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Preoperative radiochemotherapy and radical resection for stages II to IV oral and oropharyngeal cancer: grade of regression as crucial prognostic factor

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Abstract. The purpose of this study was to assess the prognostic value of histological response to preoperative radiochemotherapy in an established multimodal therapy concept for advanced oral and oropharyngeal cancer.

Two hundred and twenty-two patients who underwent preoperative radiochemotherapy (RCT: 50 Gy, mitomycin C and fluorouracil) and radical surgery were retrospectively evaluated. Resected tumours of all patients were histologically analysed and response to RCT was classified in histopathological grades of regression (RG). In a multivariate statistical analysis, RG was compared with established factors regarding their predictive value for overall and disease-specific survival.

The 5-year overall survival probability in the different groups of histopathological regression grades were: RG1 (no vital tumour): 73.4%, RG2 (minimal tumour remnants encompassing less than 5%): 72.1%, RG3 (5–50% vital tumour cells): 41.9%, RG4 (more than 50% vital tumour): 37.9%. For disease-specific survival probability no significant differences were found between both groups of ''responders'' (RG1 and RG2) nor between ''non-responders'' (RG3 and RG4), whereas responders and non-responders differed significantly from each other (log-rank test; $P < 0.001$). T-classification, N-classification and disease stage, histological grading, tumour site, age, and sex had less prognostic value than RG in a Cox regression model.

In the neoadjuvant multimodal therapy concept, histological response to preoperative RCT is a crucial prognostic factor even when surgical R0-resection is accomplished. Thus, non-responders have to be regarded as high-risk patients for recurrence and may benefit from further therapy.

Key words: oral cancer; prognostic factors; radiochemotherapy; regression grades; response; SCC.

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Multimodal therapeutic strategies are gaining importance in the treatment of advanced head and neck squamous cell carcinoma (SSC). Randomised trials have shown that a combination of concomitant radiochemotherapy (RCT) and surgery is more effective than radiotherapy alone[1], and surgical resection alone[16]. A combination known to be very effective consisting of mitomycin C, 5-fluorouracil, and irradiation in a preoperative setting followed by radical surgery is in use as standard therapy for advanced head and neck SCC at our institution[7,10]. Combined RCT treatment regimes, as the one mentioned above, often show a positive response in clinical and radiological reduction of the tumour[24]. However, on the microscopic level the rate of complete response is lower, and the risk of delayed recurrence remains a major problem[24]. In a neoadjuvant approach with radical surgery 4 to 6 weeks after preoperative RCT, response can be evaluated microscopically in the operative specimen. Classification scores of tumour regression under radiotherapy and/or chemotherapy have been proposed in various studies[5,7,8]. In this study, we apply a four-grade score previously described by Braun et al.[2,3]. Some authors have suggested that response to preoperative RCT was a valuable prognostic factor for local control and overall survival[11,13].

In a cohort of 222 consecutively treated patients, we compared histological regression grades of the resected tumours of all patients with the clinical outcome data after a median range of 24–152 months. We performed a multivariate analysis on traditional prognostic factors and histopathological regression grades in regard to locoregional failure and overall survival.

Material and method

Eligibility

Included in this retrospective analysis are all 222 patients who received the full course of multimodal therapy for advanced SCC of the oral cavity or the oropharynx at our institution between 1990 and 2000. Eligibility criteria for multimodal therapy were (unchanged since 1990): (1) histologically verified SCC of the oral cavity or oropharynx; (2) tumour stages II to IV (T2–4, N0–3) carcinoma (staging and classifications according to UICC guidelines[19]); (3) no previous treatment for oral cancer; (4) locally and regionally resectable tumour (infiltration of prevertebral fascia and muscles, of the internal carotid artery, and of the skull-base were regarded as unresectable); (5) a performance status (WHO score = 2) and functional blood parameters, compatible with general anaesthesia of extended duration and the administration of chemotherapy (Table 1).

Table 1. Patient and tumour characteristics

Patients; male/female	222; 181/41	
Age (mean ± SD)	55.7 ± 9.1 years	
Median surveillance ± SD; range	72.3 ± 32.8 months; 24–152 months	
	Frequency	Percent
Sites		
Anterior floor of mouth	43	19.4
Lateral floor of mouth	85	38.3
Retromolar trigon	32	14.4
Tonsillar fossa	16	7.2
Tongue	26	11.7
Lower gingiva	12	5.4
Upper gingiva	6	2.7
Cheek	2	0.9
T- and N-classifications		
T2	74	33.3
T3	28	12.6
T4	120	54.1
N0	120	45.9
N1	39	17.6
N2	74	33.3
N3	7	3.2
UICC disease stage		
II	47	21.1
III	33	14.9
IV	142	64.0

Excluded were patients with distant metastases in staging examinations (chest X-ray, sonography of the abdomen and scintigraphy of the skeleton) and prior history of malignancy.

Inclusion and exclusion criteria were reviewed by a multidisciplinary council consisting of senior physicians from Departments of Radiotherapy, Oncology, and Surgery. Decision in favour of multimodal therapy was found in consensus.

For diagnosis, all patients underwent a CT scan of the head and neck, sonography of the neck and examinations to rule out metastases as quoted above. Additionally, all patients underwent an inspection under general anaesthesia, in which the palpable tumour extensions were marked with an ink tattoo, a pharyngeal inspection was carried out with mirrors or endoscopes, and removal of necrotic and decayed teeth was performed. After informed consent was obtained, all patients received multimodal treatment regime consisting of mitomycin C (15–20 mg/m^2 given as intravenous bolus injection, day 1) followed immediately by a 5-day continuous infusion of 5-fluorouracil (750 mg/m^2/day) and concurrent radiation therapy of a total dose of 50 Gy given in 25 daily fractions over 5 weeks. Surgery was performed 3 to 6 weeks after completion of preoperative RCT and consisted of radical locoregional resection according to pre-RCT tumour extension (marked by an ink tattoo) with a 10 mm safety margin. Resection was carried out in en bloc-technique together with planned neck dissection (N0: levels 1 to 3; N+: levels 1 to 5). In cases of midline transgression, neck dissection was performed bilaterally. Primary reconstruction was performed in every case, predominantly with microsurgically revascularised free flaps. See Table 1 for patient and tumour characteristics.

Histological evaluation

Resected tumour specimen were routinely histologically analysed for resection margins and for determination of response to preoperative RCT. Resection margins were free of vital tumour in 214 cases (R0-resections) and tumour was found in the resection margins in eight cases (R1-resection). In these cases, the pathologist gave an estimation of the minimum distance to the resection margin in millimetres and of the most probable location. In consequence, a further resection in the reported area was performed in all eight cases. Response was classified according