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Preoperative radiochemotherapy and radical resection for stages II–IV oral and oropharyngeal cancer: outcome of 222 patients

C. Klug[1], A. Wutzl[1], C. Kermer[1], M. Voracek[2], G. Kornek[3], E. Selzer[4], C. Glaser[1], P. W. Poeschl[1], W. Millesi[5], R. Ewers[1]

[1]Department of Cranio-Maxillofacial and Oral Surgery, Medical University of Vienna, Vienna General Hospital, Waehringer Guertel 18-20, A-1090 Vienna, Austria; [2]Department of Psychology, Division of Research Methods and Differential Psychology, University of Vienna, Vienna, Austria; [3]Department of Internal Medicine I, Division of Oncology, Medical University of Vienna, Vienna, Austria; [4]Department of Radiotherapy, Centre for Excellence for Clinical and Experimental Oncology, Medical University of Vienna, Vienna, Austria; [5]Institute for Oral and Maxillofacial Surgery and Dentistry, Hospital Lainz, Ludwig Boltzmann Institute for Gerostomatology, Vienna, Austria

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Abstract. To analyse survival and locoregional control in patients with advanced oral and oropharyngeal squamous cell carcinoma (SCC) after multimodal therapy with preoperative radiochemotherapy (RCT) and radical surgery.

We included in this analysis 222 patients who underwent multimodal therapy between 1990 and 2000. Eligible were patients with UICC disease stages II–IV (T2: 33.3%; T3: 12.6%; T4: 54.1%; N0: 45.9%; N1: 17.6%; N2: 33.3%; N3: 3.2%; stage II: 21.1%; stage III: 14.9%; stage IV: 64%). Patients received preoperative radiochemotherapy consisting of Mitomycin C (15–20 mg/m^2, day 1) plus 5-Fluorouracil (750 mg/m^2/24 h-infusion, days 1–5) and concomitant radiotherapy for a total dose of 50 Gy. Radical locoregional en bloc-resection according to the pretherapeutic tumour extension was carried out in all patients.

After a median surveillance period of 72.3 months (24–152 months), 131 patients (59%) were alive, and 91 (41%) patients died; 12 (5%) of them died postoperatively, 46 (21%) due to tumour recurrence, and 33 (15%) deaths were not directly related to the primary tumour. Overall survival probability was 76% after 2 years, and 62% after 5 years. Two- and 5-year local control probability were 88 and 81%, respectively.

Regarding the high percentage of stage IV disease in the reported patients, the multimodal concept is an effective therapy offering excellent survival and local control probability.

Key words: chemotherapy; concurrent; multimodal therapy; oral cancer; outcome; radiotherapy.

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For treatment of oral and oropharyngeal cancer various therapeutic protocols are in use at different centres. This variety is demonstrated in the recent report of the DOSAK (German Austrian Swiss society for cancer in the maxillofacial region) register by HOWALDT et al.[12] for 71 institutions with more than 16,000 patients. The three cornerstones in treatment are surgery, radiotherapy (RT), and chemotherapy (ChT). For locoregionally advanced disease it is commonly accepted that the standard treatment should include a combination of surgery and RT, if the tumour is

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resectable[20,25]. Additional ChT is either applied concomitantly with RT or alone as induction-ChT[8,11,22] or as adjuvant ChT[8,16,22]. For concomitant radiochemotherapy (RCT) beneficial effects of RT and ChT were shown[1,2,14,27]. In a multidisciplinary approach comprising concomitant radiochemotherapy (RCT) and surgery protocols of pre- and postoperative setting are established[12]. From a surgical point of view, postoperative RCT is generally preferred, in order to avoid radiation-related complications during surgery and in wound healing. Arguments in favour of preoperative RT are radiobiological. It was shown that RT is likely to be more effective in otherwise unaffected and well oxygenated tissue[3,9,21]. The concept of administering RCT before surgery has been reported in studies by Dobrowsky et al.[6], Mohr et al.[20], Kirita et al.[15], and Eckardt et al.[7]. These authors report 2-year overall survival probabilities ranging from 63 to 86% and 2-year local control probabilities ranging from 68 to 84%. Considering the large proportion of advanced disease in these studies, the preoperative concept offers remarkable efficacy. However, numbers of treated patients in the above mentioned studies are still relatively small and randomized studies comparing the outcome of pre- and postoperative RCT are yet missing in literature. In this survey we report the outcome data of the so far largest reported cohort of 222 consecutively treated patients who received preoperative RCT and radical surgery for advanced oral and oropharyngeal cancer.

Method

Eligibility

Included in this retrospective survey 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 squamous cell carcinoma (SCC) of the oral cavity or oropharynx; (2) tumour stages II–IV (T2–4, N0–3) carcinoma (staging and classifications according to UICC guidelines[23,24]); (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. Patient and tumour characteristics

Patients	222
Male/female	181/41
Age, mean ± SD	55.7 ± 9.1 years
Median surveillance ± SD	72.3 ± 32.8 months
Surveillance range	24–152 months

Sites	Frequency	Percent
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

UICC stages	Frequency	Percent
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. See Tables 1 and 2 for patient and tumour characteristics.

Multimodal therapy

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 visible and 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 3–6 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 1–3; N+: levels 1–5). In cases of midline transgression neck dissection was performed bilaterally. Primary reconstruction was performed in every case, predominantly with microsurgically revascularized free flaps. Resected tumour specimen were routinely histologically analysed for resection margins. 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. A further resection in the reported area was performed in all eight cases.

Table 2. Tumour vs. node classification (UICC)

Classifications	N0	N1	N2a	N2b	N2c	N3	Total
T2	47	12	0	10	4	1	74
T3	15	6	0	5	2	0	28
T4	40	21	2	37	14	6	120
Total	102	39	2	52	20	7	222