION

Hyposalivation is the most common adverse effect among patients treated with radiotherapy for head-and-neck cancer. It impairs chewing, swallowing, and speech function, is responsible for an increased incidence of oral candidiasis, and promotes rapidly developing tooth decay. Missing saliva can induce nutritional disorders and can lead to social marginalization as well as reduced quality of life (1). Improving quality of life after irradiation and preservation of salivary gland function is a key aim in research and development of novel head-and-neck cancer treatment strategies.

Not only irradiation but also chemotherapeutic agents on their own can lead to morphologic damage in salivary gland tissue (2, 3). Chemotherapeutic agents are assumed to worsen salivary gland function (4). For example, women treated with chemotherapeutic agents for breast cancer and patients treated with chemotherapeutic agents for acute leucemia showed a singnificantly lower stimulated salivary flow rate (5). Furthermore it has been shown that the chemotherapeutic agent peplomycin reduced unstimulated flow rate by 20% (6).

Kosuda *et al*. (4) used quantitative salivary gland scintigraphy to determine dysfunction on salivary glands in patients treated with a cyclophosphamid, hydroxydaunorubicine, oncovin, and prednison (CHOP) regimen followed by radiotherapy with up to 40 Gy. They found that radiotherapy alone had a dose-dependent adverse effect on salivary gland function, but that chemotherapy before radiotherapy augmented the radiation-induced injury of the salivary glands. All of these studies included only a small number of patients. Furthermore different chemotherapeutic agents were prescribed, and most of them were not used in a concomitant radiochemotherapy setting.

Recent studies focusing on locally advanced head-and-neck cancer indicate that survival rates increase when concomitant chemotherapy is added in radical as well as postoperative radiotherapy (7, 8). Cisplatin is considered to be the gold

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standard medication for concomitant radiochemotherapy for head-and-neck cancer, because it is expected to radiosensitize tumor tissues (9, 10). Published information on the effect of concomitant chemotherapy on salivary gland complication probability is limited (11–13). Patients treated with concomitant radiochemotherapy are usually excluded from clinical studies on salivary gland dysfunction. Therefore, the objective of this prospective, nonrandomized clinical study was to determine the influence of concomitant radiochemotherapy with cisplatin on parotid gland tissue complication probability.

METHODS AND MATERIALS

Patient population

From January 2003 to June 2007, a total of 97 patients treated at the Department of Radiotherapy Martin-Luther-University Halle-Wittenberg with radiotherapy (XRT) or concomitant radiochemotherapy (XRCT) for squamuous cell carcinoma in high-risk Stage III or IV A, B were included. Tumors were classified in accordance with UICC (International Union Against Cancer) TNM classification. All schemes described accorded with national treatment guidelines. Patients were divided in two study groups based on the decision of the treating physician to apply or not apply chemotherapy. This decision typically took into account established risk factors, patient age, and performance status. In 36 patients (37%), cisplatin was added to radiotherapy, and 61 patients (63%) received irradiation without any chemotherapeutic agent. Characteristics of the patient population are shown in Table 1. The baseline characteristics were well balanced. The study was approved by the local medical faculty's ethics commitee, and written informed consent was obtained from all patients.

Table 1. Patient and tumor characteristics

Characteristic	XRT (n = 61) n (%)	XRCT (n = 36) n (%)
Gender		
Male	51 (84)	29 (81)
Female	10 (16)	7 (19)
Age (y)		
Median	61	52
Range	39–79	26–72
Neck dissection	56 (92)	34 (94)
Tumor site		
Oral cavity/oropharynx	43 (70)	27 (75)
Larynx/hypopharynx	18 (30)	9 (25)
UICC stage		
I	6 (10)	0
II	10 (16)	1 (3)
III	19 (31)	9 (25)
IVA	17 (28)	13 (36)
IVB	9 (15)	13 (36)

Abbreviations: UICC = International Union Against Cancer; XRCT = radiochemotherapy; XRT = radiotherapy.

Eligibility criteria

All patients presented with histologically proven advanced squamous cell or adenocarcinoma. The tumor sites oral cavity/oropharynx includes tumor locations of floor of mouth, the oral cavity, the tonsil, the soft palate, the tongue, and the base of the tongue. The tumor sites larynx/hypopharynx includes tumor locations of supraglottic, glottic, and subglottic larynx, hypopharynx, and cervical cancer of unknown primary (CUP). In all cases a curative-intent irradiation of the bilateral neck regions was indicated. None of the patients received previous irradiation or surgery of the parotid glands or had malignancies or other disease of the parotid glands. No use of medication with a known effect on salivary gland function was allowed.

Radiotherapy

All patients received three-dimensional conformal radiotherapy treatment (3D-CRT). Treatments were conducted on linear accelerators of 6 MV with the use of isocentric techniques (Primus, Siemens Medical Solutions, Erlangen, Germany). Patients were immobilized with individual thermoplastic head–neck–shoulder masks. A computed tomography (CT) scan (General Electric Lightspeed, Fairfield,) with slice thickness of 5 to 10 mm of the head and neck region was made for 3D-CRT treatment planning. The clinical target volumes (CTV), the spinal cord, and both parotid glands were delineated. More details were as recently described by Kuhnt *et al*. (14).

Definition of target volumes

All patients received conventionally fractionated radiotherapy with single doses of 2.0 Gy five times per week. The target volumes and doses were determined from clinical information, surgical results, and CT. Two CTVs were defined: CTV1 (dose 64–70 Gy) for high-risk target volumes (*i.e*., primary tumor region and involved neck nodes); and CTV2 (dose 50 Gy) for low-risk regions (*i.e*., prophylactic nodes down to the clavicles). Planning target volume (PTV) was defined as the CTV plus a 5- to 10-mm margin to compensate for variables of treatment setup and motion of internal organs. The limit for spinal cord dose was 45 Gy. Maximal and minimal target volume doses, the organ-at-risk doses, and the maximal dose to the spinal cord were recorded in dose–volume histograms (DVH). Dose specifications are related to a reference point according to International Commission on Radiation Units and Measurements.

Concomitant radiochemotherapy

In all cases of high-risk factors such as pT3 and pT4 stage, two or more involved lymph nodes, extracapsular nodal spread, or microscopic incomplete resection margin status of carcinoma, concomitant radiochemotherapy was indicated. Chemotherapy consisted of 25 mg of cisplatin per square meter of body surface area on Days 1 to 5 and Days 29 to 33. Cisplatin was given as a rapid infusion 30 min before irradiation.

Saliva collection

All patients underwent saliva collection at different timepoints: within 1 week before radiation treatment, during the 2nd and 6th week of irradiation, and finally at 4 weeks and 6 months posttreatment. All salivary samples were collected at least 1 h after a meal at a standardized time of day (9 AM to 11 AM). Patients were asked to rinse the mouth and swallow any residual saliva. The patients were then instructed to chew on a paraffin pellet (Ivoclar Vivadent, Liechtenstein) for 5 min. Samples were collected with the patients expectorating all saliva into cups. Saliva measurement was normalized in relation to pretreatment results and declared in percent (%), further named relative salivary flow rates. In some cases, patients produced a larger amount of saliva posttreatment than in the beginning. These measurements were regarded as free of complication and as 100% of post-therapeutic relative salivary flow rate.

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